

REVIEW

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The influence of phytoestrogens on different physiological and pathological processes: An overview

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Functional foods have nutritional properties and organic functions, which are beneficial to health. Certain types of functional food components are so-called phytoestrogens, non-steroidal compounds derived from the metabolism of precursors contained in plants, which originate secondary metabolites known to induce biological responses and by mimicry or modulating the action of endogenous estrogen. These molecules are involved in several physiological and pathological processes related to reproduction, bone remodeling, skin, cardiovascular, nervous, immune systems, and metabolism. This review aimed to present an overview of phytoestrogens regarding their chemical structure, actions, and effects in the organism given several pathologies. Several studies have demonstrated beneficial phytoestrogen actions, such as lipid profile improvement, cognitive function, menopause, oxidative stress, among others. Phytoestrogens effects are not completely elucidated, being necessary future research to understand the exact action mechanisms, whether they are via estrogen receptor or whether other hidden mechanisms produce these effects. Thus, this review makes a general approach to the phytoestrogen actions, beneficial effects, risk and limitations. However, the complexities of biological effects after ingestion of phytoestrogens and the differences in their metabolism and bioavailability indicate that interpretation of either risk or benefits needs to be made with caution.

KEYWORDS

functional foods, gut microbiome, menopause, osteoprotection, oxidative stress, phytoestrogen

1 | INTRODUCTION

Complementary and alternative medicine has increasingly investigated natural sources rich in functional foods since it is a growing tendency in contemporary society (Narukawa, 2018). In modern society, an intensification of this practice was verified and increase in the use of natural products for the complementary or alternative treatment of different pathologies (Shale, Stirk, & van Staden, 2005), especially the search for "natural" alternatives of hormone replacement treatments for women experiencing menopause (Johnson, Roberts, & Elkins, 2019).

According to the World Health Organization (WHO), more than 80% of the world's population, especially in developing nations,

resorts to medicinal plants as an option for treatment of diseases. The products from these plants are used for diverse purposes, usually associated with other medicinal products (allopathic and/or homeopathic) based on historical or personal evidence, without emphasis on the possibility or not of adverse effects (Sen & Samanta, 2014).

Functional foods are characterized by their nutritional properties and some organic functions. They are consumed in conventional diets, with content high amounts of vegetables, fruits, whole grains, legumes and demonstrate the ability to regulate body functions to help protect against diseases, such as hypertension, diabetes, cancer, coronary heart diseases, among others (Granado-Lorencio & Hernández-Alvarez, 2016). Moreover, some studies have shown the relationship between functional food consumption and the reduction of symptoms in

post-menopausal women, such as vasomotor symptoms, osteoporosis prevention and cardiovascular events (Poluzzi et al., 2014).

Some components of functional foods are called phytoestrogens, that are present in soy, flaxseed, mulberry, among others. These are non-steroidal compounds derived from the *in vivo* metabolism of precursors contained in plants, which originate secondary metabolites known by inducing biological responses and by mimicry or modulating the action of endogenous estrogen binding to estrogen receptors (ER) (Setchell, 1998). Phytoestrogens represent a diverse group of natural chemical substances similar to 17- β -estradiol (from family estrogens), the main female sex hormone. This structural similarity allows estrogenic action due to the binding to the ER (Scherr, Sarmah, di, & Cameron, 2009).

Phytoestrogens are classified into seven groups: Isoflavones, flavones, flavanones, chalcones, coumestanes, lignanes and stilbenes. The main ones being: isoflavones, lignans and coumestans. More than 1,000 compounds have been isolated from plant tissues, such as genistein and daidzein, belonging to the group of isoflavones (Plessow et al., 2003), which belong to the main group of flavonoids and are often found in legumes. Isoflavones are substances found mainly in soy belonging to the polyphenol group, a flavonoid subgroup also found in other plants, nuts, fruits, olive oil and derived beverages, such as coffee, tea, red wine and in several medicinal herbs (Hollman & Katan, 1997).

Regarding lignans, their precursors are present in the films that cover the cereals, being products from the transformation of lignin into phenolic compounds, whereas, in humans, they show anticarcinogenic and antioxidant properties, although being removed in the refinement process (Barker, 2019; Mali, Padhye, Anant, Hegde, & Kadam, 2019). Lignans can be found in plants and grains rich in fiber, such as wheat, barley, oats, beans, lentils, garlic, asparagus, broccoli, carrot and some fruits. Oily grains, such as flaxseed, contain higher concentrations of biologically active lignans (Barker, 2019). On the other hand, foods rich in coumestans include peas, beans and alfalfa shoots (Landete et al., 2016).

A great reduction in menopausal symptoms has been observed in oriental women whose soy and flaxseed consumption is frequent

when compared to the US population since women in the United States consume more processed products and fewer vegetables and fruits (Najaf Najafi & Ghazanfarpour, 2018).

Based on the above, this review aims to present an overview of phytoestrogens regarding their chemical structure, actions, and effects in the organism on some pathological processes, as shown in Figure 1.

2 | PHYTOESTROGENS ON DIET

As described above, isoflavones, lignans and coumestans are the major groups of phytoestrogens present in the diet.

Isoflavones include genistein, daidzein, glycine, formononetin and biochanin A, found in soy and legume-based foods, and usually in conjugated form. The difference between genistein and daidzein regards only to the presence of the 5-hydroxyl group of genistein. Soy is the major source of genistein and daidzein, and one of its chemical forms is the biologically inactive b-D-glycosidic compounds, which are hydrolyzed by β -glucosidases bacteria present in the intestinal mucosa when ingested, thus obtaining its bioactive form (glycosides), which once again hydrolyzed will become aglycones, which can be absorbed by the small intestine through passive diffusion (King, Broadbent, & Head, 1996).

Soy is one of the popular food additives because of high-quality protein and healthful fat, high in fiber, and free of lactose. There is evidence, for example, that they reduce risk of coronary heart disease and breast and prostate cancer. In addition, soy alleviates hot flashes and may favorably affect renal function, alleviate depressive symptoms and improve skin health (Messina, 2016). In Asian countries, where fermented soy products are part of the traditional diet, it is estimated that the number of consumed isoflavones can reach about 15–50 mg/day, while an intake lower than 2 mg/day was observed in Western countries (Elsenbrand, 2007).

The main source of phytoestrogens in the Western diet was lignans contents in the seeds, cereals, fruit, berries and vegetables (de Kleijn, van der Schouw, Wilson, Grobbee, & Jacques, 2002;

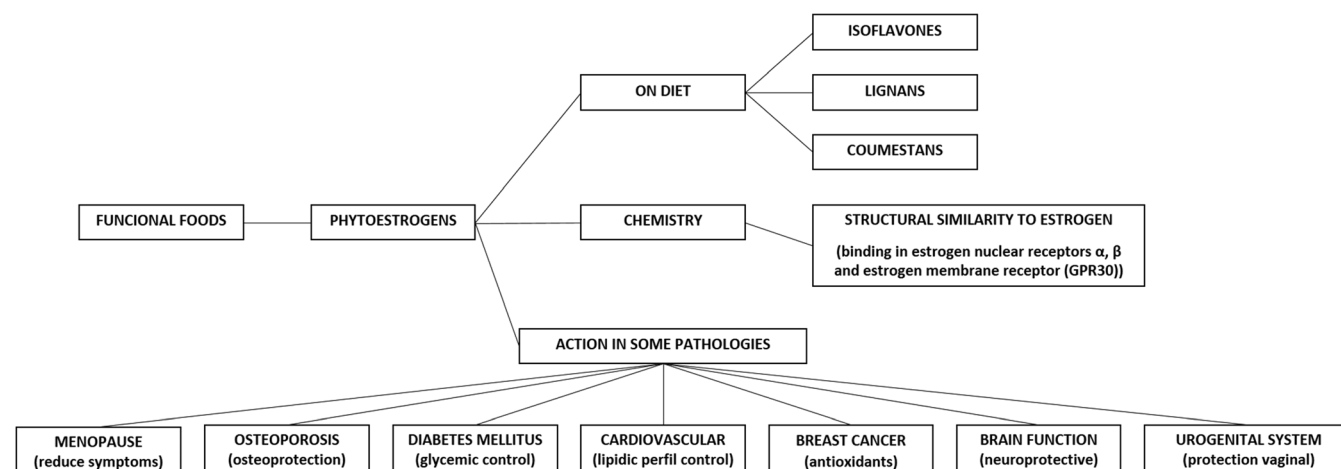


FIGURE 1 Scheme summarizing the phytoestrogens on diet, chemical characteristic, and action in some pathologies

Valsta et al., 2003). The precursors of lignans include pinoresinol, lariciresinol, secoisolariciresinol, matairesinol and others (Mali et al., 2019). Lignans are found in a wide variety of foods, including flaxseed, sesame, grains, fruits and vegetables, which are widely consumed in the Western diet and thus show the main source of phytoestrogens in this region (de Kleijn et al., 2002; Valsta et al., 2003). Studies with lignans suggest that they may protect the organism against hormone-dependent tumors, such as breast and prostate cancers (Mali et al., 2019). Additionally, protective effects against non-communicable diseases (NCDs) have been observed through a variety of mechanisms, including their antioxidant activity. This study has been developed to optimize the extraction of flaxseed oil, conserving maximum lignan contents in the oil, aiming at greater health benefits (Dixon, 2004; Lucas et al., 2002).

Although there are a large number of coumestans, only a small amount has estrogenic activity, predominantly coumestrol and methoxycoumestrol (Ndebele, Graham, & Tchounwou, 2010). Foods rich in coumestans include peas, beans and alfalfa shoots (Landete et al., 2016). Coumestrol treatment demonstrated beneficial actions concerning the production of specific thyroid autoantibodies, preventing the development of autoimmune thyroiditis by suppressing the Th1 response due to its antiestrogenic activity (Jin et al., 2016).

In a study by Whitten and collaborators, coumestrol showed to have both estrogenic and antiestrogenic effects on reproductive physiology. The coumestrol did suppress estrous cycles in adult females. Developmental actions were examined by neonatal exposure of pups through the milk of rat dams fed a coumestrol, control, or commercial soy-based diet during the critical period of the first 10 postnatal days or throughout the 21 days of lactation. The 10-day treatment did not significantly alter adult estrous cyclicity, but the 21-day treatment produced in a persistent estrus state in coumestrol-treated females by 132 days of age. In contrast, the 10-day coumestrol treatments produced significant deficits in the sexual behavior of male offspring (Whitten et al., 1995).

Studies suggest that the ingestion of products like soy-milk or foods containing large amounts of soy in childhood can influence the development of the reproductive system and cause changes in menstruation in adulthood (Upson, Harmon, Laughlin-Tommaso, Umbach, & Baird, 2016) and can anticipate menarche (Csaba, 2018). Furthermore, Infant's girls fed with soy formula since birth demonstrated evidence of estrogen response in the urogenital epithelium and the uterus, and cells of the vaginal had a higher maturation index when compared to infants fed with cow-milk formula or breast milk. Also, the reduction of uterine volumes in the first days of life was more slowly in girls fed soy formula (Adgent et al., 2018).

Moreover, several studies with animals have been demonstrated that administration of xenoestrogens, for example, genistein, in the early postnatal may acts in the estrogen receptors in the brain (Marraudino et al., 2019) and affect the normal development of many brain regions and interfere with the formation of some neuronal networks, like a dopaminergic (Ponti, Farinetti, Marraudino, Panzica, & Gotti, 2019), nitrgenic (Ponti et al., 2017; Rodriguez-Gomez, Filice, Gotti, & Panzica, 2014) and vasopressinergic (Ponti et al., 2017)

systems. Butler and collaborators using bisphenol A (BPA) and genistein, demonstrated the effects on behavioral and metabolic patterns in California mice (*Peromyscus californicus*). The results showed that early exposure to BPA or genistein could cause long-term neuro-behavioral and endocrine changes (Butler et al., 2020). Thus, these data indicate that early exposure to phytoestrogens may induce life-long effects on the differentiation of brain structures, neuronal networks, endocrine secretion and behaviors and can influence the development of the reproductive and other systems, as mentioned above.

3 | METABOLISM OF PHYTOESTROGENS

Phytoestrogens are found in plants and foods in the form of glycosidic conjugates, however, they are unconjugated like aglycones in fermented foods (Wang, Prasain, & Barnes, 2002). Isoflavones are a subclass of phytoestrogens found in soy, being the 6''-O-malonyl- β -glucoside at the 7-position of isoflavones their more predominant glycosidic conjugate. During the preparation of soy-based foods, this conjugate undergoes decarboxylation for 6''-O-acetyl- β -glucoside or hydrolysis to β -glucoside. C-Glycosides are found in the form of puerarin, 8-glucosyl daidzein (Wang et al., 2018).

Isoflavones are structurally similar to estradiol due to the presence of phenolic rings that can bind with increased affinity to the estrogen receptor of the type β (ER- β), acting as a natural selective modulator of ER (Branham et al., 2002; Diel et al., 2001). S-equol is a phytoestrogen, bacterial metabolite of isoflavone, which acts by binding to ER that are expressed in many regions of the brain. Thus, S-equol can improve the development of the cerebellum by affecting neurons and astrocytes through several signaling pathways, both via estrogen nuclear receptors and via nongenomic estrogen action (Ariyani, Miyazaki, & Koibuchi, 2019). Moreover, Marraudino and collaborators used selective ER antagonists *in vitro*, on the hypothalamic neuronal cultures, from female embryonic mice, observed that genistein acts in the arborization of neural extensions by different pathways actions (Marraudino et al., 2019).

Genistein and daidzein are isoflavones members and are in the form of 4'-methyl ethers of biochanin A and formononetin, respectively. The 6-methyl ether of 6,7,4'-trihydroxyisoflavone (glycitein) is present in the soy. Equol and O-desmethylangolensin are common metabolites of daidzein and formononetin (Wang et al., 2002).

Lignans are polyphenolic compounds, a subclass of phytoestrogens, bound by a 4-carbon bridge, shown in Figure 2. Flaxseed is particularly a source of lignans, matairesinol, and secoisolariciresinol and these are converted into the gastrointestinal tract of mammals through bacteria, into enterolactone and enterodiol, respectively. Other members of bioflavonoids, which have estrogen-like properties, include kaempferol, quercetin, apigenin and 8-prenylnaringenin (Zhang et al., 2017).

The main coumestans are coumestrol, 4'-methoxycoumestrol, repensol and trifoliol (Landete et al., 2016).

Once consumed, phytoestrogens undergo several metabolic changes in the organism. Intestinal hydrolases remove glycosidic

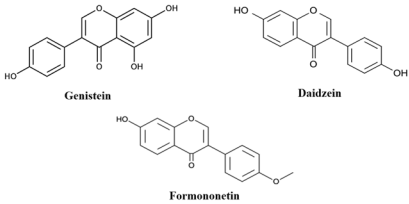
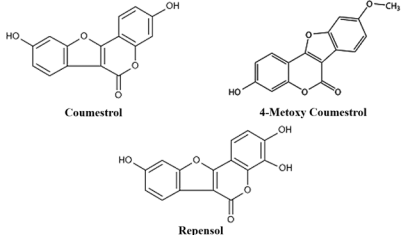
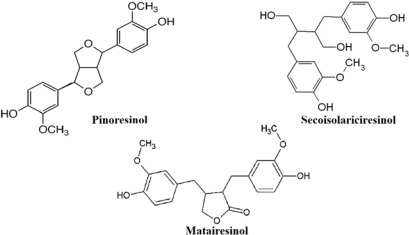
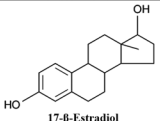
PHYTOESTROGENS	CHEMICAL STRUCTURES	BENEFITS	ADVERSE EFFECTS
ISOFLAVONES	 <p>Genistein, Daidzein, Formononetin</p>	<p>Reduction of hot flashes and vaginal dryness; Glycemic control; Osteoprotection; Reduction risk of brain and myocardial ischaemia; Neuroprotective effect; Decrease of oxidative stress; Kidneys protection.</p>	<p>Neurotoxicity (large doses); Mammary and pituitary tumors; Disorders in the reproductive tract, pituitary, adrenal and thyroid glands; Expression of genes involved in breast cancer; Growth factors for human estrogen-dependent tumor; Endocrine disruptors.</p>
COUMESTANS	 <p>Coumestrol, 4-Methoxy Coumestrol</p>	<p>Effects on reproductive physiology; Reduction of hot flashes and vaginal dryness; Cardiovascular protection; Osteoprotection.</p>	<p>Negative relationship with cognitive performance.</p>
LIGNANS	 <p>Pinoresinol, Secoisolaricresinol, Matairesinol</p>	<p>Improve of lipid profile; Osteoprotection; Glycemic control; Inhibition of AChE; Positive effects on gut microbiota.</p>	<p>No improvement in cognitive performance.</p>
ESTROGEN	 <p>17-β-Estradiol</p>	<p>Endogenous/Exogenous</p> <p>Menstrual cycle and reproduction; Osteoprotection; Neuroprotection; Improve of lipid profile; Prevention of metabolic diseases.</p>	<p>Exogenous Treatment</p> <p>Cancer risk; Cardiovascular diseases; Thrombosis risk; Pro-convulsion.</p>

FIGURE 2 Chemical structures, benefits, and adverse effects of some phytoestrogens precursors and its similarity to the estrogen structure. AChE, acetylcholinesterase; LDL, low-density lipoprotein

groups allowing rapid absorption of aglycones and distribution to body tissues (Day et al., 2000). In the liver and other tissues, phytoestrogens are converted into β -glucuronidases (Coldham & Sauer, 2000), and sulfate esters (Peterson et al., 1998; Peterson, Coward, Kirk, Falany, & Barnes, 1996; Wang et al., 2002).

From the phase I reactions, enzyme hydroxylation of cytochrome P450 is a relatively minor event for isoflavones, however, demethylation (i.e., conversion from biochanin A into genistein or matairesinol into enterodiol) occurs readily. In the liver, hepatocytes transfer isoflavones from blood to bile, returning them to the intestine (Peterson et al., 1996, 1998; Sfakianos, Coward, Kirk, & Barnes, 1997; Wang et al., 2002).

Due to the slower hydrolysis of conjugates in phase II, a ratio of isoflavones come into contact with the intestinal flora in the second intestinal passage, reducing the heterocyclic ring (of daidzein in dihydroxydaidzein and later in equol). In an alternative route, the heterocyclic ring is cleaved to form O-desmethylanagolensin and propionic acid 2-(4-hydroxyphenyl) (Coldham & Sauer, 2000; Wang et al., 2002), as well as several other phenolic acids. Thus, phytoestrogens and their metabolites range from hydrophobic chains of biochanin A to the hydrophilic conjugates of β -glucuronidases and glycosides (Wang et al., 2002).

4 | STRUCTURAL SIMILARITY TO ESTROGEN

The major action mechanism by which phytoestrogens may exert their potential effects on the body is based on its structural similarity to 17- β -estradiol (Sirtori, Arnoldi, & Johnson, 2005). The subtypes of estrogen receptors are classified in: nuclear receptors α and β ($ER\alpha$ and $ER\beta$) and a seven-transmembrane G protein-coupled receptor (GPR30, also known as GPER1) that mediated nongenomic estrogen action (Kuiper et al., 1996; Lee, Kim, & Choi, 2012; Thomas & Dong, 2006).

The estrogen receptor subtypes have different responses following their activation, such as gene regulation and cancer biology (Thomas & Gustafsson, 2011; Williams, Edvardsson, Lewandowski, Ström, & Gustafsson, 2008). Activation of $ER\alpha$ in the uterus and breast stimulates cell proliferation, necessary for tissue growth and maintenance (Harris, 2007; Thomas & Gustafsson, 2011), however, it can perform unlimited growth in $ER\alpha$ -dependent breast tumors, from which about 70% respond to anti-estrogen treatment, for example, with the Tamoxifen antagonist (Ali & Coombes, 2000). It was found that $ER\beta$ exerts antagonist effects on $ER\alpha$ mediated stimulation in cell proliferation (Covaleda et al., 2008; Strom et al., 2004; Thomas & Gustafsson, 2011).

GPER1 is associated with transcriptional and biological responses driving the progression of breast cancer as pro-migratory and metastatic genes belonging to cell adhesion molecules, triggers diverse transduction pathways including the epidermal growth factor receptor, phosphatidylinositol 3-kinase/protein kinase B, and mitogen-activated protein kinases toward (Talia et al., 2020). In male, higher estrogen levels have been related with better cognitive performance (Kulkarni, Gavrilidis, Worsley, van Rheenen, & Hayes, 2013).

Thus, different types of phytoestrogens may have different effects, depending on the target tissue and the type of activated receptor, for example, ER α is the major isoform in the uterus; ER β is predominant in the prostate and GPER1 controlling cell proliferation and expressed in the blood vessel (Barton et al., 2018; Enmark et al., 1997; Pearce & Jordan, 2004).

Using *in vitro* study models, several types of phytoestrogens were observed to verify the estrogenic activity of these compounds. These works verified that different types of phytoestrogens have a selective affinity to estrogen receptors (Boué et al., 2011; Liu et al., 2014; Marraudino et al., 2019; Park et al., 2012) and selectively increased the transcriptional activity of the estrogen response element (ERE) or activation of second messenger pathways, such as increases in intracellular free calcium or cAMP (Boué et al., 2011; Djiogoe et al., 2014; Marraudino et al., 2019; Takeuchi et al., 2009). These data demonstrated that phytoestrogens could bind in the ER- α , ER- β and GPER1 and consequently activated the ERE or second messenger pathways. However, few studies report the estrogenic effects of phytoestrogens *in vivo* by uterotrophic assay (Wang et al., 2012).

5 | ACTIONS OF PHYTOESTROGENS IN SOME PATHOLOGICAL PROCESSES

5.1 | Menopause

From the fifth or sixth decade of life, the ovaries begin to decline and there is a decrease in the plasma concentration of estrogen, leading to the climacteric syndrome, which corresponds to the period of gradual transition from the reproductive to the non-reproductive phase (Potter, Schrager, Dalby, Torell, & Hampton, 2018). Menopause is characterized with permanent end of menstrual activity for at least 12 months and is accompanied by uncomfortable changes in the organism, such as: hot flashes, atrophy and low vaginal lubrication, reduced libido, altered lipid profiles, osteoporosis, cardiovascular complications, mood disorders, among others (Cramer, Lauche, Langhorst, & Dobos, 2012; Monteleone, Mascagni, Giannini, Genazzani, & Simoncini, 2018).

Several studies have been demonstrated a positive effect of phytoestrogen action on physiology alterations observed in post-menopausal women (Chen et al., 2016; Najaf Najafi & Ghazanfarpour, 2018). The genistein supplements may promote the reduction of menopausal symptoms, but their effect may be unfavorable in women of reproductive age, for example, it may cause dysmenorrhea (Křížová, Dadáková, Kašparovská, & Kašparovský, 2019). Studies performed by

meta-analyses investigated the effects of phytoestrogens by extracts or supplements of soy isoflavones on the menopause symptoms, reporting a reduction in the frequency and severity of hot flashes (Chen, Lin, & Liu, 2015; Howes, Howes, & Knight, 2006).

Patade et al. (Patade et al., 2008), observed that the daily consumption of 30 g of milled flaxseed reduced the plasma levels of total cholesterol and low-density lipoprotein (LDL) in menopausal women.

Thus, phytoestrogens have their beneficial effects in situations of hypoestrogenism and may be an alternative or complement to reduce symptoms observed at menopause. Other effects of phytoestrogens that benefit women in the menopausal period will also be described separately in the sections below.

5.2 | Osteoporosis

Osteoporosis is a progressive bone disease characterized by reduced density and bone mass, which increases susceptibility to fractures (Rosen & Bouxsein, 2006). This pathology leads to deterioration in bone architecture because of the altered expression of several bone proteins (Galsworthy, 1994). This condition is more common in the elderly but can affect men and women of all ages (Srivastava & Deal, 2002). About 200 million women worldwide are affected by postmenopausal osteoporosis (Miyauchi et al., 2013).

Menopause leads to a reduction in estrogenic action (Potter et al., 2018), which is associated with osteoporosis since the reduction in the plasma level of estrogen is often associated with an increase in the rate of bone resorption by osteoclasts (Miyauchi et al., 2013). Hormonal therapy, besides conventional osteoporosis drugs, is also generally used to prevent and treat this condition; however, there may be some serious side effects, such as thrombosis and breast cancer (Hmamouchi et al., 2009).

The isoflavones have estrogen-like structures and bind to ER, specifically ER- β , which is predominant in the bone, brain, thymus, bladder and prostate (Benassayag, Ferre, & Perrot-Applanat, 2002). Genistein, one of the isoflavones, has inhibitory effects on bone resorption *in vitro*, similarly to estrogenic effects (Yamaguchi & Gao, 1998). It has also been shown that daidzein, genistein, and equol suppressed osteoclast activity *in vitro* (Tadaishi, Nishide, Tousen, Kruger, & Ishimi, 2014).

Greendale and collaborators investigated the cross-sectional and longitudinal relationships among the dietary intake of isoflavones with bone mineral density in the lumbar spine and femoral neck in black, white, Chinese and Japanese women during menopause. This study observed that the increase in isoflavone consumption seemed to be associated with a higher bone mineral density in the femoral neck of Japanese women, however, results for the other racial/ethnic groups did not support a relationship between dietary intake of isoflavones and increase or loss of bone mineral density in the same period. Therefore, evidence of a beneficial effect of isoflavones and other phytoestrogens on bone mineral density in post-menopausal and peri-menopausal women are still limited (Greendale et al., 2015).

In the study by Boulbaroud et al. (Boulbaroud, Mesfioui, Arfaoui, Ouichou, & el Hessni, 2008), the effects of flaxseed oil and sesame oil

intake were investigated on ovariectomized rats (OVX) related to biochemical parameters and bone histological status. It was observed that OVX rats fed flaxseed oil (10%) and sesame oil showed elongated trabeculae, less destruction, bone alterations, and a reduction in the activity of tartrate-resistant acid phosphatase (TRAP). Thus, the ingestion of phytoestrogens, for example, from flaxseed may aid in the prevention of osteoporosis associated with estrogen deficiency (Barker, 2019; Do et al., 2008; Sacco et al., 2009).

5.3 | Diabetes mellitus

The term diabetes mellitus (DM) describes a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia due to changes in insulin secretion and/or action, resulting in insulin resistance. High plasma glucose levels lead to the development of chronic degeneration associated with the failure of several organs, mainly eyes, kidneys, heart, nerves and blood vessels. The main DM types are Type 1 and Type 2 (Petersmann et al., 2019).

The role of some foods and their components in the prevention and treatment of Type 2 diabetes has been extensively investigated and demonstrated through different scientific methodologies. However, more consistent data refer to unprocessed foods (Riccardi et al., 2004). Nutritional intervention in both animals and humans suggested that ingestion of isoflavone-rich soy protein and flaxseed intake resulted in improved glycemic control and insulin resistance (Bhathena & Velasquez, 2002; Jungbauer & Medjakovic, 2014).

Fang and collaborators reported an improvement in glucose metabolism and a significant reduction in insulin level and insulin resistance in menopausal women who consumed phytoestrogens, especially genistein (Fang et al., 2016). Also, the meta-analysis suggest that supplementation with isoflavones through soy consumption could improve glucose metabolism and insulin control in the non-Asian women in post-menopause (Zhang et al., 2013).

In a study by Ricci and collaborators, including only post-menopausal women with insulin resistance, it was observed that the use of isoflavones, along with a change in lifestyle (diet and exercise), decreased insulin resistance compared to the control group that changed their lifestyle but did not use isoflavones (Ricci, Cipriani, Chiaffarino, Malvezzi, & Parazzini, 2010).

However, further research is needed to evaluate the long-term effects of phytoestrogens on type 2 diabetes (Bhathena & Velasquez, 2002).

5.4 | Cardiovascular diseases

During menopause, low estrogenic activity may influence the development of obesity, change fat distribution, plasma lipid profile, rheological properties of plasma and platelet function (Gorodeski, 1994). Such observations suggest that estrogen deficiency may promote cardiovascular disease in women and reinforces the idea that the use of phytoestrogens may be beneficial and help in reducing this risk. The

Asian population's diet is notably rich in soy compared to groups that have moved to Western societies and this supported the hypothesis that phytoestrogen may promote low rates of cardiovascular disease in these populations (Nagata, 2000; Zhang et al., 2003). However, Tokede et al. (Tokede, Onabanjo, Yansane, Gaziano, & Djoussé, 2015) suggest that isoflavone supplementation did not affect on serum lipid profiles. On the other hand, daily intake of 30 g of ground flaxseed reduced the serum concentrations of total and LDL cholesterol in menopausal women (Patade et al., 2008).

Studies have shown that estrogens are capable of influencing atherosclerosis and related clinical events (Cano, García-Pérez, & Tarín, 2010; Rossouw et al., 2007). They may act not only as protectors against atheromatous plaque formation but also as potential fragments of these already established plaques, which are important in the pathogenesis of the cardiovascular disease. The concept that phytoestrogens can act similarly comes from the observation that, in Asian populations where their consumption is high, the prevalence of the cardiovascular disease is lower compared to the populations from Western countries (González Cañete & Durán Agüero, 2014). Another study suggests that high ingestion of isoflavones was associated with a reduced risk of brain and myocardial ischemia in Japanese women, with a particularly pronounced reduction in risk in post-menopausal women (Kokubo et al., 2007).

However, the use of phytoestrogens in the protection of cardiovascular diseases in the postmenopausal period is not clear. Therefore, current evidence seems to be inferior in comparison to that available for synthetic estrogens, and possibly the potential effect of estrogens on stroke risk are not reproduced by isoflavones (Cano et al., 2010).

Currently, phytoestrogens actions on cardiovascular beneficial effects have been questioned, because data have not been able to demonstrate the real cardioprotective effect on soy protein supplementation (Jargin, 2014).

The European Food Safety Authority has not yet approved any claim related to isoflavone health effects, which could be probably because of the lack of uniformity of the effects on the "general population." The soy intake has recently been reported to improve carotid-femoral pulse wave velocity, blood pressure and endothelial function, but only in equol producers. It seems that only the equol metabolic product can take advantage of the vascular benefits of equol (Hazim et al., 2016). However, the relevancy of this biomarker for cardiovascular diseases risk is currently under debate (Bennetau-Pelissero, 2016).

5.5 | Breast cancer

Breast cancer is the most common female malignant neoplasm and the second major cause of death worldwide (Fritz et al., 2013). Synthetic and endogenous estrogens are generally associated with the etiology of breast cancer, stimulating cell growth and proliferation. Thus, longer exposure to estrogen could, therefore, be an important risk factor to promote or initiate this pathology (Liu et al., 2005). In the normal tissue and cell lines of breast cancer, ER α participates in cell proliferation and cell survival, whereas ER β modulates ER α

activity. It has been suggested that low concentration of genistein may interact with ER β and may form heterodimers with ER α to reduce recruitment of co-regulator proteins and thereby also reduce proliferation-related transcriptional activity (Molina, Bustamante, Bhoola, Figueroa, & Ehrenfeld, 2018).

Non-genomic actions of phytoestrogens may also be important in measuring the risk of breast cancer. Phytoestrogens may under certain conditions act as antioxidants and protect against damage to genetic material (Ogawara, Akiyama, & Ishida, 1986; Sierens, Hartley, Campbell, Leatham, & Woodside, 2001). Asian women have demonstrated a reduction of three-fold in the risk of breast cancer, as well as a lower serum estrogen concentration, which can be attributed to different lifestyles and diet, including routine consumption of foods containing phytoestrogens (Fritz et al., 2013; Mense, Hei, Ganju, & Bhat, 2008).

In the mammary tissue of postmenopausal women, there is an increased expression of CYP19, aromatase that catalyzes the conversion of androgens to estrogens. This enzymatic increase has been associated with the development of breast cancer. Treatment with different forms of phytoestrogens has been demonstrated inhibition of CYP19A1 and 17 β - and 3 β -hydroxysteroid enzymes involved in the biosynthesis of estrogens. These results provide promising insights into the search for new pharmacological compounds capable of inhibiting the progression of breast cancer (Molina et al., 2018).

Epidemiological studies have also suggested that high consumption of foods rich in phytoestrogens, such as soy and unrefined grains, may decrease the risk of colorectal, prostate and breast cancer, among other cancer. Furthermore, the higher consumption of phytoestrogens in the diet of Asian women may be related to a lower incidence of breast cancer (Mense et al., 2008). Other *in vitro* studies have demonstrated a weak proliferative effect of isoflavones on breast cancer cells or even blockage of these effects, which are promoted by estradiol in these cells (Pitkin, 2012). Thus, experimental data on phytoestrogens are far from being conclusive, especially on the mechanisms that may promote or inhibit cell growth (Baber, 2010). Moreover, variance in efficacy indicates that the molecular and cellular responses of phytoestrogens may be concentration-dependent.

Dietary phytoestrogens may have repercussions on homeostasis of normal tissue and cell lines of breast cancer at various levels: interacting with ER α /ER β and GPER-1 and modulating transcription and signaling pathways; interfering with estrogen biosynthetic enzymes; through cross-talk of GPER-1 with tyrosine kinase receptors; inducing apoptosis, proliferation or cell differentiation. However, tumor cells are part of a very complex microenvironment generating paracrine and autocrine interactions orchestrated by tumor cells (Molina et al., 2018).

5.6 | Brain function

Cognitive decline has been associated with the aging process commonly found in older age (Small, Dixon, & McArdle, 2011), especially among post-menopausal women (Berent-Spillon et al., 2012).

This prevalence in women seems to be related to loss of estrogenic action (Daniel, 2013), since, estradiol plays an important role in neurological maintenance in the formation of synapses and dendritic spicules, being fundamental in the neurobiology of aging since endocrine and neural senescence overlap in time (Morrison, Brinton, Schmidt, & Gore, 2006).

However, estrogen therapy still shows conflicting results, in which the exerted effects are protective or detrimental (Brinton, 2004). Interestingly, ER loss indicates an association with reduced neuroprotection by estrogen, since there seems to be a specific beneficial role of ER α in brain aging (Schreihofer & Ma, 2013).

The consumption of isoflavones from soy evidenced a neuroprotective effect on rats (Bagheri, Roghani, Joghataei, & Mohseni, 2012; Neese, Korol, Katzenellenbogen, & Schantz, 2010) and mice (Yao et al., 2013), although the consumption of large doses (20 mg/day) also had negative effects on the brain of rats, such as cellular toxicity, apoptosis and increase in lactate dehydrogenase, a marker of neural damage (Choi & Lee, 2004). Protective effects of genistein were observed in the cerebral cortex of elderly rats obtaining less harmful action than synthetic estradiol (Morán, Garrido, Alonso, Cabello, & González, 2013).

Neuroprotective effects of phytoestrogens found in soy have shown positive effects on animals and cell culture, however, have produced non-conclusive findings in clinical trials and observational studies in humans (Soni et al., 2014). Dadzein exert an antiapoptotic and antineurotoxic effect through GPER-1 and ER α , thereby reversing the toxic effects of glutamate in the neuronal cell. Furthermore, the treatment *in vitro* with genistein exerts an effect on the development of hypothalamic neurons, altering some specific parameters of the neurogenic process as increased neuritic arborization through the ER α , ER β and GPER1 (Marraudino et al., 2019).

Different types of lignans showed positive effects on cognitive performance (Mao et al., 2015) and in the markers of Alzheimer's disease, for example, the extract of fruits rich in lignans (ESP-806) significantly inhibited the activity of acetylcholinesterase (AChE) in the hippocampus of mice (Jeong et al., 2013). Thus, an adequate dietary intake of lignans may act in the prevention and treatment of neurological diseases, such as Alzheimer's.

In studies with humans, it has been observed that the consumption of lignans is associated with an improvement in cognitive function (Greendale et al., 2012; Nooyens et al., 2015), however, coumestrol intake was not related to improvement in cognitive performance (Greendale et al., 2012).

In the case of estrogen and phytoestrogen treatment, it is possible to observe that there are factors that influence the results, such as age, gender, ethnicity and menopausal status, as well as the duration of consumption and the used cognitive test. Soni et al. (Soni et al., 2014) demonstrated that the metabolic capacity to produce equol, which generally decreases with age, was also influenced by the studied population, differing between Asian and non-Asian populations.

Lignans and isoflavones are associated with increased cognitive performance in women after the sixth decades of life. However, lignan showed a negative linear relationship with the processing speed of

cognitive performance, so that smaller amounts of lignans were associated with a better processing speed (Alwerdt, Valdés, Chanti-Ketterl, Small, & Edwards, 2016). Further research with phytoestrogens is a potential target for intervention to maintaining mental and cognitive health among post-menopausal women.

In male, estrogen related with better cognitive, moreover, poor cognition, deficit memory and depressive symptoms have been found in men with low testosterone levels (Kulkarni et al., 2013). Phytoestrogens also exert direct effects on androgen receptors in the brain and together with ER actions may effectively modulate the neural circuit functions. Male mouse treated with low phytoestrogen diet demonstrated a reduction in activation of second messengers correlate with plasticity in the hippocampus synapse; profound decrease in long-term potentiation (LTP) in the ventral hippocampus; reduction of intermale aggression; altered territorial marking behavior; and a general disturbance of social behavior (Çalışkan et al., 2019; Sandhu, Demiray, Yanagawa, & Stork, 2020). Furthermore, acute perfusion of equol was able to rescue this LTP deficit, demonstrating a possible modulation of phytoestrogen on the hippocampus plasticity and memory (Çalışkan et al., 2019).

5.7 | Urogenital system

The study of genitourinary health is of great interest since symptoms caused by vulvovaginal atrophy can affect 20 to 45% of middle-aged and older women. In contrast to vasomotor symptoms, which generally decline over time, vulvovaginal atrophy may be progressive and irreversible if there is no treatment (Santoro & Komi, 2009; The North American Menopause Society, 2013). This change harms women's life quality and sexual health (Simon, Kokot-Kierepa, Goldstein, & Nappi, 2013).

Estrogen has a trophic effect on the multilayered squamous vaginal epithelium, promoting normal coloration, wrinkles and moisture. At menopause, low estrogenic action greatly affects the urogenital system, causing atrophy and resulting in altered epithelial morphology, reduced vascular flow, reduced the secretion of mucous glands in the vagina, decreased the action of vaginal bacterial flora and hence increased vaginal pH, which induces recurrent urogenital infections (Gass et al., 2012; Sturdee & Panay, 2010). Without estrogenic action, epithelial proliferation and its protection are reduced (Constantine et al., 2019), elastin becomes fragmented and collagen is subjected to hyalinization, resulting in vaginal dryness, irritation, dysuria and dyspareunia (Archer, 2010; The North American Menopause Society, 2013).

The consequences of urogenital atrophy intensify many years after menopause. Wilcox and collaborators demonstrated positive effects of isoflavones on vaginal epithelial maturation in postmenopausal women (Wilcox, Wahlqvist, Burger, & Medley, 1990). Combined administration or individual treatment of phytoestrogens was associated with improved hot flashes and vaginal dryness (Chen, Lin, & Liu, 2015).

Some studies have shown that a diet containing a dietary supplement of soy or any other source of phytoestrogens acts positively on the urogenital system in postmenopausal women (Manonai,

Chittacharoen, Theppisai, & Theppisai, 2007; Uesugi, Toda, Okuhira, & Chen, 2003).

6 | EFFECTS OF PHYTOESTROGENS BY NON-HORMONAL ACTION

6.1 | Oxidative stress and cytokines

Oxidative stress plays an important function in the human organism, for example, in skin aging and dermal damage. Phytochemicals with polyphenolic structures have been demonstrated the potential significance and application in the treatment of human cancers and other age-related diseases like skin aging. Isoflavonoid molecules have a capacity of protection against free radicals that shown to decrease oxidative stress. Equol is an isoflavonoid molecule that demonstrates an important decrease in oxidative stress (Lephart, 2016).

Equol has been shown influences at several different steps of the oxidative stress cascade, for example, protects DNA and enhances nerve and tissue repair, inhibits AP-1 (nuclear transcription element) and neoplastic cell growth and inhibits pro-inflammatory transcription factor NF-kappaB, while at the same time inhibit matrix metalloproteinases actions and simultaneously stimulate collagen and elastin, improving dermal health (Lephart, 2016).

Cisplatin is an antineoplastic agent causing lipid peroxidation (one oxidative stress marker) and protein nitration. Treatment with daidzein reduced 39.9% of lipid peroxidation (Hydroxynonenal adducts) and 48.7% of protein nitration, caused by cisplatin (Meng et al., 2017). This lipid peroxidation is also attenuated by flavonoids and antioxidants (Sahu, Kumar, & Sistla, 2015). Reactive oxygen species (ROS)-generating enzyme NOX2 is one among several sources for oxidative stress (Mukhopadhyay et al., 2010). Daidzein also attenuated cisplatin-induced NOX2 expression. However, daidzein did not change any oxidative stress marker when administered alone (Meng et al., 2017).

One of the most common compounds of isoflavone is genistein, which exerts significant neuroprotection against ischemic injury (Castelló-Ruiz et al., 2011; Wang et al., 2014). This neuroprotective effects of genistein involved inhibition of oxidative stress (Liang et al., 2008), which refers to a relative surplus of ROS and contributes largely to the injury of cerebral ischemia. Thus, 10 mg/kg once daily treatment with genistein for 2 weeks significantly improved neurological outcome, decreased infarct size and decreased the neuronal damage in ovariectomized rats to the Middle Cerebral Artery Occlusion and Reperfusion (MCAO-R) lesion (Miao, Xia, Che, & Song, 2018).

The potential risk of apoptotic death induced by oxidative injury and elevated ROS levels may lead to neurotoxic effects. A formulation of Genistein-Transfersomes (GEN-TF2) was able to reduce the apoptotic cells generated by H₂O₂ treatment. These data confer on the antioxidant and antiapoptotic activities by GEN-TF2. Therefore, a suitable intranasal delivery system as a therapeutic adjuvant in neurodegenerative diseases related to oxidative stress could be considered (Langasco et al., 2019).

Diosgenin, a well-known sapogenin derived from plants, is used as the principal substrate for the production of synthetic steroids by the pharmaceutical industry (Chen, Lin, & Liu, 2015). Furthermore, diosgenin treatment reduces both IL-2 (Th1) and IL-10 (Th2) cytokine production, suggesting that it has an anti-inflammation potential through the inhibition of T-cell immune responses in mouse primary splenocytes (Ku & Lin, 2013). Diosgenin treatment demonstrated significantly attenuates in the lung histopathological changes and infiltration of inflammatory cells, on LPS-induced acute lung injury in mice (Gao et al., 2013). Moreover, diosgenin inhibits the growth of tumor cells by stimulating both specific and non-specific cellular immune responses, instead of a direct cytotoxic effect (He et al., 2012).

Daidzein has a protective action on the kidneys by reduced cisplatin-induced macrophage accumulation. It inhibits the production of nitric oxide and IL-6 in a lipopolysaccharide-induced macrophage (Choi et al., 2012), and IL-18 induced by cisplatin (Meng et al., 2017).

Increased production of ROS associated with diabetes and together with decreased lactate synthesis lead to regression of the testis (Oliveira, Silva, & Silva Junior, 2016). Treatment with genistein in mice with Type 2 diabetes has caused a decline in the elevated level of circulating glucose, which may result in reduced production of ROS because of the increased expression of antioxidant enzymes (SOD and CAT), but decreased lipid peroxidation (LPO) expression and increased lactate production due to the increase in lactate dehydrogenase (LDH). Thus, treatment with genistein increases the production of antioxidants and lactate, which possibly contributes to suppress germ cell loss and improve spermatogenesis in diabetic mice (Verma, Samanta, & Krishna, 2019).

Savoia et al. (Savoia et al., 2018), demonstrated that both 17 β -estradiol and genistein reduced the release of ROS while increasing the level of glutathione, which was accompanied by maintenance of cell viability (human keratinocytes and fibroblasts from skin biopsy) and an improvement in the rate of proliferation. As updated information on the effects of 17 β -estradiol and genistein on the release of ROS and nitric oxide (NO) is scarce, these findings increase knowledge about the subject. Besides, the confirmation of the cytoprotective effects of estrogen and genistein were previously described by other authors (Thornton, 2013). Although its accurate mechanism of action is unclear, a role could be played by its anti-inflammatory and antioxidant action. The results regarding the modulation of NO release and mitochondrial membrane potential could suggest a possible mechanism by which estrogens/phytoestrogens exert their protective effects against peroxidation (Verma et al., 2019).

Moreover, genistein has a potent capacity to reduce the production of ROS by tumor cell types and cells of the immune system. The production of ROS has been postulated to play a role in tumor promotion, therefore, the ROS scavenging or antioxidant effect of genistein might be related to anticarcinogenesis (Hwang & Choi, 2015).

6.2 | Microbiota

Gut microbiota plays a relevant role in human health but the relationship between microbial ecology and host health continues to be a

matter of controversy. Polyphenols content in the diet is higher than previously believed because of the presence of nonextractable compounds, also, the difference in the intestinal microbiota of the western and Japanese population, suggesting that early exposure to a diet containing phytoestrogen may favor the population of microbiota that helps in phytoestrogen metabolism (Pérez-Jiménez & Saura-Calixto, 2015). The interaction between gut microbiota and polyphenols favors the bioavailability of these molecules for intestinal absorption (Marchesi et al., 2016; Marín, Miguélez, Villar, & Lombó, 2015).

There is a two-way interaction in which polyphenols modulate gut microbiota and, reciprocally, microbes may modulate the activity of polyphenols by regulating their bioavailability and also converting naturally occurring polyphenols into metabolites, which can exert different effects on the organism. Gut microbiota is, therefore, a key player for explaining the variable and controversial effects of dietary polyphenols on human health (Tomás-Barberán, Selma, & Espín, 2016).

Gut microbiota catabolizes dietary polyphenols and modulates their activity. In turn, polyphenols modulate gut microbiota beyond the "prebiotic like" effect, promoting the growth of beneficial microorganisms such as *Akkermansia* spp. and *Faecalibacterium* spp. Differences in gut microbiota ecology determine polyphenol metabolism, producing different metabolites that could modulate health effects (Tomás-Barberán et al., 2016). Recent studies in humans have described new intermediate microbial metabolites for the bioavailability of enterolactone and enterodiol, which could also be responsible for the positive health effects after lignan consumption (Quartieri et al., 2016).

The gut microbiota plays an important role in the metabolism of flavonoids. It is already known that sugars that are not digested and fermentable, such as fructooligosaccharides (FOS) are called prebiotics, which increases the production of short-chain fatty acids and hydrogen gas. The fermentation of saccharides and non-digestible starches in the colon has been shown to facilitate equol production. Also, the hydrogen gas produced during fermentation in the colon stimulated the production of equol (Murota, Nakamura, & Uehara, 2018).

7 | ADVERSE EFFECTS OF PHYTOESTROGENS

In contrast to these beneficial health claims, the effect of phytoestrogens may also cast doubt on their use since they might act as endocrine disruptors, suggesting a probability to cause adverse health effects (Csaba, 2018; Rietjens, Louisse, & Beekmann, 2017). For this fact, the health benefits or risks of phytoestrogens are still controversial (Andres, Abraham, Appel, & Lampen, 2011; Rietjens, Sotoca, Vervoort, & Louisse, 2013; Wuttke, Jarry, & Seidlová-Wuttke, 2007).

The distribution of phytoestrogens and their metabolites in different organs and body fluids is another important aspect. Urpi-Sarda et al. (Urpi-Sarda et al., 2008), reported the highest accumulation of equol and daidzein in the kidney, followed by liver, reproductive tract, thyroid and muscle from ewes that long-term exposure to red clover silage (daily intake of 157.6 mg/kg b.w. of phytoestrogens). Moreover, ewes supplementation with subterranean clover (formononetin,

biochanin A, genistein and daidzein) produced pathophysiological and morphological changes in the reproductive tract, as well as in the pituitary, adrenal and thyroid glands (Adams, 1995).

Genistein interacts with thyroid hormone receptors at nutritional doses (1 mM *in vitro*) (Hofmann, Schomburg, & Köhrle, 2009) and inhibits thyroid peroxidase (Doerge & Chang, 2002). These two properties impair the natural production and action of thyroid hormones in rodents. Soy and/or its isoflavones interfere in the iodination of human thyroid hormones *in vitro* (Renko et al., 2015) and these substances have been shown to disrupt the human thyroid function (Fruzza, Demeterco-Berggren, & Jones, 2012). Goiters were observed in hypothyroid babies, in the early 1960s, when soy-based infant formulas were first commercialized in the USA (Conrad, Chiu, & Silverman, 2004). A case of interaction between thyroid hormone and soy protein supplement was reported (Bell & Ovalle, 2001). There is a possible effect that chronic use of genistein is responsible for stepping forward of menarche (Csaba, 2018).

The American National Toxicology Program (USA-NTP) showed a significant increase in mammary and pituitary adenomas and carcinomas in the offspring of Sprague-Dawley rats exposed to genistein (8–40 mg/kg-bw/day) (National Toxicology Program, 2008). Genistein also induces the expression of genes involved in breast cancer cell proliferation in women with estrogen-dependent breast cancer (Shike et al., 2014). Genistein and daidzein may also be growth factors for human estrogen-dependent tumor cells, both *in vitro* (Carreau, Flouriot, Bennetau-Pelissero, & Potier, 2009) and in animal models of xenograft nude mice (Du et al., 2012). Similarly, soy isoflavones demonstrated alteration in the mammary density in Western postmenopausal women (Isidoro et al., 2016).

On the other hand, current hypotheses suggest that genistein may be protective against the cancer promotion, and act as a growth factor on estrogen-dependent tumor cells. Studies have shown that isoflavones may be both protective for tumors of the estradiol receptor β (ER β), and tumors bearing the ER β 2 variant (Dey, Barros, Warner, Ström, & Gustafsson, 2013). However, these results are very contradictory.

In a meta-analysis carried out to quantitatively evaluate the high intake of soy isoflavones associated with an increased risk of uterine fibroids, it was thus observed that high intake of soy isoflavones or soy-based foods during childhood and adulthood was associated with an increased risk of uterine fibroids in premenopausal women (Qin et al., 2019). Furthermore, as described in the Phytoestrogens on diet section, high intake soy milk, soy-based foods or genistein administration in the infancy may cause alterations in the dopaminergic (Ponti et al., 2019), nitrgergic (Ponti et al., 2017; Rodriguez-Gomez et al., 2014) and vasopressinergic systems (Ponti et al., 2017), in the urogenital epithelium and the uterus, uterine volume (Adgent et al., 2018), menstruation in the adulthood (Upson et al., 2016) and studies in mice have demonstrated changes in the gene expression and microRNA profiles in hippocampus and hypothalamus, demonstrating neurobehavioral and neuroendocrine changes (Butler et al., 2020).

There are several controversial data on the effects of phytoestrogens and some works suggest that phytoestrogens can affect

several physiological and pathophysiological processes related to different organs and systems. However, it is not yet established that due to these effects, phytoestrogens and phytoestrogen-containing diet can be useful for the prevention and treatment of pathophysiological processes (Sirotkin, 2014).

Thus, it has been concluded that in spite of increasing currently preclinical and clinical studies, concrete evidence is still lacking to support the overall risk-benefit profile of phytoestrogens (Poluzzi et al., 2014).

All the actions of phytoestrogens on the different systems of the organism are summarizing in Figure 3.

7.1 | Where are we now?

Currently, the estrogenic effects of genistein on the reproductive system and mammary and pituitary adenocarcinomas were reaffirmed by the USA-NTP, thereby allowing protective doses to be defined in humans. Since then, several studies have shown controversial results in either the beneficial or adverse effects of phytoestrogen. Regarding the adverse effects of isoflavones, it would seem reasonable to return to traditional Asian exposure levels rather than supplementation to favor the positive health effects of isoflavones (Isidoro et al., 2016).

When analyzing dietary intake, the isoflavones are currently present in our diet in the milligram range, whereas estradiol is only present in the nanogram range. Moreover, the phytoestrogen exposure has become more widespread with the progressive internationalization of soybean use in human and cattle food (Isidoro et al., 2016). In addition, the interaction between the gut microbiome and polyphenols and consequently bioavailability of phytoestrogens for intestinal absorption (Marín et al., 2015), is a possible crucial factor for the action in the organism as well as for controversial data in different works.

Further prospective epidemiological studies using improved food databases and markers of consumption are needed to identify the specific compounds that provide cancer protection. Furthermore, is necessary to determine precisely how the complex metabolism of phytoestrogens may interact with other mechanisms to prevent cancer (Russo et al., 2018).

8 | FINAL CONSIDERATIONS

Hormone therapy (HT) administered systemically or intravaginally, is a well-established treatment to reverse these manifestations due to low estrogenic action mainly in postmenopausal women. However, for some women, the risks of HT may overcome its benefits. Therefore, alternative treatments are sought to eliminate these potential risks (Stuenkel et al., 2012; The North American Menopause Society, 2013).

Phytoestrogens are plant-derived compounds found in large varieties of food, especially soy. Several beneficial effects, risk and limitations of phytoestrogens were reported in this review.

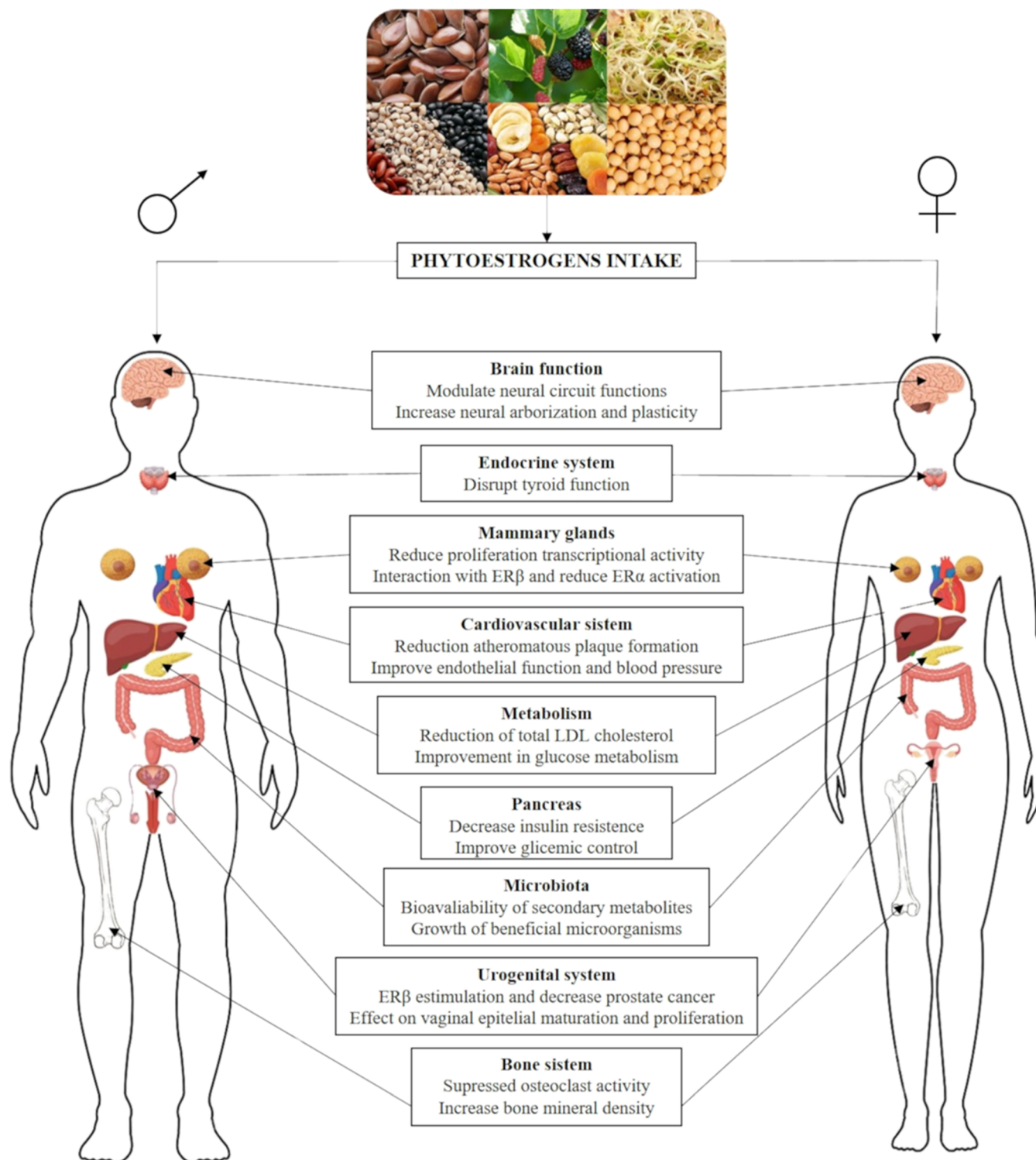


FIGURE 3 Scheme summarizing the actions of phytoestrogens on the different systems of the organism [Colour figure can be viewed at wileyonlinelibrary.com]

Considering the benefits, several authors have identified the reduction in menopausal symptoms, such as protection against loss of bone mineral density, glycemic control and insulin resistance, reduction of plasma level of total and LDL cholesterol, decreased risk of cardiovascular diseases and breast cancer, improvement of urogenital health

and cognitive function, among other benefits of phytoestrogen on the physiological and pathological processes described above.

Some concerns were expressed about the possible adverse effects of phytoestrogens, due to their affinity with ER. However, recent clinical studies involving menopausal women have not shown

an increased risk of breast cancer or increased endometrial hyperplasia after treatment with equol (Aso et al., 2012; Oyama et al., 2012). Whereas some studies demonstrated that phytoestrogen may cause endocrine disruption or induces expression of genes involved in some cell proliferation (Csaba, 2018; Shike et al., 2014).

There is a direct relationship between phytoestrogen and gut microbiota (Marchesi et al., 2016; Murota et al., 2018; Tomás-Barberán et al., 2016). The production of second metabolites from phytoestrogen by interaction with microbiota and bioavailability of these molecules for intestinal absorption, may affect the action on the organism and explaining the variable and controversial effects on human health.

The effects of phytoestrogens are not completely elucidated. Thus, future research is necessary to understand the exact action mechanisms and dosages that are beneficial to the body, showing whether these effects are actually due to similarity to the molecular structure of estrogen and with consequent action on its receptor or if other hidden mechanisms produce these effects.

9 | CONCLUSION

Phytoestrogens have several benefits to the organism like antioxidants, neuroprotection, improve the immune system, cardiovascular protection, among others. There are complexities of the biological effects of phytoestrogens after ingestion because the interaction between the gut microbiome and the differences in their metabolism with consequent bioavailability indicates that an explanation about either risk or benefits needs to be made with caution.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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REFERENCE

- Adams, N. R. (1995). Detection of the effects of phytoestrogens on sheep and cattle. *Journal of Animal Science*, 73(5), 1509–1515. <https://doi.org/10.2527/1995.7351509x>
- Adgent, M. A., Umbach, D. M., Zemel, B. S., Kelly, A., Schall, J. I., Ford, E. G., ... Stallings, V. A. (2018). A longitudinal study of estrogen-responsive tissues and hormone concentrations in infants fed soy formula. *Journal of Clinical Endocrinology and Metabolism*, 103(5), 1899–1909. <https://doi.org/10.1210/jc.2017-02249>
- Ali, S., & Coombes, R. C. (2000). Estrogen receptor alpha in human breast cancer: Occurrence and significance. *Journal of Mammary Gland Biology and Neoplasia*, 5(3), 271–281. <https://doi.org/10.1023/A:1009594727358>
- Alwerdt, J., Valdés, E. G., Chanti-Ketterl, M., Small, B. J., & Edwards, J. D. (2016). The relationship between phytoestrogens and speed of processing. *Menopause*, 23(8), 911–918. <https://doi.org/10.1097/GME.0000000000000632>
- Andres, S., Abraham, K., Appel, K. E., & Lampen, A. (2011). Risks and benefits of dietary isoflavones for cancer. *Critical Reviews in Toxicology*, 41(6), 463–506. <https://doi.org/10.3109/10408444.2010.541900>
- Archer, D. F. (2010). Efficacy and tolerability of local estrogen therapy for urogenital atrophy. *Menopause*, 17(1), 194–203. <https://doi.org/10.1097/gme.0b013e3181a95581>
- Ariyani, W., Miyazaki, W., & Koibuchi, N. (2019). A novel mechanism of sequal action in neurons and astrocytes: The possible involvement of gpr30/gper1. *International Journal of Molecular Sciences*, 20(20), 1–14. <https://doi.org/10.3390/ijms20205178>
- Aso, T., Uchiyama, S., Matsumura, Y., Taguchi, M., Nozaki, M., Takamatsu, K., ... Ohta, H. (2012). A natural S-Equol supplement alleviates hot flushes and other menopausal symptoms in Equol non-producing postmenopausal Japanese women. *Journal of Women's Health*, 21(1), 92–100. <https://doi.org/10.1089/jwh.2011.2753>
- Baber, R. (2010). Phytoestrogens and post reproductive health. *Maturitas*, 66(4), 344–349. <https://doi.org/10.1016/j.maturitas.2010.03.023>
- Bagheri, M., Roghani, M., Joghataei, M. T., & Mohseni, S. (2012). Genistein inhibits aggregation of exogenous amyloid-beta 1-40 and alleviates astrogliosis in the hippocampus of rats. *Brain Research*, 1429, 145–154. <https://doi.org/10.1016/j.brainres.2011.10.020>
- Barker, D. (2019). Lignans. *Molecules*, 24(7), 2–5. <https://doi.org/10.3390/molecules24071424>
- Barton, M., Filardo, E. J., Lolait, S. J., Thomas, P., Maggiolini, M., & Prossnitz, E. R. (2018). Historical and personal perspectives. *Journal of Steroid Biochemistry and Molecular Biology*, 176(2), 4–15. <https://doi.org/10.1016/j.jsbmb.2017.03.021>
- Bell, D. S. H., & Ovalle, F. (2001). Use of soy protein supplement and resultant need for increased dose of levothyroxine. *Endocrine Practice*, 7(3), 193–194. <https://doi.org/10.4158/EP.7.3.193>
- Benassayag, C., Ferre, F., & Perrot-Applanat, M. (2002). Phytoestrogens as modulators of steroid action in target cells. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, 777, 233–248. [https://doi.org/10.1016/S1570-0232\(02\)00340-9](https://doi.org/10.1016/S1570-0232(02)00340-9)
- Bennetau-Pelissero, C. (2016). Risks and benefits of phytoestrogens: Where are we now. *Current Opinion in Clinical Nutrition and Metabolic Care*, 19(6), 477–483. <https://doi.org/10.1097/MCO.0000000000000326>
- Berent-Spillion, A., Persad, C. C., Love, T., Sowers, M. F., Randolph, J. F., Zubieta, J. K., & Smith, Y. R. (2012). Hormonal environment affects cognition independent of age during the menopause transition. *Journal of Clinical Endocrinology and Metabolism*, 97(9), E1686–E1694. <https://doi.org/10.1210/jc.2012-1365>
- Bhatena, S. J., & Velasquez, M. T. (2002). Beneficial role of dietary phytoestrogens in obesity and diabetes. *American Journal of Clinical Nutrition*, 76, 1191–1201. <https://doi.org/10.1093/ajcn/76.6.1191>
- Boué, S. M., Burow, M. E., Wiese, T. E., Shih, B. Y., Elliott, S., Carter-Wientjes, C. H., ... Bhatnagar, D. (2011). Estrogenic and antiestrogenic activities of phytoalexins from red kidney bean (*Phaseolus vulgaris* L.). *Journal of Agricultural and Food Chemistry*, 59(1), 112–120. <https://doi.org/10.1021/jf102255u>
- Boulbaroud, S., Mesfioui, A., Arfaoui, A., Ouichou, A., & el Hessni, A. (2008). Preventive effects of flaxseed and sesame oil on bone loss in ovariectomized rats. *Pakistan Journal of Biological Sciences*, 11(13), 1696–1701. <https://doi.org/10.3923/pjbs.2008.1696.1701>
- Branham, W. S., Dial, S. L., Moland, C. L., Hass, B. S., Blair, R. M., Fang, H., ... Sheehan, D. M. (2002). Phytoestrogens and Mycoestrogens bind to the rat uterine estrogen receptor. *The Journal of Nutrition*, 132(4), 658–664. <https://doi.org/10.1093/jn/132.4.658>
- Brinton, R. D. (2004). Impact of estrogen therapy on Alzheimer's disease: A fork in the road? *CNS Drugs*, 18(7), 405–422. <https://doi.org/10.2165/00023210-200418070-00001>

- Butler, M. C., Long, C. N., Kinkade, J. A., Green, M. T., Martin, R. E., Marshall, B. L., ... Rosenfeld, C. S. (2020). Endocrine disruption of gene expression and microRNA profiles in hippocampus and hypothalamus of California mice: Association of gene expression changes with behavioural outcomes. *Journal of Neuroendocrinology*, 32, 1–22. <https://doi.org/10.1111/jne.12847>
- Çalışkan, G., Raza, S. A., Demiray, Y. E., Kul, E., Sandhu, K. V., & Stork, O. (2019). Depletion of dietary phytoestrogens reduces hippocampal plasticity and contextual fear memory stability in adult male mouse. *Nutritional Neuroscience*, 8305, 1–12. <https://doi.org/10.1080/1028415X.2019.1698826>
- Cano, A., García-Pérez, M. Á., & Tarín, J. J. (2010). Isoflavones and cardiovascular disease. *Maturitas*, 67, 219–226. <https://doi.org/10.1016/j.maturitas.2010.07.015>
- Carreau, C., Flouriot, G., Bennetau-Pelissero, C., & Potier, M. (2009). Respective contribution exerted by AF-1 and AF-2 transactivation functions in estrogen receptor α induced transcriptional activity by isoflavones and equol: Consequence on breast cancer cell proliferation. *Molecular Nutrition and Food Research*, 53(5), 652–658. <https://doi.org/10.1002/mnfr.200800061>
- Castelló-Ruiz, M., Torregrosa, G., Burguete, M. C., Salom, J. B., Gil, J. V., Miranda, F. J., ... Alborch, E. (2011). Soy-derived phytoestrogens as preventive and acute neuroprotectors in experimental ischemic stroke: Influence of rat strain. *Phytomedicine*, 18(6), 513–515. <https://doi.org/10.1016/j.phymed.2011.02.001>
- Chen, F.-P., Chang, C. J., Chao, A.-S., Huang, H.-Y., Huang, J.-P., Wu, M.-H., ... Tsai, Y.-C. (2016). Efficacy of Femarelle for the treatment of climacteric syndrome in postmenopausal women: An open label trial. *Taiwanese Journal of Obstetrics and Gynecology*, 55(3), 336–340. <http://dx.doi.org/10.1016/j.tjog.2016.04.008>
- Chen, M. N., Lin, C. C., & Liu, C. F. (2015). Efficacy of phytoestrogens for menopausal symptoms: A meta-analysis and systematic review. *Climacteric*, 18(2), 260–269. <https://doi.org/10.3109/13697137.2014.966241>
- Chen, Y., Tang, Y.-M., Yu, S.-L., Han, Y.-W., Kou, J.-P., Liu B.-L., Yu, B.-Y. (2015). Advances in the pharmacological activities and mechanisms of diosgenin. *Chinese Journal of Natural Medicines*, 13(8), 578–587. [http://dx.doi.org/10.1016/s1875-5364\(15\)30053-4](http://dx.doi.org/10.1016/s1875-5364(15)30053-4)
- Choi, E. J., & Lee, B. H. (2004). Evidence for genistein mediated cytotoxicity and apoptosis in rat brain. *Life Sciences*, 75(4), 499–509. <https://doi.org/10.1016/j.lfs.2004.01.010>
- Choi, E. Y., Jin, J. Y., Lee, J. Y., Choi, J. I., Choi, I. S., & Kim, S. J. (2012). Anti-inflammatory effects and the underlying mechanisms of action of daidzein in murine macrophages stimulated with Prevotella intermedia lipopolysaccharide. *Journal of Periodontal Research*, 47(2), 204–211. <https://doi.org/10.1111/j.1600-0765.2011.01422.x>
- Coldham, N. G., & Sauer, M. J. (2000). Pharmacokinetics of [14C]genistein in the rat: Gender-related differences, potential mechanisms of biological action, and implications for human health. *Toxicology and Applied Pharmacology*, 164(2), 206–215. <https://doi.org/10.1006/taap.2000.8902>
- Conrad, S. C., Chiu, H., & Silverman, B. L. (2004). Soy formula complicates management of congenital hypothyroidism. *Archives of Disease in Childhood*, 89, 37–40. <https://doi.org/10.1136/adc.2002.009365>
- Constantine, G., Millheiser, L. S., Kaunitz, A. M., Parish, S. J., Graham, S., Bernick, B., Mirkin, S. (2019). Early onset of action with a 17 β -estradiol, softgel, vaginal insert for treating vulvar and vaginal atrophy and moderate to severe dyspareunia. *Menopause*, 26, (11), 1259–1264. <http://dx.doi.org/10.1097/gme.0000000000001394>
- Sotoca Covalada, A. M., van den Berg, H., Vervoort, J., van der Saag, P., Ström, A., Gustafsson, J.-Å., ..., Murk, A. J. (2008). Influence of Cellular ER α /ER β Ratio on the ER α -Agonist Induced Proliferation of Human T47D Breast Cancer Cells. *Toxicological Sciences*, 105(2), 303–311. <http://dx.doi.org/10.1093/toxsci/kfn141>
- Cramer, H., Lauche, R., Langhorst, J., & Dobos, G. (2012). Effectiveness of yoga for menopausal symptoms: A systematic review and meta-analysis of randomized controlled trials. *Evidence-Based Complementary and Alternative Medicine*, 2012, 1–11. <https://doi.org/10.1155/2012/863905>
- Csaba, G. (2018). Effect of endocrine disruptor phytoestrogens on the immune system: Present and future. *Acta Microbiologica et Immunologica Hungarica*, 65(1), 1–14. <https://doi.org/10.1556/030.65.2018.018>
- Daniel, J. M. (2013). Estrogens, estrogen receptors, and female cognitive aging: The impact of timing. *Hormones and Behavior*, 63, 231–237. <https://doi.org/10.1016/j.yhbeh.2012.05.003>
- Day, A. J., Cañada, F. J., Díaz, J. C., Kroon, P. A., Mclauchlan, R., Faulds, C. B., ... Williamson, G. (2000). Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. *FEBS Letters*, 468(2–3), 166–170. [https://doi.org/10.1016/S0014-5793\(00\)01211-4](https://doi.org/10.1016/S0014-5793(00)01211-4)
- Dey, P., Barros, R. P. A., Warner, M., Ström, A., & Gustafsson, J. Å. (2013). Insight into the mechanisms of action of estrogen receptor β in the breast, prostate, colon, and CNS. *Journal of Molecular Endocrinology*, 51 (3), T61–T74. <https://doi.org/10.1530/JME-13-0150>
- Diel, P., Smolnikar, K., Schulz, T., Laudendach-Leschowski, U., Michna, H., & Vollmer, G. (2001). Phytoestrogens and carcinogenesis - differential effects of genistein in experimental models of normal and malignant rat endometrium. *Human Reproduction*, 16(5), 997–1006. <https://doi.org/10.1093/humrep/16.5.997>
- Dixon, R. A. (2004). PHYTOESTROGENS. *Annual Review of Plant Biology*, 55, 225–261. <https://doi.org/10.1146/annurev.arplant.55.031903.141729>
- Djiogue, S., Halabalaki, M., Njamen, D., Kretzschmar, G., Lambrinidis, G., Hoepfing, J., ... Vollmer, G. (2014). Erythroidine alkaloids: A novel class of phytoestrogens. *Planta Medica*, 80(11), 861–869. <https://doi.org/10.1055/s-0034-1382861>
- Do, S. H., Lee, J. W., Jeong, W. I., Chung, J. Y., Park, S. J., Hong, I. H., ... Jeong, K. S. (2008). Bone-protecting effect of Rubus coreanus by dual regulation of osteoblasts and osteoclasts. *Menopause*, 15(4), 676–683. <https://doi.org/10.1097/gme.0b013e31815bb687>
- Doerge, D. R., & Chang, H. C. (2002). Inactivation of thyroid peroxidase by soy isoflavones, in vitro and in vivo. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, 777, 269–279. [https://doi.org/10.1016/S1570-0232\(02\)00214-3](https://doi.org/10.1016/S1570-0232(02)00214-3)
- Du, M., Yang X., Hartman J. A., Cooke P. S., Doerge D. R., Ju Y. H., Helferich W. G. (2012). Low-dose dietary genistein negates the therapeutic effect of tamoxifen in athymic nude mice. *Carcinogenesis*, 33, (4), 895–901. <http://dx.doi.org/10.1093/carcin/bgs017>
- Elsenbrand, G. (2007). Isoflavones as phytoestrogens in food supplements and dietary foods for special medical purposes. *Molecular Nutrition and Food Research*, 51(10), 1305–1312. <https://doi.org/10.1002/mnfr.200700217>
- Enmark, E., Peltö-Huikko, M., Grandien, K., Lagercrantz, S., Lagercrantz, J., Fried, G., ... Gustafsson, J. Å. (1997). Human estrogen receptor β -gene structure, chromosomal localization, and expression pattern. *Journal of Clinical Endocrinology and Metabolism*, 82(12), 4258–4265. <https://doi.org/10.1210/jcem.82.12.4470>
- Fang, K., Dong, H., Wang, D., Gong, J., Huang, W., & Lu, F. (2016). Soy isoflavones and glucose metabolism in menopausal women: A systematic review and meta-analysis of randomized controlled trials. *Molecular Nutrition and Food Research*, 60(7), 1602–1614. <https://doi.org/10.1002/mnfr.201501024>
- Fritz, H., Seely, D., Flower, G., Skidmore, B., Fernandes, R., Vadeboncoeur, S., ... Fergusson, D. (2013). Soy, red clover, and isoflavones and breast cancer: A systematic review. *PLoS One*, 8, e81968. <https://doi.org/10.1371/journal.pone.0081968>
- Fruzza, A. G., Demeterco-Berggren, C., & Jones, K. L. (2012). Unawareness of the effects of soy intake on the Management of Congenital

- Hypothyroidism. *Pediatrics*, 130(3), e699–e702. <https://doi.org/10.1542/peds.2011-3350>
- Galsworthy, T. D. (1994). Osteoporosis: Statistics, intervention, and prevention. *Annals of the New York Academy of Sciences*, 30(736), 158–164. <https://doi.org/10.1111/j.1749-6632.1994.tb12828.x>
- Gao, M., Chen, L., Yu, H., Sun, Q., Kou, J., & Yu, B. (2013). Diosgenin down-regulates NF- κ B p65/p50 and p38MAPK pathways and attenuates acute lung injury induced by lipopolysaccharide in mice. *International Immunopharmacology*, 15(2), 240–245. <https://doi.org/10.1016/j.intimp.2012.11.019>
- Gass, M. L. S., Manson, J. E., Cosman, F., Grodstein, F., Craig, J. V., Karas, R. H., ... Utian, W. H. (2012). The 2012 Hormone Therapy Position Statement of The North American Menopause Society. *Menopause: The Journal of The North American Menopause Society*, 19(3), 257–271. <http://dx.doi.org/10.1097/gme.0b013e31824b970a>
- González Cañete, N., & Durán Agüero, S. (2014). Soya isoflavones and evidences on cardiovascular protection. *Nutrición Hospitalaria*, 29(6), 1271–1282. <https://doi.org/10.3305/nh.2014.29.6.7047>
- Gorodeski, G. I. (1994). Impact of the menopause on the epidemiology and risk factors of coronary artery heart disease in women. *Experimental Gerontology*, 29(3–4), 357–375. [https://doi.org/10.1016/0531-5565\(94\)90017-5](https://doi.org/10.1016/0531-5565(94)90017-5)
- Granado-Lorencio, F., & Hernández-Alvarez, E. (2016). Functional foods and health effects: A nutritional biochemistry perspective. *Current Medicinal Chemistry*, 23(26), 2929–2957. <https://doi.org/10.2174/0929867323666160615105746>
- Greendale, G. A., Huang, M. H., Leung, K., Crawford, S. L., Gold, E. B., Wight, R., ... Karlamangla, A. S. (2012). Dietary phytoestrogen intakes and cognitive function during the menopausal transition: Results from the study of Women's health across the nation phytoestrogen study. *Menopause*, 19(8), 894–903. <https://doi.org/10.1097/gme.0b013e318242a654>
- Greendale, G. A., Tseng, C. H., Han, W., Huang, M. H., Leung, K., Crawford, S., ... Karlamangla, A. S. (2015). Dietary isoflavones and bone mineral density during midlife and the menopausal transition: Cross-sectional and longitudinal results from the study of Women's health across the nation phytoestrogen study. *Menopause*, 22(3), 279–288. <https://doi.org/10.1097/GME.0000000000000305>
- Harris, H. A. (2007). Estrogen receptor- β : Recent lessons from in vivo studies. *Molecular Endocrinology*, 21(1), 1–13. <https://doi.org/10.1210/me.2005-0459>
- Hazim, S., Curtis, P. J., Schär, M. Y., Ostertag, L. M., Kay, C. D., Minihane, A. M., & Cassidy, A. (2016). Acute benefits of the microbial-derived isoflavone metabolite equol on arterial stiffness in men prospectively recruited according to equol producer phenotype: A double-blind randomized controlled trial. *American Journal of Clinical Nutrition*, 103(3), 694–702. <https://doi.org/10.3945/ajcn.115.125690>
- He, Z., Tian, Y., Zhang, X., Bing, B., Zhang, L., Wang, H., & Zhao, W. (2012). Anti-tumour and immunomodulating activities of diosgenin, a naturally occurring steroidal saponin. *Natural Product Research*, 26(23), 2243–2246. <https://doi.org/10.1080/14786419.2011.648192>
- Hmamouchi, I., Allali, F., Khazzani, H., Bennani, L., Mansouri, L. E. L., Ichchou, L., ... Hajjaj-Hassouni, N. (2009). Low bone mineral density is related to atherosclerosis in postmenopausal Moroccan women. *BMC Public Health*, 9(388), 1–18. <https://doi.org/10.1186/1471-2458-9-388>
- Hofmann, P. J., Schomburg, L., & Köhrle, J. (2009). Interference of endocrine disruptors with thyroid hormone receptor-dependent transactivation. *Toxicological Sciences*, 110(1), 125–137. <https://doi.org/10.1093/toxsci/kfp086>
- Hollman, P. C. H., & Katan, M. B. (1997). Absorption, metabolism and health effects of dietary flavonoids in man. *Biomedicine and Pharmacotherapy*, 51(8), 305–310. [https://doi.org/10.1016/S0753-3322\(97\)88045-6](https://doi.org/10.1016/S0753-3322(97)88045-6)
- Howes, L. G., Howes, J. B., & Knight, D. C. (2006). Isoflavone therapy for menopausal flushes: A systematic review and meta-analysis. *Maturitas*, 55, 203–211. <https://doi.org/10.1016/j.maturitas.2006.03.008>
- Hwang, K. A., & Choi, K. C. (2015). Anticarcinogenic effects of dietary phytoestrogens and their Chemopreventive mechanisms. *Nutrition and Cancer*, 67, 796–803. <https://doi.org/10.1080/01635581.2015.1040516>
- Isidoro, B., Lope, V., Whelan, D., Pedraz, C., Sánchez-Contador, C., Santamariña, C., ... Pollán, M. (2016). Use of hormone therapy and isoflavones and mammographic density in Spain. *Menopause*, 23(5), 556–564. <https://doi.org/10.1097/GME.0000000000000569>
- Jargin, S. V. (2014). Soy and phytoestrogens: Possible side effects. *GMS German Medical Science*, 12, 1–5. <https://doi.org/10.3205/000203>
- Jeong, E. J., Lee, H. K., Lee, K. Y., Jeon, B. J., Kim, D. H., Park, J.-H., ..., Sung, S. H. (2013). The effects of lignan-riched extract of *Shisandra chinensis* on amyloid- β -induced cognitive impairment and neurotoxicity in the cortex and hippocampus of mouse. *Journal of Ethnopharmacology*, 146(1), 347–354. <http://dx.doi.org/10.1016/j.jep.2013.01.003>
- Jin, X., Wang, S., Zhao, X., Jin, Q., Fan, C., Li, J., ... Teng, W. (2016). Coumestrol inhibits autoantibody production through modulating Th1 response in experimental autoimmune thyroiditis. *Oncotarget*, 7(33), 52797–52809. <https://doi.org/10.18632/oncotarget.10353>
- Johnson, A., Roberts, L., & Elkins, G. (2019). Complementary and alternative medicine for menopause. *Journal of Evidence-Based Integrative Medicine*, 24, 1–14. <https://doi.org/10.1177/2515690X19829380>
- Jungbauer, A., & Medjakovic, S. (2014). Phytoestrogens and the metabolic syndrome. *Journal of Steroid Biochemistry and Molecular Biology*, 139, 277–289. <https://doi.org/10.1016/j.jsbmb.2012.12.009>
- King, R. A., Broadbent, J. L., & Head, R. J. (1996). Absorption and excretion of the soy Isoflavone Genistein in rats. *The Journal of Nutrition*, 126(1), 176–182. <https://doi.org/10.1093/jn/126.1.176>
- de Kleijn, M. J. J., van der Schouw, Y. T., Wilson, P. W. F., Grobbee, D. E., & Jacques, P. F. (2002). Dietary intake of phytoestrogens is associated with a favorable metabolic cardiovascular risk profile in postmenopausal U.S. women: The Framingham study. *The Journal of Nutrition*, 132(2), 276–282. <https://doi.org/10.1093/jn/132.2.276>
- Kokubo, Y., Iso, H., Ishihara, J., Okada, K., Inoue, M., Tsugane, S., & JPHC Study Group. (2007). Association of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: The Japan public health center-based (JPHC) study cohort I. *Circulation*, 116(22), 2553–2562. <https://doi.org/10.1161/CIRCULATIONAHA.106.683755>
- Křížová, L., Dadáková, K., Kašparovská, J., & Kašparovský, T. (2019). Isoflavones. *Molecules*, 24(6), 1–62. <https://doi.org/10.3390/molecules24061076>
- Ku, C. M., & Lin, J. Y. (2013). Anti-inflammatory effects of 27 selected terpenoid compounds tested through modulating Th1/Th2 cytokine secretion profiles using murine primary splenocytes. *Food Chemistry*, 141(2), 1104–1113. <https://doi.org/10.1016/j.foodchem.2013.04.044>
- Kuiper, G. G., Enmark, E., Peltö-Huikko, M., Nilsson, S., Gustafsson, J. A. (1996). Cloning of a novel receptor expressed in rat prostate and ovary. *Proceedings of the National Academy of Sciences*, 93(12), 5925–5930. <http://dx.doi.org/10.1073/pnas.93.12.5925>
- Kulkarni, J., Gavrilidis, E., Worsley, R., van Rheenen, T., & Hayes, E. (2013). The role of estrogen in the treatment of men with schizophrenia. *International Journal of Endocrinology and Metabolism*, 11(3), 129–136. <https://doi.org/10.5812/ijem.6615>
- Landete, J. M., Arqués, J., Medina, M., Gaya, P., de Las Rivas, B., & Muñoz, R. (2016). Bioactivation of phytoestrogens: Intestinal Bacteria and health. *Critical Reviews in Food Science and Nutrition*, 56(11), 1826–1843. <https://doi.org/10.1080/10408398.2013.789823>

- Langasco, R., Fancello, S., Rassu, G., Cossu, M., Cavalli, R., Galleri, G., ... Gavini, E. (2019). Increasing protective activity of genistein by loading into transfersomes: A new potential adjuvant in the oxidative stress-related neurodegenerative diseases? *Phytomedicine*, 52, 23–31. <https://doi.org/10.1016/j.phymed.2018.09.207>
- Lee, H.-R., Kim, T.-H., & Choi, K.-C. (2012). Functions and physiological roles of two types of estrogen receptors, ER α and ER β , identified by estrogen receptor knockout mouse. *Laboratory Animal Research*, 28(2), 71–76. <https://doi.org/10.5625/lar.2012.28.2.71>
- Lephart, E. D. (2016). Skin aging and oxidative stress: Equol's anti-aging effects via biochemical and molecular mechanisms. *Ageing Research Reviews*, 31, 36–54. <https://doi.org/10.1016/j.arr.2016.08.001>
- Liang, H. W., Qiu, S. F., Shen, J., Sun, L. N., Wang, J. Y., Bruce, I. C., & Xia, Q. (2008). Genistein attenuates oxidative stress and neuronal damage following transient global cerebral ischemia in rat hippocampus. *Neuroscience Letters*, 438(1), 116–120. <https://doi.org/10.1016/j.neulet.2008.04.058>
- Liu, B., Edgerton, S., Yang, X., Kim, A., Ordóñez-Ercan, D., Mason, T., ... Thor, A. (2005). Low-dose dietary phytoestrogen abrogates tamoxifen-associated mammary tumor prevention. *Cancer Research*, 65(3), 879–886.
- Liu, X., Nam, J. W., Song, Y. S., Viswanath, A. N. I., Pae, A. N., Kil, Y. S., ... Chang, M. (2014). Psoralidin, a coumestan analogue, as a novel potent estrogen receptor signaling molecule isolated from *Psoralea corylifolia*. *Bioorganic and Medicinal Chemistry Letters*, 24(5), 1403–1406. <https://doi.org/10.1016/j.bmcl.2014.01.029>
- Lucas, E. A., Wild, R. D., Hammond, L. J., Khalil, D. A., Juma, S., Daggy, B. P., ... Arjmandi, B. H. (2002). Flaxseed improves lipid profile without altering biomarkers of bone metabolism in postmenopausal women. *Journal of Clinical Endocrinology and Metabolism*, 87(4), 1527–1532. <https://doi.org/10.1210/jcem.87.4.8374>
- Mali, A. V., Padhye, S. B., Anant, S., Hegde, M. V., & Kadam, S. S. (2019). Anticancer and antimetastatic potential of enterolactone: Clinical, pre-clinical and mechanistic perspectives. *European Journal of Pharmacology*, 852(December 2018), 107–124. <https://doi.org/10.1016/j.ejphar.2019.02.022>
- The North American Menopause Society. (2013). Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society. *Menopause*, 20(9), 888–902. <https://doi.org/10.1097/GME.0b013e3182a122c2>
- Manonai, J., Chittacharoen, A., Theppisai, U., & Theppisai, H. (2007). Effect of *Pueraria mirifica* on vaginal health. *Menopause*, 14(5), 919–924. <https://doi.org/10.1097/gme.0b013e3180399486>
- Mao, X., Liao, Z., Guo, L., Xu, X., Wu, B., Xu, M., ... Jia, Y. (2015). Schisandrin C ameliorates learning and memory deficits by A β 1–42--induced oxidative stress and neurotoxicity in mice. *Phytotherapy Research*, 29(9), 1373–1380. <https://doi.org/10.1002/ptr.5390>
- Marchesi, J. R., Adams, D. H., Fava, F., Hermes, G. D. A., Hirschfield, G. M., Hold, G., ... Hart, A. (2016). The gut microbiota and host health: A new clinical frontier. *Gut*, 65(2), 330–339. <https://doi.org/10.1136/gutjnl-2015-309990>
- Marín, L., Miguélez, E. M., Villar, C. J., & Lombó, F. (2015). Bioavailability of dietary polyphenols and gut microbiota metabolism: Antimicrobial properties. *BioMed Research International*, 2015, 1–18. <https://doi.org/10.1155/2015/905215>
- Marraudino, M., Farinetti, A., Arevalo, M. A., Gotti, S., Panzica, G. C., & García-Segura, L. M. (2019). Sexually dimorphic effect of Genistein on hypothalamic neuronal differentiation in vitro. *International Journal of Molecular Sciences*, 20(10), 1–9. <https://doi.org/10.3390/ijms20102465>
- Meng, H., Fu, G., Shen, J., Shen, K., Xu, Z., Wang, Y., ... Pan, H. (2017). Ameliorative Effect of Daidzein on Cisplatin-Induced Nephrotoxicity in Mice via Modulation of Inflammation, Oxidative Stress, and Cell Death. *Oxidative Medicine and Cellular Longevity*, 2017, 1–10. <http://dx.doi.org/10.1155/2017/3140680>
- Mense, S. M., Hei, T. K., Ganju, R. K., & Bhat, H. K. (2008). Phytoestrogens and breast cancer prevention: Possible mechanisms of action. *Environmental Health Perspectives*, 116(4), 426–433. <https://doi.org/10.1289/ehp.10538>
- Messina, M. (2016). Soy and health update: Evaluation of the clinical and epidemiologic literature. *Nutrients*, 8(12), 1–42. <https://doi.org/10.3390/nu8120754>
- Miao, Z.-Y., Xia, X., Che, L., Song, Y.-T. (2018). Genistein attenuates brain damage induced by transient cerebral ischemia through up-regulation of Nrf2 expression in ovariectomized rats. *Neurological Research*, 40(8), 1–7. <http://dx.doi.org/10.1080/01616412.2018.1462879>
- Miyauchi, Y., Sato, Y., Kobayashi, T., Yoshida, S., Mori, T., Kanagawa, H., ... Miyamoto, T. (2013). HIF1 is required for osteoclast activation by estrogen deficiency in postmenopausal osteoporosis. *Proceedings of the National Academy of Sciences*, 110(41), 16568–16573. <https://doi.org/10.1073/pnas.1308755110>
- Molina, L., Bustamante, F. A., Bhoola, K. D., Figueroa, C. D., & Ehrenfeld, P. (2018). Possible role of phytoestrogens in breast cancer via GPER-1/GPR30 signaling. *Clinical Science*, 132(24), 2583–2598. <https://doi.org/10.1042/CS20180885>
- Monteleone, P., Mascagni, G., Giannini, A., Genazzani, A. R., & Simoncini, T. (2018). Symptoms of menopause - global prevalence, physiology and implications. *Nature Reviews Endocrinology*, 14(4), 199–215. <https://doi.org/10.1038/nrendo.2017.180>
- Morán, J., Garrido, P., Alonso, A., Cabello, E., & González, C. (2013). 17 β -estradiol and genistein acute treatments improve mouse cerebral cortex homeostasis aspects deteriorated by aging in female rats. *Experimental Gerontology*, 48(4), 414–421. <https://doi.org/10.1016/j.exger.2013.02.010>
- Morrison, J. H., Brinton, R. D., Schmidt, P. J., & Gore, A. C. (2006). Estrogen, menopause, and the aging brain: How basic neuroscience can inform hormone therapy in women. *Journal of Neuroscience*, 26(41), 10332–10348. <https://doi.org/10.1523/jneurosci.3369-06.2006>
- Mukhopadhyay, P., Pan, H., Rajesh, M., Bátkai, S., Patel, V., Harvey-White, J., ... Pacher, P. (2010). CB 1 cannabinoid receptors promote oxidative/nitrosative stress, inflammation and cell death in a murine nephropathy model. *British Journal of Pharmacology*, 160(3), 657–668. <https://doi.org/10.1111/j.1476-5381.2010.00769.x>
- Murota, K., Nakamura, Y., & Uehara, M. (2018). Flavonoid metabolism: The interaction of metabolites and gut microbiota. *Bioscience, Biotechnology and Biochemistry*, 82(4), 600–610. <https://doi.org/10.1080/09168451.2018.1444467>
- Nagata, C. (2000). Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *International Journal of Epidemiology*, 29(5), 832–836. <https://doi.org/10.1093/ije/29.5.832>
- Najaf Najafi, M., & Ghazanfarpour, M. (2018). Effect of phytoestrogens on sexual function in menopausal women: A systematic review and meta-analysis. *Climacteric*, 21(5), 437–445. <https://doi.org/10.1080/13697137.2018.1472566>
- Narukawa, M. (2018). Physiological responses to taste signals of functional food components. *Bioscience, Biotechnology and Biochemistry*, 82(2), 200–206. <https://doi.org/10.1080/09168451.2017.1422385>
- National Toxicology Program [Ed.]. (2008). Toxicology and carcinogenesis studies of genistein (Cas no. 446-72-0) in Sprague-Dawley rats (feed study). *National Toxicology Program Technical Report Series*, 545, 1–240.
- Ndebele, K., Graham, B., & Tchounwou, P. B. (2010). Estrogenic activity of coumestrol, DDT, and TCDD in human cervical cancer cells. *International Journal of Environmental Research and Public Health*, 7(5), 2045–2056. <https://doi.org/10.3390/ijerph7052045>
- Neese, S. L., Korol, D. L., Katzenellenbogen, J. A., & Schantz, S. L. (2010). Impact of estrogen receptor alpha and beta agonists on delayed alternation in middle-aged rats. *Hormones and Behavior*, 58(5), 878–890. <https://doi.org/10.1016/j.yhbeh.2010.08.017>

- Nooyens, A. C. J., Milder, I. E. J., van Gelder, B. M., Bueno-de-Mesquita, H. B., van Boxtel, M. P. J., & Verschuren, W. M. M. (2015). Diet and cognitive decline at middle age: The role of antioxidants. *British Journal of Nutrition*, 113(9), 1410–1417. <https://doi.org/10.1017/S0007114515000720>
- Ogawara, H., Akiyama, T., & Ishida, J. (1986). A specific inhibitor for tyrosine protein kinase from pseudomonas. *The Journal of Antibiotics*, 39, 606–608. <https://doi.org/10.7164/antibiotics.39.606>
- Oliveira, J. S., Silva, A. A. N., & Silva Junior, V. A. (2016). Phytotherapy in reducing glycemic index and testicular oxidative stress resulting from induced diabetes: A review. *Brazilian Journal of Biology*, 77(1), 68–78. <https://doi.org/10.1590/1519-6984.09915>
- Oyama, A., Ueno, T., Uchiyama, S., Aihara, T., Miyake, A., Kondo, S., & Matsunaga, K. (2012). The effects of natural S-equol supplementation on skin aging in postmenopausal women: A pilot randomized placebo-controlled trial. *Menopause*, 19(2), 202–210. <https://doi.org/10.1097/gme.0b013e318227427b>
- Park, J.-W., Kim, D.-H., Ahn, H.-N., Song, Y.-S., Lee, Y.-J., Ryu, J.-H. (2012). Activation of Estrogen Receptor by Bavachin from *Psoralea corylifolia*. *Biomolecules and Therapeutics*, 20(2), 183–188. <http://dx.doi.org/10.4062/biomolther.2012.20.2.183>
- Patade, A., Devareddy, L., Lucas, E. A., Korlagunta, K., Daggy, B. P., & Arjmandi, B. H. (2008). Flaxseed reduces Total and LDL cholesterol concentrations in native American postmenopausal women. *Journal of Women's Health*, 17(3), 356–366. <https://doi.org/10.1089/jwh.2007.0359>
- Pearce, S. T., & Jordan, V. C. (2004). The biological role of estrogen receptors alpha and beta in cancer. *Critical Reviews in Oncology/Hematology*, 50(1), 3–22. <https://doi.org/10.1016/j.critrevonc.2003.09.003>
- Pérez-Jiménez, J., & Saura-Calixto, F. (2015). Macromolecular antioxidants or non-extractable polyphenols in fruit and vegetables: Intake in four European countries. *Food Research International*, 74, 315–323. <https://doi.org/10.1016/j.foodres.2015.05.007>
- Petersmann, A., Müller-Wieland, D., Müller, U. A., Landgraf, R., Nauck, M., Freckmann, G., ... Schleicher, E. (2019). Definition, classification and diagnosis of diabetes mellitus. *Experimental and Clinical Endocrinology & Diabetes*, 127(Suppl 1), S1–S7. <https://doi.org/10.1055/a-1018-9078>
- Peterson, T. G., Coward, L., Kirk, M., Falany, C. N., & Barnes, S. (1996). The role of metabolism in mammary epithelial cell growth inhibition by the isoflavones genistein and biochanin a. *Carcinogenesis*, 17(9), 1861–1869. <https://doi.org/10.1093/carcin/17.9.1861>
- Peterson, T. G., Ji, G. P., Kirk, M., Coward, L., Falany, C. N., & Barnes, S. (1998). Metabolism of the isoflavones genistein and biochanin a in human breast cancer cell lines. *American Journal of Clinical Nutrition*, 68, 1505S–1511S. <https://doi.org/10.1093/ajcn/68.6.1505S>
- Pitkin, J. (2012). Alternative and complementary therapies for the menopause. *Menopause International*, 18(1), 20–27. <https://doi.org/10.1258/mi.2012.012001>
- Plessow, D., Waldschläger, J., Richter, D. U., Jeschke, U., Bruer, G., Briese, V., & Friese, K. (2003). Effects of phytoestrogens on the trophoblast tumour cell lines BeWo and Jeg3. *Anticancer Research*, 23 (2A), 1081–1086.
- Poluzzi, E., Piccinini, C., Raschi, E., Rampa, A., Recanatini, M., & Ponti, F. (2014). Phytoestrogens in Postmenopause: The state of the art from a chemical, pharmacological and regulatory perspective. *Current Medicinal Chemistry*, 21(4), 417–436. <https://doi.org/10.2174/09298673113206660297>
- Ponti, G., Rodríguez-Gomez, A., Farinetti, A., Marraudino, M., Filice, F., Foglio, B., ... Gotti, S. (2017). Early postnatal genistein administration permanently affects nitrenergic and vasopressinergic systems in a sex-specific way. *Neuroscience*, 346, 203–215. <https://doi.org/10.1016/j.neuroscience.2017.01.024>
- Ponti, G., Farinetti, A., Marraudino, M., Panzica, G. C., & Gotti, S. (2019). Postnatal genistein administration selectively abolishes sexual dimorphism in specific hypothalamic dopaminergic system in mice. *Brain Research*, 1724, 1–10. <https://doi.org/10.1016/j.brainres.2019.146434>
- Potter, B., Schrager, S., Dalby, J., Torell, E., & Hampton, A. (2018). Primary care—Clinics in office practice. *Menopause*, 45(4), 625–641. <https://doi.org/10.1016/j.pop.2018.08.001>
- Qin, H., Lin, Z., Vásquez, E., Luan, X., Guo, F., & Xu, L. (2019). High soy isoflavone or soy-based foods intake during infancy and in adulthood is associated with an increased risk of uterine fibroids in premenopausal women: A meta-analysis. *Nutrition Research*, 71, 30–42. <https://doi.org/10.1016/j.nutres.2019.06.002>
- Quartieri, A., García-Villalba, R., Amaretti, A., Raimondi, S., Leonardi, A., Rossi, M., & Tomàs-Barberà, F. (2016). Detection of novel metabolites of flaxseed lignans in vitro and in vivo. *Molecular Nutrition and Food Research*, 60(7), 1590–1601. <https://doi.org/10.1002/mnfr.201500773>
- Renko, K., Schäche, S., Hoefig, C. S., Welsink, T., Schwiebert, C., Braun, D., ... Schomburg, L. (2015). An improved nonradioactive screening method identifies Genistein and Xanthohumol as potent inhibitors of iodothyronine deiodinases. *Thyroid*, 25(8), 962–968. <https://doi.org/10.1089/thy.2015.0058>
- Riccardi, G., Aggett, P., Brighenti, F., Delzenne, N., Frayn, K., Nieuwenhuizen, A., ... Vessby, B. (2004). PASSCLAIM1?Body weight regulation, insulin sensitivity and diabetes risk. *European Journal of Nutrition*, 43, II/7–II/46. <https://doi.org/10.1007/s00394-004-1202-7>
- Ricci, E., Cipriani, S., Chiaffarino, F., Malvezzi, M., & Parazzini, F. (2010). Effects of soy isoflavones and genistein on glucose metabolism in perimenopausal and postmenopausal non-Asian women: A meta-analysis of randomized controlled trials. *Menopause*, 17(5), 1080–1086. <https://doi.org/10.1097/gme.0b013e3181dd05a9>
- Rietjens, I. M. C. M., Sotoca, A. M., Vervoort, J., & Lousse, J. (2013). Mechanisms underlying the dualistic mode of action of major soy isoflavones in relation to cell proliferation and cancer risks. *Molecular Nutrition and Food Research*, 57(1), 100–113. <https://doi.org/10.1002/mnfr.201200439>
- Rietjens, I. M. C. M., Lousse, J., & Beekmann, K. (2017). The potential health effects of dietary phytoestrogens. *British Journal of Pharmacology*, 174(11), 1263–1280. <https://doi.org/10.1111/bph.13622>
- Rodríguez-Gomez, A., Filice, F., Gotti, S., & Panzica, G. C. (2014). Perinatal exposure to genistein affects the normal development of anxiety and aggressive behaviors and nitric oxide system in CD1 male mice. *Physiology & Behavior*, 133, 107–114. <https://doi.org/10.1016/j.physbeh.2014.05.020>
- Rosen, C. J., & Bouxsein, M. L. (2006). Mechanisms of disease: Is osteoporosis the obesity of bone? *Nature Clinical Practice Rheumatology*, 2, 35–43. <https://doi.org/10.1038/ncprheum0070>
- Rossouw, J. E., Prentice, R. L., Manson, J. A. E., Wu, L. L., Barad, D., Barnabei, V. M., ... Stefanick, M. L. (2007). Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *Journal of the American Medical Association*, 297(13), 1465–1477. <https://doi.org/10.1001/jama.297.13.1465>
- Russo, G. I., di Mauro, M., Regis, F., Reale, G., Campisi, D., Marranzano, M., ... Morgia, G. (2018). Association between dietary phytoestrogens intakes and prostate cancer risk in Sicily. *The Aging Male*, 21(1), 48–54. <https://doi.org/10.1080/13685538.2017.1365834>
- Sacco, S. M., Jiang, J. M. Y., Reza-López, S., Ma, D. W. L., Thompson, L. U., & Ward, W. E. (2009). Flaxseed combined with low-dose estrogen therapy preserves bone tissue in ovariectomized rats. *Menopause*, 16(3), 545–554. <https://doi.org/10.1097/gme.0b013e31818fc00a>
- Sahu, B. D., Kumar, J. M., & Sistla, R. (2015). Baicalein, a bioflavonoid, prevents cisplatin-induced acute kidney injury by up-regulating antioxidant defenses and down-regulating the MAPKs and NF- κ B pathways. *PLoS One*, 10(7), 1–19. <https://doi.org/10.1371/journal.pone.0134139>
- Sandhu, K. V., Demiray, Y. E., Yanagawa, Y., & Stork, O. (2020). Dietary phytoestrogens modulate aggression and activity in social behavior

- circuits of male mice. *Hormones and Behavior*, 119, 1–9. <https://doi.org/10.1016/j.yhbeh.2019.104637>
- Santoro, N., & Komi, J. (2009). Prevalence and impact of vaginal symptoms among postmenopausal women. *Journal of Sexual Medicine*, 6(8), 2133–2142. <https://doi.org/10.1111/j.1743-6109.2009.01335.x>
- Savoia, P., Raina, G., Camillo, L., Farruggio, S., Mary, D., Veronese, F., ... Grossini, E. (2018). Anti-oxidative effects of 17 β -estradiol and genistein in human skin fibroblasts and keratinocytes. *Journal of Dermatological Science*, 92(1), 62–77. <https://doi.org/10.1016/j.jdermsci.2018.07.007>
- Scherr, F. F., Sarmah, A. K., di, H. J., & Cameron, K. C. (2009). Degradation and metabolite formation of 17 β -estradiol-3-sulphate in New Zealand pasture soils. *Environment International*, 35(2), 291–297. <https://doi.org/10.1016/j.envint.2008.07.002>
- Schreihöfer, D. A., & Ma, Y. (2013). Estrogen receptors and ischemic neuroprotection: Who, what, where, and when? *Brain Research*, 1514, 107–122. <https://doi.org/10.1016/j.brainres.2013.02.051>
- Sen, T., & Samanta, S. K. (2014). Medicinal Plants, Human Health and Biodiversity: A Broad Review. *Advances in Biochemical Engineering/Biotechnology*, 147, 59–110. https://doi.org/10.1007/10_2014_273
- Setchell, K. D. R. (1998). Phytoestrogens: The biochemistry, physiology, and implications for human health of soy isoflavones. *American Journal of Clinical Nutrition*, 68, 1333S–1346S. <https://doi.org/10.1093/ajcn/68.6.1333S>
- Sfakianos, J., Coward, L., Kirk, M., & Barnes, S. (1997). Biochemical and molecular roles of nutrients intestinal uptake and biliary excretion of the Isoflavone Genistein in rats. *The Journal of Nutrition*, 127(7), 1260–1268. <https://doi.org/10.1093/jn/127.7.1260>
- Shale, T. L., Stirk, W. A., & van Staden, J. (2005). Variation in antibacterial and anti-inflammatory activity of different growth forms of *Malva parviflora* and evidence for synergism of the anti-inflammatory compounds. *Journal of Ethnopharmacology*, 96(1–2), 325–330. <https://doi.org/10.1016/j.jep.2004.09.032>
- Shike, M., Doane, A. S., Russo, L., Cabal, R., Reis-Filo, J., Gerald, W., ... Norton, L. (2014). The effects of soy supplementation on gene expression in breast cancer: A randomized placebo-controlled study. *Journal of the National Cancer Institute*, 106(9), 1–12. <https://doi.org/10.1093/jnci/dju189>
- Sierens, J., Hartley, J. A., Campbell, M. J., Leathem, A. J. C., & Woodside, J. V. (2001). Effect of phytoestrogen and antioxidant supplementation on oxidative DNA damage assessed using the comet assay. *Mutation Research - DNA Repair*, 485(2), 169–176. [https://doi.org/10.1016/S0921-8777\(00\)00069-0](https://doi.org/10.1016/S0921-8777(00)00069-0)
- Simon, J. A., Kokot-Kierepa, M., Goldstein, J., & Nappi, R. E. (2013). Vaginal health in the United States: Results from the vaginal health: Insights, views & attitudes survey. *Menopause*, 20(10), 1043–1048. <https://doi.org/10.1097/GME.0b013e318287342d>
- Sirotkin, A. V. H. A. H. (2014). Phytoestrogens and their effects. *European Journal of Pharmacology*, 741, 230–236. <https://doi.org/10.1016/j.ejphar.2014.07.057>
- Sirtori, C. R., Arnoldi, A., & Johnson, S. K. (2005). Phytoestrogens: End of a tale? *Annals of Medicine*, 37(6), 423–438. <https://doi.org/10.1080/07853890510044586>
- Small, B. J., Dixon, R. A., & McArdle, J. J. (2011). Tracking cognition-health changes from 55 to 95 years of age. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, 66B(S1), i153–i161. <https://doi.org/10.1093/geronb/gbq093>
- Soni, M., Rahardjo, T. B. W., Soekardi, R., Sulistyowati, Y., Lestariningsih, Y.-U., A., ..., Hogervorst, E. (2014). Phytoestrogens and cognitive function: a review. *Maturitas*, 77(3), 209–220. <http://dx.doi.org/10.1016/j.maturitas.2013.12.010>
- Srivastava, M., & Deal, C. (2002). Osteoporosis in elderly: Prevention and treatment. *Clinics in Geriatric Medicine*, 18(3), 529–555. [https://doi.org/10.1016/s0749-0690\(02\)00022-8](https://doi.org/10.1016/s0749-0690(02)00022-8)
- Strom, A., Hartman, J., Foster, J. S., Kietz, S., Wimalasena, J., & Gustafsson, J. A. (2004). Estrogen receptor inhibits 17 -estradiol-stimulated proliferation of the breast cancer cell line T47D. *Proceedings of the National Academy of Sciences*, 101(6), 1566–1571. <https://doi.org/10.1073/pnas.0308319100>
- Stuenkel, C. A., Gass, M. L. S., Manson, J. A. E., Lobo, R. A., Pal, L., Rebar, R. W., & Hall, J. E. (2012). A decade after the Women's health initiative—The experts Do agree. *The Journal of Clinical Endocrinology & Metabolism*, 97(8), 2617–2618. <https://doi.org/10.1210/jc.2012-2403>
- Sturdee, D. W., & Panay, N. (2010). Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric*, 13(6), 509–522. <https://doi.org/10.3109/13697137.2010.522875>
- Tadaishi, M., Nishide, Y., Tousen, Y., Kruger, M. C., & Ishimi, Y. (2014). Cooperative effects of soy isoflavones and carotenoids on osteoclast formation. *Journal of Clinical Biochemistry and Nutrition*, 54(2), 109–115. <https://doi.org/10.3164/jc.13-94>
- Takeuchi, S., Takahashi, T., Sawada, Y., Iida, M., Matsuda, T., & Kojima, H. (2009). Comparative study on the nuclear hormone receptor activity of various phytochemicals and their metabolites by reporter gene assays using Chinese hamster ovary cells. *Biological & Pharmaceutical Bulletin*, 32(2), 195–202. <https://doi.org/10.1248/bpb.32.195>
- Talia, M., de Francesco, E., Rigracciolo, D., Muoio, M., Muglia, L., Belfiore, A., ... Lappano, R. (2020). The G protein-coupled estrogen receptor (GPER) expression correlates with pro-metastatic pathways in ER-negative breast Cancer: A bioinformatics analysis. *Cell*, 9(3), 1–13. <https://doi.org/10.3390/cells9030622>
- Thomas, C., & Gustafsson, J. Å. (2011). The different roles of ER subtypes in cancer biology and therapy', *Nature Reviews Cancer*. *Nature Publishing Group*, 11(8), 597–608. <https://doi.org/10.1038/nrc3093>
- Thomas, P., & Dong, J. (2006). Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: A potential novel mechanism of endocrine disruption. *Journal of Steroid Biochemistry and Molecular Biology*, 102(1–5 SPEC. ISS), 175–179. <https://doi.org/10.1016/j.jsmb.2006.09.017>
- Thornton, M. J. (2013). Estrogens and aging skin. *Dermato-Endocrinology*, 5(2), 264–270. <https://doi.org/10.4161/derm.23872>
- Tokede, O. A., Onabanjo, T. A., Yansane, A., Gaziano, J. M., & Djoussé, L. (2015). Soya products and serum lipids: A meta-analysis of randomised controlled trials. *British Journal of Nutrition*, 114(6), 831–843. <https://doi.org/10.1017/S0007114515002603>
- Tomás-Barberán, F. A., Selma, M. V., & Espín, J. C. (2016). Interactions of gut microbiota with dietary polyphenols and consequences to human health. *Current Opinion in Clinical Nutrition and Metabolic Care*, 19(6), 471–476. <https://doi.org/10.1097/MCO.0000000000000314>
- Uesugi, T., Toda, T., Okuhira, T., & Chen, J. T. (2003). Evidence of estrogenic effect by the three-month-intervention of Isoflavone on vaginal maturation and bone metabolism in early postmenopausal women. *Endocrine Journal*, 50(5), 613–619. <https://doi.org/10.1507/endocrj.50.613>
- Upson, K., Harmon, Q. E., Laughlin-Tommaso, S. K., Umbach, D. M., & Baird, D. D. (2016). Soy-based infant formula feeding and heavy menstrual bleeding among young African American women. *Epidemiology*, 27(5), 716–725. <https://doi.org/10.1097/EDE.0000000000000508>
- Urpi-Sarda, M., Morand, C., Besson, C., Kraft, G., Viala, D., Scalbert, A., ... Manach, C. (2008). Tissue distribution of isoflavones in ewes after consumption of red clover silage. *Archives of Biochemistry and Biophysics*, 476(2), 205–210. <https://doi.org/10.1016/j.abb.2008.05.002>
- Valsta, L. M., Kilkinen, A., Mazur, W., Nurmi, T., Lampi, A. M., Ovaskainen, M. L., ... Pietinen, P. (2003). Phyto-oestrogen database of foods and average intake in Finland. *British Journal of Nutrition*, 89(S1), S31–S38. <https://doi.org/10.1079/bjn2002794>
- Verma, R., Samanta, R., & Krishna, A. (2019). Comparative effects of estrogen and phytoestrogen, Genistein on testicular activities of Streptozotocin-induced type 2 diabetic mice. *Reproductive Sciences*, 26(9), 1294–1306. <https://doi.org/10.1177/1933719118815576>

- Wang, C. C., Prasain, J. K., & Barnes, S. (2002). Review of the methods used in the determination of phytoestrogens. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, 777, 3–28. [https://doi.org/10.1016/S1570-0232\(02\)00341-0](https://doi.org/10.1016/S1570-0232(02)00341-0)
- Wang, S., Aarts, J. M.M.J.G., Evers, N. M., Peijnenburg, A. A.C.M., Rietjens, I. M.C.M., Bovee, T. F.H. (2012). Proliferation assays for estrogenicity testing with high predictive value for the in vivo uterotrophic effect. *The Journal of Steroid Biochemistry and Molecular Biology*, 128(3–5), 98–106. <http://dx.doi.org/10.1016/j.jsbmb.2011.11.009>.
- Wang, S., Wei, H., Cai, M., Lu, Y., Hou, W., Yang, Q., ... Xiong, L. (2014). Genistein attenuates brain damage induced by transient cerebral ischemia through up-regulation of ERK activity in ovariectomized mice. *International Journal of Biological Sciences*, 10(4), 457–465. <https://doi.org/10.7150/ijbs.7562>
- Wang, T., Liu, Y., Li, X., Xu, Q., Feng, Y., & Yang, S. (2018). Isoflavones from green vegetable soya beans and their antimicrobial and antioxidant activities. *Journal of the Science of Food and Agriculture*, 98(5), 2043–2047. <https://doi.org/10.1002/jsfa.8663>
- Whitten, P. L., Lewis, C., Russell, E., & Naftolin, F. (1995). Potential adverse effects of phytoestrogens. *Journal of Nutrition*, 125, 771S–776S. https://doi.org/10.1093/jn/125.3_Suppl.771S
- Wilcox, G., Wahlqvist, M. L., Burger, H. G., & Medley, G. (1990). Oestrogenic effects of plant foods in postmenopausal women. *BMJ*, 301(6757), 905–906. <https://doi.org/10.1136/bmj.301.6757.905-a>
- Williams, C., Edvardsson, K., Lewandowski, S. A., Ström, A., & Gustafsson, J. Å. (2008). A genome-wide study of the repressive effects of estrogen receptor beta on estrogen receptor alpha signaling in breast cancer cells. *Oncogene*, 27(7), 1019–1032. <https://doi.org/10.1038/sj.onc.1210712>
- Wuttke, W., Jarry, H., & Seidlová-Wuttke, D. (2007). Isoflavones-safe food additives or dangerous drugs? *Ageing Research Reviews*, 6, 150–188. <https://doi.org/10.1016/j.arr.2007.05.001>
- Yamaguchi, M., & Gao, Y. H. (1998). Inhibitory effect of genistein on bone resorption in tissue culture. *Biochemical Pharmacology*, 55(1), 71–76. [https://doi.org/10.1016/S0006-2952\(97\)00402-4](https://doi.org/10.1016/S0006-2952(97)00402-4)
- Yao, J., Zhao, L., Mao, Z., Chen, S., Wong, K. C., To, J., & Brinton, R. D. (2013). Potentiation of brain mitochondrial function by S-equol and R/S-equol estrogen receptor β -selective phytoSERM treatments. *Brain Research*, 1514, 128–141. <https://doi.org/10.1016/j.brainres.2013.02.021>
- Zhang, F. F., Haslam, D. E., Terry, M. B., Knight, J. A., Andrulis, I. L., Daly, M. B., ... John, E. M. (2017). Dietary isoflavone intake and all-cause mortality in breast cancer survivors: The breast Cancer family registry. *Cancer*, 123(11), 2070–2079. <https://doi.org/10.1002/cncr.30615>
- Zhang, X., Shu, X. O., Gao, Y. T., Yang, G., Li, Q., Li, H., ... Zheng, W. (2003). Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. *The Journal of Nutrition*, 133(9), 2874–2878. <https://doi.org/10.1093/jn/133.9.2874>
- Zhang, Y. B., Chen, W. H., Guo, J. J., Fu, Z. H., Yi, C., Zhang, M., & Na, X. L. (2013). Soy isoflavone supplementation could reduce body weight and improve glucose metabolism in non-Asian postmenopausal women-a meta-analysis. *Nutrition*, 29(1), 8–14. <https://doi.org/10.1016/j.nut.2012.03.019>

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