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The Physiology of Menopausal Transition and the Role of Solgen/Soybean Isoflavones Supplementation in Midlife Women

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ABSTRACT

Menopause is a natural physiological process marking the end of menstrual cycles that typically occurs between ages 45-59 and may significantly affect women's quality of life. It is characterized by hormonal fluctuations that ultimately lead to a reduction in estrogen and progesterone levels, which results in biological changes and subsequent symptoms. Symptoms vary considerably among women, due to individual, genetic and lifestyle factors, and commonly include vasomotor symptoms (hot flashes and night sweats), sleep disturbances, cognitive and mood changes, genitourinary syndrome of menopause, bone and muscle loss, metabolic and cardiovascular alterations and skin modifications.

Menopausal hormone therapy (HT) has long been considered the most effective treatment for alleviating menopausal symptoms and reducing the risk of osteoporosis or cardiovascular disease, however, concerns regarding its safety profile, especially a possible cardiovascular risk, have led to an individualized benefit-risk evaluation and increased interest in non-hormonal alternatives.

Soy isoflavones have been extensively investigated clinical and preclinically to be a potential alternative treatment for the management of midlife symptoms. Due to their structural similarities to estrogen, isoflavones modulate estrogen receptors. Moreover, they have also demonstrated anti-inflammatory and antioxidant properties. Regulatory assessments, including EFSA risk assessment, support the safety of soy isoflavones at established intake levels.

SOLGEN® is an ingredient containing the isoflavones genistin, daidzin, genistein, daidzein, glycitein and glycitin and has been investigated in clinical studies in women.

This review summarizes the current scientific evidence on soy isoflavones/SOLGEN® supplementation for menopausal symptoms and other conditions, such as endometriosis or polycystic ovary syndrome.

Keywords

Menopause, Estrogen receptors, Menopausal hormone therapy, Soy, Isoflavones, Phytoestrogens, Menopausal symptoms, Hot flashes, Aging, Phytohormones.

Introduction

Menopause is a natural biological process, which involves approximately one third of the life of a woman and marks the permanent cessation of menstruation. It can lead to a significant impact on women's quality of life, affecting both their personal and professional lives. Globally, an estimated 657 million women between ages 45 and 59 experience menopause [1].

It is characterized by physiological changes due to the reduction in estrogen levels. Many symptoms, such as hot flashes, insomnia or mood changes may start before the establishment of menopause, showing a manifestation of incipient ovarian failure [1].

The physiological underlying cause of menopause manifestations is complex and not limited to estrogen deprivation. Studies have shown that individual, geographical and genetic factors affect symptom prevalence and severity [2].

Prior to menopause comes the transitional stage perimenopause, which can last several years. This phase is defined by irregularities or suppressions in the menstrual cycle. In perimenopause, estrogens and other sex hormones are fluctuating, which posteriorly leads to definitive estrogen deprivation, marking menopause phase. Postmenopause follows the final menstrual period. Subsequently, anovulation causes the loss of progesterone production [3,4]. Ovaries continue to maintain testosterone levels for years [5]. Additionally, circulating adrenal androgens in midlife women may vary in late menopause. Particularly, an increase in dehydroepiandrosterone sulfate (DHEAS) occurs in most women between menopausal transition and early postmenopause [6]. These hormonal fluctuations lead to central nervous system (CNS) and peripheral symptoms prolonged in time [2].

A decline in inhibin B levels occurs, reducing its suppressive effect on the follicle-stimulating hormone (FSH) from the pituitary [3], which leads to increases in FSH, promoting erratic increases in estradiol firstly [2]. Eventually, the ovary response to gonadotropin stimulation is reduced, which produces a decline in estradiol levels instead. Consequently, luteinizing hormone (LH) stimulation is debilitated and ovulation does not occur [2]. Menopausal symptoms develop from ovarian failure due to the depletion of ovarian follicles, a process that lasts several years, during the menopausal transition [3].

Menopausal symptoms

The intensity and presence of menopausal symptoms can be influenced by ethnicity, age at menopause, educational level, smoking, alcohol or caffeine consumption, and other chronic conditions [7].

Vasomotor symptoms

These are the most frequent symptoms during menopause. Approximately 75% of women experience vasomotor symptoms from the beginning of menopause [8,9]. It can start approximately 2 years before the last menstrual period and perpetuate for 4 years after in half of women, with the most intense ones occurring one year after menopause [10]. Several studies reported that a percentage ranging from 12% to 30% of women continue suffering these symptoms more than 10 years after menopause [10-12].

The prevalence and severity can vary depending on factors such as ethnicity, lifestyle, and geographic region. A prevalence of 74% has been reported in Europe, while in North America it ranges from 36% to 50%, and in Asia from 22% to 63% [13].

Vasomotor symptoms include hot flashes and sweating, sometimes experiencing a posterior sensation of coldness [2], during day and night.

The hypothesized underlying cause is alterations in thermoregulation mechanisms [2]. Menopause is associated with a decrease in the thermoneutral zone, meaning that slight modifications of core temperature lead to a triggered thermoregulatory reaction, producing peripheral vasodilation, shivering or sweating [8]. Dysfunction in thermoregulation may be due to the erratic adaptation of the brain to desynchronization in hormonal cycles and sex hormone levels, with alterations in noradrenergic and serotoninergic pathways that participate in regulating the thermoneutral core [14].

Furthermore, evidence has shown that increased cortisol levels may aggravate vasomotor symptoms [2] due to an activation of stress response, enhancing adrenaline, noradrenaline and catecholamines and ultimately inducing vasodilation [15]. Severe vasomotor symptoms are related to an activation of the hypothalamus-pituitary-adrenal axis and higher urinary cortisol secretion has been reported in women with severe hot flashes compared with women who present less symptoms [15]. Moreover, increased salivary cortisol levels have been associated with more frequent and severe vasomotor symptoms [16]. Higher serum cortisol and noradrenaline levels were also reported in menopausal transition [17].

Nocturnal hot flashes and sweats are more frequent during the first 4 hours of sleep, associated with higher waking episodes [2].

Sleep disorders

Night sweats, along with psychological factors, increase the risk of sleep difficulties, which are also frequent in menopause, reported by approximately half of menopausal women [18-20]. Evidence suggests that rapid-eye-movement (REM) sleep suppresses hot flashes, reducing awakenings [21]. Depressive symptoms may also increase the risk of sleep disruption [22]. Moreover, the risk of sleep disorders in menopausal women may be increased by obstructive sleep apnea, independent of body weight [23]. Additionally, sleep disturbances augment the risk of cognitive impairment in postmenopausal women [24], especially executive function, episodic memory and attention [25].

Decreased inhibin B levels have shown to strongly predict poor sleep quality in postmenopause [26]. Increased urinary FSH levels have been related to sleep disfunction in premenopause and perimenopause [27]. An earlier circadian phase due to the early release of melatonin in postmenopausal women may be responsible of the early morning awakenings often experienced by menopausal women [28,29].

Cognitive impairment

Clinical evidence indicates that menopause leads to cognitive changes [8]. A meta-analysis by Weber et al. [30] showed that postmenopausal women performed significantly worse delayed verbal memory tasks and verbal fluency tasks than pre- and perimenopausal women. Menopausal transition increases the vulnerability to cognitive dysfunction. However, data from the

Study of Women's Health Across the Nation (SWAN) cohort reveal that reduction in cognitive performance-particularly lack of learning- is isolated to the perimenopausal stage [31], which suggests that the effect of menopause on cognitive performance is transient [2].

Additionally, depressive symptoms and anxiety seem to contribute to cognitive decline [32].

Estradiol is suggested to participate in cognitive performance [2], as various areas of the CNS express estrogen receptors (ER), where its activation by estrogens may regulate synapses and neurotransmitters release [33]. Change and posterior decrease in estrogen levels during menopausal transition may be the underlying cause of cognitive impairments, improving after postmenopause. Moreover, increase of LH might lead to cognitive dysfunction [34].

Mental health symptoms

A significant change in mental health is common within menopause, with an increase in mental diseases such as anxiety and depression. These symptoms are often experienced at the beginning of perimenopause and are not always recognized [35]. However, individual and psychological variations influence mental health.

Estrogen decline is one of the leading causes, as it contributes to the modulation of neurotransmitters, such as dopamine, serotonin, glutamate, acetylcholine or GABA [36]. Testosterone also modulates neurotransmitters [35]. Moreover, progesterone participates in modulating the GABAergic system, which has a key role in suppressing anxiety symptoms [37]. Evidence reported lower circulating serotonin levels in postmenopausal women, increasing after estrogen administration [38], which traduces in an association between fluctuating estrogen in menopause with the augmented risk of depressive symptoms [39].

Urogenital and sexual dysfunction

This condition has been denominated the genitourinary syndrome of menopause [40]. Symptoms include vaginal dryness, subsequent dyspareunia, recurrent urogenital infections, pruritus, dysuria, involuntary urination, pain, urgency or discomfort [2]. Urogenital symptoms persist in postmenopause, having an impact on overall health and wellness [41], with vulvovaginal atrophy being still underdiagnosed and mistreated [42].

Menopausal transition produces hormonal changes in libido, reporting a reduction in sexual desire and pain during sexual activity [43,44]. Moreover, depressive symptoms and a reduction in self-esteem may contribute to the loss of libido in menopause [45].

Evidence has revealed an increase in symptoms of urinary incontinence within menopause [46]. Approximately half of menopausal women will experience stress incontinence and 20% urge incontinence [45]. The risk of urge incontinence increases with age; while stress incontinence increases with obesity and metabolic changes [2].

Female lower genital tract function is estrogen-dependent, as genital and urinary tissues express a high quantity of ER during fertile years [47]. Due to estrogen decline, vaginal and urinary tract tissues go under atrophy during menopause [8]. Moreover, menopause leads to a reduction in collagen and elastin and an alteration of morphology of the epithelium and function of vaginal cells, as well as a decrease in vascularization, all of this leading to reduced lubrication and vaginal elasticity [47,48].

Altered bone and muscle health

Bone loss increases abruptly during the first 5 years of postmenopause, affecting trabecular bone tissue [2], and bone mineral density is reduced sharply during late perimenopause [49]. An imbalance in bone remodeling can lead to osteopenia and osteoporosis, a systemic skeletal condition that decreases bone mineral density, bone strength and increases the fragility of the skeleton, augmenting the risk of fractures [50], particularly in the spine, hip and wrist [51]. An increased porosity of the bone cortex has been reported [50].

In menopause, muscle mass is also affected. Evidence reported a reduction of 0.6%-1.5% of muscle mass due to menopausal transition [52,53]. Total body potassium, a marker of lean body mass, is significantly reduced the first 3 years after menopause [54]. Inflammatory factors, inactivity, strength and body mass index (BMI) also contribute to the decline in muscle mass [55-57].

Bone resorption and remodeling are mediated by estrogens [8]. The decline in estrogen in postmenopause reduces bone remodeling, which results in increased resorption. Estrogen reduction causes an excessive production of the receptor activator of nuclear factor-κB ligand (RANKL) by osteoblasts, which produces osteoclastogenesis and bone resorption [58]. Osteoprotegerin, which inhibits RANKL, is also reduced, leading to an augment in RANKL activity. Moreover, vitamin D3 deficiency and its impaired production, along with a decline in calcium absorption, both participate in the increased bone resorption [59]. Furthermore, loss of skeletal muscle mass may contribute to decreased bone formation due to impaired downregulation of sclerostin production by osteocytes, which is mediated by estrogens [60]. Decrease in estradiol is thought to contribute to the loss of muscle mass [61]. Reduced bone formation and increased bone resorption lead to less bone strength, which may cause osteoporosis [8].

Metabolic changes

The prevalence of obesity is higher during postmenopause compared to premenopause [62]. Menopause itself is not associated with weight gain; however, it leads to a redistribution of body fat and an increase in adiposity [8]. Modifications in body shape are common, particularly the accumulation of visceral fat in the abdominal region.

The estrogen decline and associated abdominal obesity may result in metabolic consequences, including insulin resistance, diabetes, metabolic syndrome and dyslipidemia -increased LDL and triglyceride levels and decreased HDL- [63]. Consequently, visceral adipose tissue significantly increases the risk of cardiovascular disease (CVD).

Cardiovascular risk

Cardiovascular (CV) events and atherosclerosis rise in postmenopausal women. Metabolic changes contribute to these conditions, and it has been seen that postmenopausal women present increased heart fat, independently of obesity or ethnicity [64]. It has been hypothesized that pro-inflammatory cytokines and adipokines in visceral adipose tissue may contribute to CV changes [65]. Blood pressure also increases with menopause [66].

Postmenopausal estrogen deficiency activates the renin-angiotensin system, upregulates the vasoconstrictor endothelin and causes an impairment of nitric oxide-mediated vasodilation [8]. Postmenopausal women often experience elevated plasma endothelin -1 (ET-1) levels as a result of declining estrogen levels, which contribute to increased vascular resistance, endothelial dysfunction and a higher CV risk. Elevated ET-1 levels reduce blood flow by blocking the vasodilatory effects mediated by endothelin-B (ET-B) receptors [67]. Moreover, estrogens promote vascular elasticity and restoration [68], and due to its reduction in menopause, the risk of vascular disease augments. Visceral adiposity and dyslipidemia, next to insulin resistance and increased blood pressure are also CV risk factors [8]. Endothelin and angiotensin II promote oxidative stress, which can contribute to atherosclerosis [69]. Early menopause has been associated with increased risk of stroke, coronary heart disease and mortality [70].

Skin modifications

Estrogen contributes to skin structure and function. Wrinkling, loss of skin elasticity and loss of hydration occur in menopause [71], due to a decrease in estrogen, which causes reduction in collagen, elasticity (elastin proteoglycan) and water retention [72,73]. Additionally, mucosal changes also occur, augmenting the permeability, which facilitates the access to pathogens [74]. Hair is

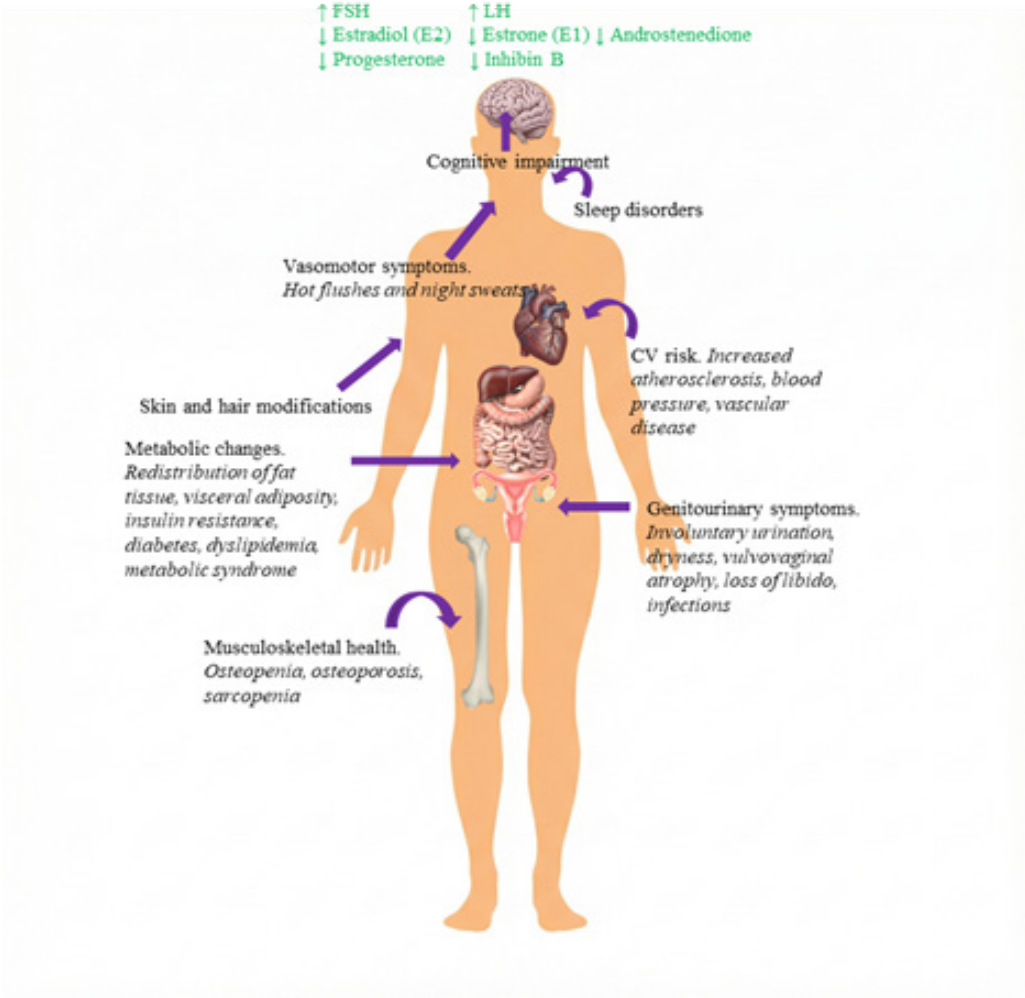

Figure 1: Menopause symptoms and hormone fluctuations. Inspired by Monteleone et al. "Symptoms of menopause —global prevalence, physiology and implications" [2] Image was created using PowerPoint, Freepik and google images.

also affected; female pattern hair loss and frontal fibrosing alopecia are both associated with menopause, as well as hirsutism, due to the participation of estrogens and androgens in the regulation of the hair cycle [75].

Collagen decreases by 30% during the first 5 years after menopause [76].

Skin of menopausal women becomes fragile, due to the decrease in estrogen in the epidermis, which interlinks epidermal cells to maintain cell integrity [77,78]. This might also be the cause of vascular fragility; however, it has not been studied yet [79]. Loss of estrogen also leads to a reduction in dermal thickness, in the proliferation of keratinocytes and fibroblasts, and in cellular viability and extracellular matrix components, along with an increase of ROS and oxidative stress, as estrogen does not eject its antioxidant properties [77].

Testosterone is metabolized to the active form of dihydrotestosterone by 5 alpha-reductase, which is the cause of involution of scalp hair follicles in menopause [80], but on facial hair, hyperandrogenism causes the opposite effect, with an excessive facial hair growth [81].

Menopausal hormone therapy (HT, also commonly referred as MHT) for menopausal symptoms

HT was very popular in the 60-70s to offset the physical changes and symptoms of menopause [82], until the scientific evidence started to reveal an increased risk of adverse events. In particular, with the publications of Heart and Estrogen/Progestin Replacement Study and Women's Health Initiative randomized trials in the end of the 90s-early 00s, which reported an excess of CV risk, HT prescription was dramatically reduced [82-84]. The term used in the past was hormone replacement therapy (HRT), although recent guidelines and consensus supported by societies such as the North American Menopause Society, the American College of Obstetricians and Gynecologists or the Society for Women's Health Research currently use the term HT, avoiding the concept of "replacement" as it is not a pathological condition that requires any replacement [85-87].

HT may be composed of estrogen alone or estrogen and progestogen, and it includes systemic therapy, transdermal formulations, compounded hormone therapy and vaginal estrogen therapy. It is normally indicated to treat intense hot flashes and sweats, and as a possible preventive treatment for osteoporosis.

HT has to be benefit-risk balanced prior to prescription. Among the most common adverse events evaluated and reported in recent systematic reviews and meta-analyses are: increased risk of stroke and venous thrombosis (independently of estrogen alone or in combination) [88,89], increased risk of breast cancer in specifical conditions and patients and proportionally higher with duration of treatment [90,91], increased incidence and recurrence of CV disease [89], augmented incidence of gallbladder disease [89], and increased lung cancer mortality [89]. Estrogen therapy alone increases the risk of endometrial hyperplasia and cancer [82]. A large meta-analysis involving over 44,000 postmenopausal women revealed that receiving HT at early ages was associated with less CV events than women receiving HT in the late period (more than 10 years after menopause or at age >60 years old), however, the risk of stroke and venous thromboembolism was still increased [92].

Non-pharmacological treatment

Non-pharmacological options for alleviating menopause symptoms include lifestyle modifications, such as regular physical activity, a balanced diet, weight management, limiting alcohol and caffeine intake, smoking cessation, and good sleep hygiene. Clinical guidelines these measures, indicating that healthy lifestyle patterns can help reduce overall symptom burden and improve quality of life during the menopausal transition [93,94].

Stress-reduction techniques—such as mindfulness, yoga, or cognitive-behavioral therapy (CBT)—have also shown benefits for certain CNS-related symptoms, particularly mood disturbances, sleep problems, and other symptoms such as vasomotor symptoms, as they are exacerbated with increased cortisol levels. Moreover, mindfulness-based interventions have been associated with improvements in stress perception and symptom tolerance [95,96].

Frequency and severity of symptoms such as hot flashes can be reduced by environmental adjustments, including wearing layered clothing, avoiding triggers such as spicy foods and high temperatures, and regulating indoor temperatures. Behavioral measures for vasomotor symptoms are supported by clinical evidence and expert consensus [96,97].

To address other symptoms such as the genitourinary syndrome of menopause, which include urinary complaints, vaginal dryness and atrophy, non-hormonal local measures including vaginal lubricants and moisturizers are recommended as first-line therapy when hormone therapy is not desired or contraindicated. These strategies are also supported by clinical guidelines [98].

Isoflavone-rich foods or supplements may also ameliorate menopausal symptoms, such as vasomotor symptoms. Systematic reviews and meta-analyses indicate modest but significant benefits in reducing hot flashes, with a favorable safety profile [96,99,100].

Soy isoflavones

Increasing research has been focused on soy isoflavones in recent years to improve physiological symptoms in midlife women, particularly during the perimenopausal and postmenopausal phases, with over 25,000 articles indexed in PubMed [101].

Isoflavones include genistein, daidzein, glycitein, and their respective glucosides. These phytoestrogens are naturally present at high levels in soybeans [102].

Isoflavones are similar to 17β-estradiol in chemical structure and are capable of binding to ER and activate related gene expressions, which is why they are classified as phytoestrogens [101]. They act as selective ER modulators, exerting estrogenic or anti-estrogenic effects [103]. ER include nuclear ER α and β and membrane G protein-coupled ER 1 (GPER1) [104], but phytoestrogens preferentially bind to ER β [105-108].

Phytoestrogens can act as estrogen agonist in estrogen-depleted conditions. In estrogen-repleted conditions, they may be ineffective or act as antagonist, due to the weaker binding affinity of isoflavones compared with 17β-estradiol [109,110].

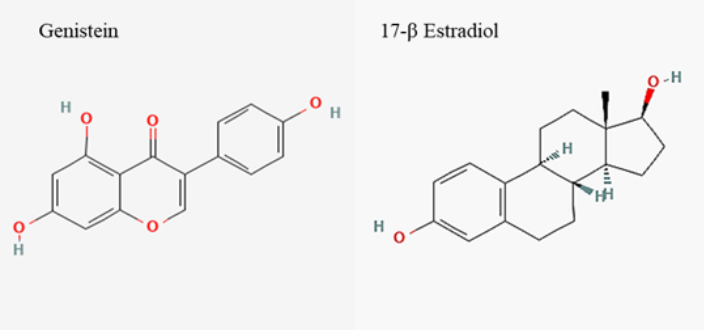

Figure 2: Genistein vs 17-β estradiol. Images are extracted from PubChem.

In addition to the estrogen activity, recent investigations have demonstrated that isoflavones exert antioxidant and anti-inflammatory effects [111].

Anti-inflammatory action was reported both *in vitro* and *in vivo* [112,113]. Phytoestrogens are believed to down-regulate cytokine-induced signal transduction [114]. Moreover, soy isoflavones and their metabolites modulate natural killer (NK) cell function. Cellular analyses indicate that when immune cells (peripheral blood mononuclear cells) (PBMCs) are pre-treated with genistein and the metabolite equol, interferon-gamma (IFN-γ) levels are reduced when NK cells are activated by IL-12 and IL-18, without changing their cytotoxic activity. Genistein decreases MAPK phosphorylation and IL-18 receptor expression on NK cells. A decrease in IFN-γ levels was also seen in mice after IL-12/IL-18 stimulation [115].

Antioxidant activity was also proven *in vitro* [116] and *in vivo* [117] and it is more accentuated in aglycons than glycosides [118]. Genistein may specifically increase the expression of various antioxidant enzymes and therefore reduce oxidative stress [119].

The health implications of soy isoflavones include potential improvements in menopausal symptoms related to estrogen depletion, along with their antioxidant and anti-inflammatory effects. This review examines the available evidence on isoflavones effectiveness in alleviating menopausal symptoms.

Soy isoflavones metabolism and equol

Isoflavone aglycones are absorbed more quickly and are more bioavailable than highly polar conjugated species [120,121]. Genistin and daidzin are hydrolyzed by bacteria in large intestine, removing the sugar moiety, which results in their respective aglycones, genistein and daidzein [121]. Subsequent absorption occurs and these compounds are conjugated in the liver with glucuronic acid or sulfate, circulate hepatically and are mainly excreted in the urine [122]. The glucuronide fraction, which is believed to be biologically inactive, predominates, constituting approximately 90% of circulating isoflavones [123]. Sulfated and free fractions are the minority and are considered biologically active [122].

Additionally, isoflavones can be metabolized by specific intestinal bacteria: daidzein can be alternatively transformed into equol or O-desmethylangolensin (O-DMA), which are biologically active metabolites. Equol is absorbed more efficiently through the intestinal wall than daidzein [117]. Moreover, genistein can be transformed into *p*-ethyl-phenol and 6-hydroxy-*O*-DMA, whereas glycitein is stable [117]. *In vitro* studies indicate that the highest estrogenic potency of isoflavones and metabolites is exhibited in genistein and equol, followed by glycitein and daidzein [117].

It is estimated that 30-50% of individuals have the ability to produce equol –equol producers–, depending on genetic factors, while 80-95% are able to produce O-DMA [124]. It was previously believed that the ability to produce equol could not be altered [125], nevertheless, evidence indicates that it may change through the years in some women [126-128]. *In vitro* studies showed that equol is more estrogenic and potent than daidzein and that it presents anti-androgenic properties [129,130].

Evidence suggests that isoflavones absorption, distribution, metabolism and excretion (ADME) vary through populations, age and gender [131-133].

Soy isoflavones safety

In male and female patients consuming soy-supplemented diets, no adverse effects have been reported in diverse clinical studies with different doses and duration of supplementation [122].

In studies with female and male patients, daily doses of approximately 111-278 mg did not cause any adverse effects [122,134]. The excretion half-lives of daidzein and genistein were slightly increased in a study with soy milk consumption, however, no adverse effects were reported and no modifications in soy isoflavones metabolic pathways were observed [135]. Evidence from single-dose studies shows that doses of 30-450 mg of total aglycone isoflavones are well tolerated in adults [121,136].

Overall, current available literature supports the safety of soy isoflavones. Dietary intervention studies using doses ranging from 51 to 106 mg, or even higher, indicate that these quantities are well tolerated in humans and do not cause any adverse events [122].

The European Food Safety Authority (EFSA) risk assessment [111] for peri- and postmenopausal women taking food supplements containing isolated isoflavones concluded that the stipulated doses of 35-150 mg/day do not produce adverse effects related to breast tissues, uterus or thyroid gland.

Breast and uterus tissues

A systematic review was performed to investigate associations between consumption of isoflavones from food supplements and adverse effects in peri- and postmenopausal women, with no increased risk of breast cancer -observational studies-, as well as no effect on mammographic density or on the expression of proliferation marker Ki-67 -interventional studies-. Additionally, endometrial thickness was not affected and no effect was reported on histopathological changes in the uterus with 150 mg/day supplementation [111]. A study of premenopausal women consuming soy from textured vegetable protein showed no effect on breast epithelial cell proliferation, mitosis or B-cell lymphoma protooncogene expression [137]. A recent systematic review by Boutas et al. [138] reported no effects or even a protective effect on breast cancer risk. Among the evaluated studies, some of them found no significant association between isoflavone intake and breast cancer risk [139,140], including a study with 300,000 women in China, in which no dose-dependent relation was found between breast cancer risk and soy isoflavone consumption [141]. Decreased breast cancer risk was found in patients consuming higher soy isoflavones doses compared with lower doses [142]. Moreover, soy consumption in fertile years was associated with a protective effect in premenopause [143].

Furthermore, isoflavones show higher affinity for ER β, not having any effects on cell proliferation, which is mainly α-mediated [108].

Thyroid function

Thyroid hormones levels were not affected following soy isoflavones supplementation [111]. No effects or little effects have been reported on thyroid function. However, current evidence suggests that soy foods may reduce the absorption of thyroid hormone in hypothyroid patients receiving supplementation, possibly requiring to separate the intake of soy isoflavones and thyroid hormone, or adjusting the dose of thyroid hormone, while not affecting thyroid function [144].

Reproductive effects

Moreover, existing data does not indicate adverse reproductive effects in humans. Evidence supports the safety of soy isoflavone consumption in pregnant women, vegetarians and vegans, and in women with breast or endometrial cancer [122]. However, although the overall safety profile is well established, further research is warranted to fully understand long-term effects and specific population outcomes.

In vivo reproductive toxicity studies found no risk on maternal reproductive function, nursing behavior and fetal development, as well as clinical studies evaluating reproductive effects of phytoestrogens [145-147]. However, evidence of soy isoflavones consumption on reproductive years, as well as during pregnancy, is limited and incongruent.

SOLGEN®

SOLGEN® (Tradichem Group, S.L.) is a unique and natural isoflavone ingredient derived from non-GMO soybeans. It is standardized to contain high percentages of the glycoside isoflavones genistin and daidzin, along with smaller amounts of genistein, daidzein, glycitein, and glycitin. The glycoside forms are transformed into the aglycones in the gut, although both structures show beneficial effects on human health. SOLGEN® composition provides a broad spectrum of isoflavones, which are recognized for their potential benefits in alleviating menopausal symptoms and supporting physiological changes associated with estrogen deficiency.

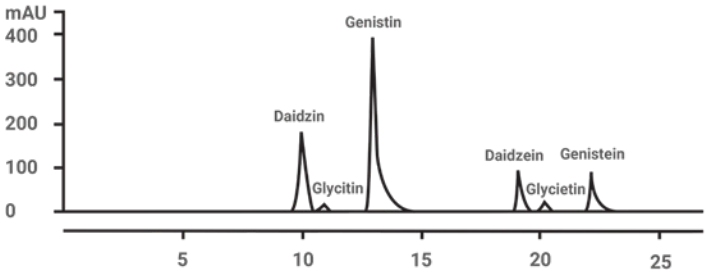

Figure 3: HPLC of SOLGEN®.

SOLGEN® has been extensively studied in numerous clinical trials addressing menopause and postmenopause-related issues, including bone mineral density loss, cognitive function, skin aging, and endometrial health.

In this review, we provide a comprehensive overview of the available scientific evidence regarding SOLGEN® and soy isoflavones, highlighting their effects across the various physiological changes experienced by women during and after the menopausal transition.

SOLGEN® production process involves the following general stages: cleaning and preparation of soybean seeds to ensure purity and quality, and post-harvest processing, fumigation, shipping and storage.

After crushing 4 fractions are obtained: 40% protein, 18% oil (0,5% lecithin), 30% carbohydrates (15% soluble fraction) and 12% moisture.

The soluble fraction of carbohydrates is concentrated to obtain molasses, which is subsequently transferred to a suitable holding vessel prior to feeding into the isoflavones separation process.

The molasses is heated under controlled pH and temperature and subsequently cooled to obtain separately the isoflavone fraction from the remaining soluble fraction (supernatant) by centrifugation. Following this separation, a concentration stage is processed.

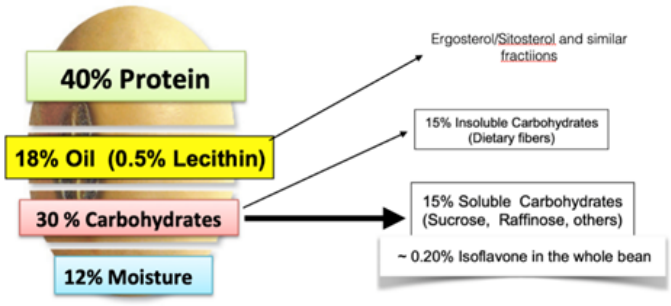

Figure 4: Parts of the soybean.

The supernatant liquid obtained from the previous step is subjected to a reverse phase chromatographic separation.

After a pH adjustment, the liquid is loaded onto the absorbent resin. Various fractions including the isoflavones, bind to the resin column until the column reaches saturation, when the isoflavones start to be lost in the loading fraction. The column is then washed with water in order to remove unbound and undesired impurities.

Isoflavones and other phenolic compounds bind to the resin at various ionic strengths. These compounds are removed by using aqueous alcohol solutions at various concentrations with different components being released at each alcohol concentration.

The different fractions are concentrated on the required brix, pasteurized and then spray-dried to obtain a dry concentrated isoflavone product (SOLGEN®).

Benefits of SOLGEN/ISOFLAVONES supplementation

In this review, we summarize the current scientific evidence on SOLGEN®/soybean isoflavones for menopausal symptoms and physiological changes in women.

Since the 1990s, research on soy isoflavones has increased notably due to recognition of its physiological effects and hormonal properties [101]. As mentioned previously, strong affinity of isoflavones and equol for ER β supports their role as a safe and effective option for managing menopausal symptoms. Early evidence first focused mainly on hot flashes and night sweats; however, current research explores a wide range of midlife symptoms. The Spanish Menopause Society has included isoflavones as an alternative treatment for hot flashes [148].

A systematic review and meta-analysis by Hooper et al. [149] reported a decrease in FSH and LH levels in premenopausal women, increased estradiol levels in postmenopausal women, and an overall 20% improvement in menopausal symptoms compared with placebo when consuming soy isoflavones. Moreover, a meta-analysis by Viscardi et al. [150] on measures of estrogenicity supports the hypothesis that soy isoflavones act as selective ER modulators (SERM), unlike estrogen, and that isoflavones show greater affinity for ER β, associated with antiproliferative effects, and exert tissue-specific effects that may ameliorate symptoms of menopause. In contrast, HT produced significant effects on measures of estrogenicity, contrarily to isoflavones, supporting safety claims for soy isoflavones.

Hot flashes and night sweats

The etiology of hot flashes has not been fully established yet [151]. The efficacy of soy isoflavones against menopausal hot flashes has been extensively studied and demonstrated in multiple meta-analyses and reviews, showing their ability to compensate for estrogen decline that ultimately leads to vasomotor symptoms [108,152-155].

Recent studies recommend isoflavones as a treatment option, with most reporting symptoms relief and none reporting side effects [156]. A dose of 72 mg over 6 months significantly reduced hot flashes [157], and another study using 60 mg intake daily over 3 months reported a 57% decrease in severity and frequency [158]. Soy nut consumption resulted in over 40% reduction in hot flashes in menopausal women, regardless of individual equol production variability [159]. Additionally, severe hot flashes decreased by 92% with a vegan diet supplemented with soybeans [160].

A clinical study evaluating supplementation with a soy extract rich in daidzin and genistin reported a 68.4% reduction in hot flashes and a 78.4% decrease in night sweats at 16 weeks (without placebo) [161]. A systematic review and meta-analysis by Taku et al. [151] showed 20.6% lower frequency and 26.2% less severity of hot flashes compared with placebo. A dose-response effect with genistein was found: conclusive benefits were reported only when genistein was supplemented with ≥30 mg/day [162].

Placebo appears to have a relevant effect. A meta-analysis by Li et al. [163] reported reductions in hot flashes with both soy isoflavones and placebo, and a reduction of 25.2% when eliminating the placebo effect. This meta-analysis also suggests that isoflavones require long-term use -at least 12 months- to achieve its maximum efficacy.

Regarding sleep disorders, recent reports demonstrate effectiveness of isoflavones in reducing insomnia. A study in postmenopausal women with insomnia found that isoflavone treatment reduced the symptoms, increasing sleep efficiency, as observed by polysomnographic analysis [164]. Sleep disturbances were seen to be reduced in a six-month prospective observational study in menopausal women with 60 mg of isoflavones [165]. Moreover, a clinical trial evaluating a nutraceutical composed of a combination of soy isoflavones, black cohosh, chasteberry and evening primrose oil extract in postmenopausal women demonstrated a statistically significant reduction in sleep problems, along with mood symptoms, hot flashes and sweats [166]. A positive correlation between daily isoflavone consumption and improvements in sleep was found in adult Asian populations [167,168].

Cognition

Evidence indicates that soy supplementation improves memory

and frontal lobe function in young patients. A meta-analysis by Cheng et al. [169] revealed that supplementation with isoflavones improved overall cognitive function and visual memory in postmenopausal women. Similarly, results from another meta-analysis by Cui et al. [170] showed that soy isoflavones benefit cognitive function in adults, particularly memory-related.

Moreover, Cheng et al. found that earlier initiation of supplementation had more pronounced improvements in cognition: in postmenopausal women under 60 years, a positive effect was reported in summary cognitive function [171], while no positive effects were observed in postmenopausal women when supplementation started after age 60 [172]. Cognitive improvements have also been documented in premenopausal women and men [170]. In young patients of both sexes, a soy-rich diet significantly enhanced short- and long-term memory tasks [173].

The effects of SOLGEN® on cognitive function were evaluated in 33 postmenopausal women. Treatment with isoflavones led to significant improvements in long-term recall of pictures, mental flexibility, sustained attention and planning [174].

Furthermore, preclinical evidence suggests that soy isoflavones may improve Alzheimer's disease [169,170]. Isoflavone aglycones and equol have shown in vitro the ability to inhibit β-amyloid fibril aggregation [175], and promote its clearance via peroxisome proliferator-activated receptor γ (PPAR- γ)/apolipoprotein E activation [176]. Anti-inflammatory and antioxidant effects of isoflavones, along with their suppression of mitochondrial apoptosis that leads to neuron death [177] and the subsequent alleviation in cognitive impairment may further contribute to mitigating Alzheimer's symptoms [178]. Clinical data are still limited as existing studies do not include dementia at onset.

Equol may lead to more pronounced benefits than isoflavones, as it presents higher antioxidant effects, extended bioavailability, higher affinity to ER β and higher mitochondrial activity [179,180].

Selective binding to ER β by isoflavones is hypothesized to be the cause of their cognitive benefits, as estrogen contributes to various brain processes and ER β is widely expressed in the brain [170]. Episodic memory may be enhanced due to the elevated expression of ER β, particularly in the hippo campus and prefrontal cortex [169,181,182].

Anxiety and depression

Increasing evidence indicates that SOLGEN® isoflavones may exert an antidepressant effect [183]. Messina et al. [184] suggested that isoflavones could be a safe and well-tolerated option for managing depressive symptoms [184].

A moderate dose of 25 mg/day of aglycones reduced depressive symptoms in peri- and postmenopausal women [185]. Moreover, 100 mg/day in clinically depressed postmenopausal women decreased symptoms similarly to various antidepressants and exerted a more pronounced effect when combined with them [186].

In osteopenic postmenopausal women, genistein (54 mg/day) improved depressive symptoms and overall quality of life versus placebo [187]. Additionally, daidzein administration in rats produced antidepressant effects through the microbiota-gut-brain axis, which suggests that daidzein may mitigate depression symptoms in all patients -beyond menopausal women-, via gut microbiome regulation [188].

A review by McLaren et al. [189] showed wide variability in reducing depressive symptoms in menopausal women due to different chemical profile of soy isoflavones.

Isoflavones are hypothesized to compensate variable and low levels of 17β-estradiol, which, as mentioned before, modulate serotonin neurotransmission.

Urogenital health and sexual dysfunction

Phytoestrogens are hypothesized to improve symptoms related to the urogenital system in postmenopausal women through modulation of ER β found in the urogenital tract. Urogenital tissues (bladder, urethra, vaginal mucosa or pubo-cervical fascia) [190] also express GPER1, which possess high affinity for genistein and daidzein [191]. Conclusive evidence supporting the use of isoflavones in urogenital symptoms is still needed. In particular, no evidence demonstrates a preventive effect on stress or urge urinary incontinence. Further studies evaluating interindividual variability and isoflavone metabolism are needed to assess a potential influence on these symptoms [192].

Topical application of soy isoflavones in a vaginal gel led to improvements in vaginal dryness and atrophy symptoms, maturation values, vaginal pH, morphology and expression of ER in vaginal epithelium [193-196]. Moreover, local administration also increased the number of blood vessels in the vaginal epithelium [197]. Genistein was found to be more effective than hyaluronic acid for alleviating vaginal dryness, itching and enhancing general health [195].

In contrast, oral supplementation only reduced vaginal dryness, without estrogenic effects on maturation value, vaginal pH or endometrial thickness [198].

Effects of a dietary supplement containing the high genistein soybean extract SOLGEN® and pumpkin seed extract in perimenopausal women with urinary incontinence were decreases in mean urgency grade, nocturia and the use of daily pantyliners, as well as an improvement in quality of life by 92.3% [199]. The same supplement evaluated in 30 perimenopausal Spanish women with urinary incontinence showed statistically significant improvements in nocturnal urinary episodes, with a 69% reduction of nocturia [200].

Equol has also demonstrated effectiveness in postmenopausal

vaginal symptoms, including vaginal maturation value, vaginal pH and atrophy [201].

Bone health

Estrogen loss during menopause increases the risk of bone loss, as estrogen plays a key role in the preservation of bone health and calcium homeostasis [202]. Soy isoflavones may improve bone metabolism. A proposed mechanism by Hooshiar et al. [203] is through modulation of the RANKL/RANK/OPG pathway, strongly related to the structural similarity of isoflavones to estrogen. Isoflavones have been shown to reduce RANKL levels via a decrease in gene expression in osteoblasts and an increase in OPG levels, a bone resorption inhibitor. *In vitro* studies revealed that this is due to an enhanced osteoblast gene expression.

A meta-analysis by Akhlaghi et al. [204] reported that soy isoflavone consumption significantly improved bone mineral density (BMD) in femoral neck, hip and lumbar spine. These effects were more pronounced in normal weight patients and interventions longer than one year. Dosage was also an important factor influencing the impact of isoflavones. Additionally, markers of bone turnover including osteoprotegerin, pyridinoline and C-telopeptides were also modified by isoflavones, however, unlike BMD influences, overweight individuals and lower dosages showed greater benefits [204]. Inpan et al. [205] also showed in a recent meta-analysis and systematic review that isoflavones, particularly genistein and with doses of at least 50 mg/day, effectively improved bone mineral density in postmenopausal women.

SOLGEN® prevents bone mineral loss during menopause by reducing intracellular reactive oxygen species (ROS) in a dose-dependent manner [206].

A study of 200 women supplemented with SOLGEN® for 6 months demonstrated a significant reduction in type I collagen crosslinked beta C-telopeptide (βCTX) (bone-resorption marker) and in type I procollagen-N-propeptide (P1NP) (bone formation marker), presenting a beneficial effect on bone health, in a similar mode of action as antiresorptive agents [207]. Rapid bone loss in early postmenopausal years is associated with increased biochemical markers of bone resorption and, subsequently, bone formation [207].

Glucose and insulin resistance

The incidence of diabetes and insulin resistance increases in women after menopause [208], which is attributed to estrogen reduction. Clinical evidence indicates that phytoestrogens may improve glucose metabolism [209-211], although it remains controversial.

Supplementation with soy isoflavones at doses above 40 mg/day enhanced glycometabolism [211,212]. A meta-analysis by Fang et al. [103] concluded that soy isoflavones may improve fasting blood glucose (FBG), insulin levels, and homeostasis model assessment of insulin resistance (HOMA-IR). Evidence suggests that the lowest levels of heterogeneity were with genistein alone [103]. Other studies found inconsistent results, showing no significant effects on plasma glucose [213], insulin [214] or modest effects on fasting glucose [215].

SOLGEN® was administered to 24 obese, postmenopausal women with type II diabetes, resulting in significant improvements in glycated hemoglobin (HbA1c), fasting insulin and insulin resistance, along with lipid profile and systolic and diastolic blood pressure, with no changes in body weight [216]. These results suggest that soy isoflavones may improve glycemic control and insulin resistance.

A study in 32 postmenopausal women with diet-controlled type II diabetes found that SOLGEN® reduced insulin resistance, improved glycemic control and decreased LDL cholesterol, which translates into improvements in glycemic control and CV risk markers in these patients [217]. In contrast, a study evaluating SOLGEN® supplementation in postmenopausal Chinese women with prediabetes or initial untreated diabetes reported no favorable changes [218].

Regarding body composition, although some studies reported no changes in body weight, a trial conducted among 180 postmenopausal women with mild hyperglycemia observed a mild favorable effect of soy isoflavones on body weight, body mass index and body fat percentage after 6 months of supplementation [219].

CV protection

Literature indicates that soy isoflavones contained in foods and supplements may protect against CVD [220], by maintaining vascular endothelial health and endothelial cell protection [221,222]. This protective effect is believed to result from the similarities in structure of isoflavones to estrogen, along with antioxidative and anti-inflammatory effects, not mediated by ER.

- Estrogenic effects have demonstrated to be protective, as they inhibit arteriosclerosis and can prevent CVD [221]. In ovariectomized rats, increased soy isoflavone intake reduced myocardial infarct size, enhanced endothelium-dependent relaxation of the aorta after ischemia and reperfusion, and improved ventricle function, effects attributed to phytoestrogens [221,223].
- Antioxidative effects of isoflavones are thought to protect the endothelium by inducing antioxidant enzymes and attenuating oxidase expression and activity. Particularly, genistein, daidzein and equol have shown antioxidant activity [221]. Equol has also been demonstrated to prevent endothelial nitric oxide production in ovariectomized rats [224]. Moreover, isoflavones induced superoxide dismutase (SOD) and glutathione peroxidase activity [221]. In endothelial cells from stroke-prone hypertensive rats, genistein reduced oxidative stress by decreasing angiotensin II–enhanced p22phox NADPH oxidase and superoxides [225].
- Anti-inflammatory effects also participate in CVD protection. Soy isoflavones have been shown to reduce inflammatory

markers, such as IL-6, C-reactive protein (CRP) and TNF-α in patients with ischemic cardiomyopathy [226]. Genistein exerts several anti-inflammatory actions, including inhibition of TNF-α-induced vascular endothelial inflammation [221]; inhibition of ox-LDL-induced expression of adhesion molecules such as E-selectin, P-selectin, MCP-1, VCAM-1 and ICAM-1 in human endothelial cells; and suppression of NF-kB signaling pathway [227].

In postmenopausal women, SOLGEN® enhanced endothelium-dependent vasodilation by augmenting plasma NOx concentrations, suggesting that isoflavones may help increase endothelial NO production [228]. A study in healthy European postmenopausal women reported a decrease in serum levels of CRP compared with placebo, suggesting that SOLGEN® isoflavones may produce an attenuation of endothelial inflammation [229].

Skin modifications

Declining estrogen levels leads to a more pronounced skin aging. Evidence suggests that soy isoflavones, especially genistein and daidzein, exert protective, anti-aging and anti-inflammatory properties on skin cells [230].

A review by Wójciak et al. [231] examining soy isoflavones applied topically identified several mechanisms through which soy isoflavones exert their effects as modulation of signaling pathways. Isoflavones can contribute to anti-aging effects and skin health via several pathways, including ROS/NF-κB and STAT3, PI3K-Akt, TGF-β/Smad, JAK-STAT, AMPK and MAPK [232-235]. Chiang et al. [232] demonstrated that isoflavone extracts inhibit UVB-induced MAPK phosphorylation. Genistein has been shown to inhibit the ROS/Akt/NF-κB pathway and promote AMPK activation [233]. *In vitro* studies suggest that isoflavone extracts reduce MAPK, NF-κB and JAK-STAT activation in normal human epidermal keratinocytes [235].

Topical isoflavones application prior to UVB irritation reduced COX-2 and PCNA expression, along with decreasing epidermal thickness [236]. Genistein decreases inflammatory factors including IL-1β, IL-6, IL-8, chemokine ligand 2 (CCL2), IL-17 and IL-23, along with suppressing TNF-α-induced inflammation [233,234]. *In vitro* studies revealed reductions in IL-22, IL-17A and TNF- α. [235]. Additionally, genistein improved pathological scores of skin lesions in mice induced with psoriasis. This evidence, next to the inhibition of the expression of inflammatory factors, could open a new path in psoriasis treatment [234,235].

In the human skin fibroblasts and keratinocytes, it was observed that genistein protects against peroxidation by regulating the oxidant/antioxidant system and mitochondria membrane potential, through modulation of ER, GPER30 and kinase activation [237]. Additionally, various studies indicate that oral administration of SOLGEN®/soybean isoflavones, particularly genistein, promotes skin repair and improves skin changes [238,239]. In a study in women in their late 30s and early 40s, supplementation with soy isoflavones showed a statistically significant improvement in fine wrinkles and malar skin elasticity [240].

SOLGEN® has also been shown to improve skin aging in healthy postmenopausal women: reducing forehead, perioral and periocular wrinkles, hyperpigmentation, under-eye dark circles and overall appearance [241].

Additional potential benefits

Endometriosis

Endometriosis is an estrogen-dependent inflammatory disease [242]. Isoflavones have been investigated as a potential treatment due to their similarities to estrogen. Results indicate that isoflavones may play a role in endometriosis.

A study in rats evaluated the effect of broccoli extract in combination with soy isoflavones for the treatment of endometriosis, which resulted in a significant improvement of the histopathological grade of endometriotic lesions, suggesting a therapeutic effect [243,244].

Moreover, a recent study revealed that isoflavones rich in daidzein inhibit cell growth and inflammation in endometriosis [245]. In a mouse model of endometriosis, daidzein-rich isoflavones reduced IL-6, IL-8, cyclooxygenase-2 (COX-2), aromatase and PGE_2 levels [221]. Additionally, genistein caused regression of endometriotic implants in a rat model [246].

However, the effects of soy isoflavones on endometriosis require to be further studied as current evidence is still unclear.

Fertility treatments

A study by Vanegas et al. [247] evaluated phytoestrogens intake on women undergoing infertility treatment with assisted reproductive technology. Results showed that soy isoflavones intake was positively related to live birth rates. However, evidence remains limited.

Polycystic ovary syndrome and its comorbidities

Polycystic ovary syndrome (PCOS) is a reproductive disorder associated with metabolic features, such as insulin resistance, glucose tolerance and obesity [248].

In a clinical study on 70 women diagnosed with PCOS, soy isoflavone supplementation significantly reduced circulating serum levels of insulin, insulin resistance, free androgen index and serum triglycerides compared with placebo. There was also an improvement in plasma total glutathione and insulin sensivity [249].

Another study evaluating twelve women with PCOS, obesity, hyperinsulinemia and dyslipidemia investigated the effects of genistein, leading to reductions in low-density lipoprotein (LDL) cholesterol and triglycerides [250].

Table 1: Summary of SOLGEN® studies.

Author, year, study type	Evaluation	Patients (n)	Duration of treatment	Results
Jayagopal et al. [216], 2002, interventional	Effect of SOLGEN® vs placebo on women with type 2 diabetes	n=32 (62.5±6.77 years)	12 weeks	Improvements on insulin resistance, glycemic control and serum lipoproteins ($p<0.05$)
Duffy et al. [174], 2003, interventional	Effect of SOLGEN® vs placebo on memory	n=33 (aged 50-65)	12 weeks	Improvements in episodic memory ($p<0.03$)
Hall et al. [229], 2005, interventional	Effect of SOLGEN® vs placebo on inflammatory biomarkers of CV disease risk	n=117 (aged 45-70)	8 weeks	Beneficial effects on C-reactive protein (CRP) concentrations ($p<0.05$) and may improve VCAM-1
Weickert et al. [252] 2006, interventional	Effect of SOLGEN® vs placebo on body weight	n=34 (59±6 years)	8 weeks	Increase in pre-prandial peptide YY, no effect on ghrelin and body weight ($p=0.01$)
Skovgaard et al. [241], 2006, interventional	Effect of SOLGEN® vs placebo on skin aging	n=80 (aged 45-65)	6 months	Improvement of wrinkles, pigmentation, laxity and sagging ($p<0.05$)
Fuchs et al. [253], 2007, interventional	Effect of SOLGEN® vs placebo on proteomic biomarkers of peripheral blood mononuclear cells	n=27 (aged 45-70)	8 weeks	Anti-inflammatory response in blood mononuclear cells
Hall et al. [228], 2008, interventional	Effect of SOLGEN® vs placebo on nitric oxide-dependent vasorelaxation	n=22 (aged 54-70)	1 week	Increases in endothelium-dependent vasodilation ($p<0.01$)
Liu et al. [219], 2010, interventional	Effect of SOLGEN® vs placebo on body composition	n=180 (aged 48-70)	6 months	Mild favorable effect ($p<0.05$)
Sathyapalan et al. [207], 2016, interventional	Effect of SOLGEN® on bone turnover markers	n=200 (2 years after the onset of their menopause)	6 months	Beneficial effect on bone health ($p<0.01$)

In rat models, soy isoflavones significantly decreased body weight and ovarian volume, and improved estrous cycle. Moreover, serum testosterone and LH were reduced, as well as oxidative stress and inflammation. Additionally, estradiol levels were increased, and improvements in follicles and corpus luteum formation were observed [251].

Discussion

Menopause involves one third of women's lives and defines the end of the reproductive period, typically between 45-55. The menopausal transition starts with the first establishments of menstrual irregularities due to variations and posterior decline in hormone levels and ends with the final menstrual period, defining menopause when one year of amenorrhea has occurred. Menopausal transition is a critical life stage, characterized by physiological, hormonal and social changes. Challenges related to physical and psychological changes, such as body or mood changes, impact women's identity and social life, with possible negative experiences influenced by gendered social stereotypes about aging.

Menopausal symptoms are abruptly permanent, with 90% of menopausal women assessing for help in relieving symptoms to their healthcare providers [254]. The World Health Organization (WHO) defines the menopausal transition as a critical phase of a woman's life and considers physical, psychological and social health to be an integral part of public health care during and after menopause [255]. In 2020, 985 million women were estimated to be 50 or older [256], and this number is expected to increase by time due to global aging of the worldwide population and evolution in life expectancy. To improve the quality of life and overall health of an increasing older female population, further clinical research is needed to assess menopause symptoms, as various of them can continue for several years or never disappear without treatment.

HT is contraindicated due to its common short term and long term side effects and its health risks. Many women prefer the use of alternative options, such as soy isoflavones supplementation for alleviating menopause-related symptoms.

Substantial clinical evidence supports that SOLGEN®/soybean isoflavones are safe and effective in various conditions, not only in postmenopausal changes but also in other midlife health aspects, opening a new path for their use in women. However, further research is still needed to evaluate additional benefits of phytoestrogens supplementation.

References

1. Luan H, Liu Q, Guo Y, et al. Effects of soy isoflavones on menopausal symptoms in perimenopausal women: a systematic review and meta-analysis. PeerJ. 2025; 13: e19715.
2. Monteleone P, Mascagni G, Giannini A, et al. Symptoms of menopause-global prevalence, physiology and implications. Nat Rev Endocrinol. 2018; 14: 199-215.
3. Susan R Davis, Irene Lambrinoudaki, Maryann Lumsden, et al. Menopause. Nat Rev Dis Primers. 2015; 1: 15004.

4. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. Menopause. 2012; 19: 387-395.
5. Fogle RH, Stanczyk FZ, Zhang X, et al. Ovarian androgen production in postmenopausal women. J Clin Endocrinol Metab. 2007; 92: 3040-3043.
6. McConnell DS, Stanczyk FZ, Sowers MR, et al. Menopausal transition stage-specific changes in circulating adrenal androgens. Menopause. 2012; 19: 658-663. -
7. Hutchings HA, Taylor N, Remesh A, et al. A study evaluating quality of life and factors affecting it before, during and after menopause. Eur J Obstet Gynecol Reprod Biol. 2023; 289: 100-107.
8. Davis SR, Lambrinoudaki I, Lumsden M, et al. Menopause. Nat Rev Dis Primer. 2015; 1: 15004.
9. Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. Am J Med. 2005; 118; 12B: 14-24.
10. Politi MC, Schleinitz MD, Col NF. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. J Gen Intern Med. 2008; 23: 1507-1513.
11. Freeman EW, Sammel MD, Lin H, et al. Duration of Menopausal Hot Flushes and Associated Risk Factors. Obstet Gynecol. 2011; 117: 1095-1104.
12. Zeleke BM, Bell RJ, Billah B, et al. Vasomotor and sexual symptoms in older Australian women: a cross-sectional study. Fertil Steril. 2016; 105: 149-155.e1.
13. Nappi RE, Kroll R, Siddiqui E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. Menopause. 2021; 28: 875.
14. Rossmanith WG, Ruebberdt W. What causes hot flushes? The neuroendocrine origin of vasomotor symptoms in the menopause. Gynecol Endocrinol. 2009; 25: 303-314.
15. Woods NF, Carr MC, Tao EY, et al. Increased urinary cortisol levels during the menopause transition: Menopause. 2006; 13: 212-221.
16. Gibson CJ, Thurston RC, Matthews KA. Cortisol dysregulation is associated with daily diary-reported hot flashes among midlife women. Clin Endocrinol (Oxf). 2016; 85: 645-651.
17. Gordon JL, Rubinow DR, Thurston RC, et al. Cardiovascular, hemodynamic, neuroendocrine, and inflammatory markers in women with and without vasomotor symptoms. Menopause. 2016; 23: 1189-1198.
18. Zervas IM, Lambrinoudaki I, Spyropoulou AC, et al. Additive effect of depressed mood and vasomotor symptoms on postmenopausal insomnia. Menopause. 2009; 16: 837-842.
19. Joffe H, Massler A, Sharkey K. Evaluation and Management of Sleep Disturbance During the Menopause Transition. Semin Reprod Med. 2010; 28: 404-421.
20. Polo-Kantola P. Sleep problems in midlife and beyond. Maturitas. 2011; 68: 224-232.
21. Freedman RR, Roehrs TA. Effects of REM sleep and ambient temperature on hot flash-induced sleep disturbance. Menopause. 2006; 13: 576-583.
22. Pien GW, Sammel MD, Freeman EW, et al. Predictors of Sleep Quality in Women in the Menopausal Transition. Sleep. 2008; 31: 991-999.
23. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014; 383: 736-747.
24. Monterrosa-Castro Á, Chedraui P, Blümel JE, et al. Sleep disturbances are associated with cognitive impairment in postmenopausal women. Women Health. 2025; 65: 783-794.
25. Kerner N, Roose S. Obstructive Sleep Apnea is Linked to Depression and Cognitive Impairment: Evidence and Potential Mechanisms. Am J Geriatr Psychiatry. 2016; 24.
26. Freeman EW, Sammel MD, Lin H, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. Obstet Gynecol. 2007; 110: 230-240.
27. Kravitz HM. Relationship of Day-to-day Reproductive Hormone Levels to Sleep in Midlife Women. Arch Intern Med. 2005; 165: 2370.
28. Epperson CN, Sammel MD, Freeman EW. Menopause effects on verbal memory: findings from a longitudinal community cohort. J Clin Endocrinol Metab. 2013; 98: 3829-3838.
29. Pines A. Circadian rhythm and menopause. Climacteric J Int Menopause Soc. 2016; 19: 551-552.
30. Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: A systematic review and meta-analysis. J Steroid Biochem Mol Biol. 2014; 142: 90-98.
31. Greendale GA, Huang MH, Wight RG, et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. Neurology. 2009; 72: 1850-1857.
32. Greendale GA, Derby CA, Maki PM. Perimenopause and cognition. Obstet Gynecol Clin North Am. 2011; 38: 519-535.
33. Genazzani AR, Pluchino N, Luisi S, et al. Estrogen, cognition and female ageing. Hum Reprod Update. 2007; 13: 175-187.
34. Blair JA, Palm R, Chang J, et al. Luteinizing hormone downregulation but not estrogen replacement improves ovariectomy-associated cognition and spine density loss independently of treatment onset timing. Horm Behav. 2016; 78: 60-66.
35. Kulkarni J, Gurvich C, Mu E, et al. Menopause depression: Under recognised and poorly treated. Aust N Z J Psychiatry. 2024; 58: 636-640.
36. Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front Neurosci. 2015; 9.
37. Bitran D, Shiekh M, McLeod M. Anxiolytic effect of progesterone is mediated by the neurosteroid allopregnanolone at brain GABAA receptors. J Neuroendocrinol. 1995; 7: 171-177.

38. Gonzales GF, Carrillo C. Blood serotonin levels in postmenopausal women: effects of age and serum oestradiol levels. Maturitas. 1993; 17: 23-29.
39. McLaren S, Seidler K, Neil J. Investigating the Role of 17β-Estradiol on the Serotonergic System, Targeting Soy Isoflavones as a Strategy to Reduce Menopausal Depression: A Mechanistic Review. J Am Nutr Assoc. 2024; 43: 221-235.
40. Portman DJ, Gass MLS. Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause. 2014; 21: 1063-1068.
41. Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA) - results from an international survey. Climacteric J Int Menopause Soc. 2012; 15: 36-44.
42. Nappi RE, Palacios S, Panay N, et al. Vulvar and vaginal atrophy in four European countries: evidence from the European REVIVE Survey. Climacteric J Int Menopause Soc. 2016; 19: 188-197.
43. Avis NE, Brockwell S, Randolph JF, et al. Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health Across the Nation. Menopause. 2009; 16: 442-452.
44. Nappi RE, Cucinella L, Martella S, et al. Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). Maturitas. 2016; 94: 87-91.
45. Dundon CM, Rellini AH. More than sexual function: predictors of sexual satisfaction in a sample of women age 40-70. J Sex Med. 2010; 7: 896-904.
46. Legendre G, Ringa V, Panjo H, et al. Incidence and remission of urinary incontinence at midlife: a cohort study. BJOG Int J Obstet Gynaecol. 2015; 122: 816-824.
47. Nappi RE, Palacios S. Impact of vulvovaginal atrophy on sexual health and quality of life at postmenopause. Climacteric J Int Menopause Soc. 2014; 17: 3-9.
48. Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. Mayo Clin Proc. 2010; 85: 87-94.
49. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. J Clin Endocrinol Metab. 2008; 93: 861-868.
50. Sandhu SK, Hampson G. The pathogenesis, diagnosis, investigation and management of osteoporosis. J Clin Pathol. 2011; 64: 1042-1050.
51. van Staa TP, Dennison EM, Leufkens HGM, et al. Epidemiology of fractures in England and Wales. Bone. 2001; 29: 517-522.
52. Juppi HK, Sipilä S, Cronin NJ, et al. Role of Menopausal Transition and Physical Activity in Loss of Lean and Muscle Mass: A Follow-Up Study in Middle-Aged Finnish Women. J Clin Med. 2020; 9: 1588.
53. Rolland YM, Perry HM, Patrick P, et al. Loss of appendicular muscle mass and loss of muscle strength in young postmenopausal women. J Gerontol A Biol Sci Med Sci. 2007; 62: 330-335.
54. Aloia JF, McGowan DM, Vaswani AN, et al. Relationship of menopause to skeletal and muscle mass. Am J Clin Nutr. 1991; 53: 1378-1383.
55. Hansen RD, Allen BJ. Habitual physical activity, anabolic hormones, and potassium content of fat-free mass in postmenopausal women. Am J Clin Nutr. 2002; 75: 314-320.
56. Schaap LA, Pluijm SMF, Deeg DJH, et al. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med. 2006; 119: 526.e9-17.
57. Kenny AM, Dawson L, Kleppinger A, et al. Prevalence of sarcopenia and predictors of skeletal muscle mass in nonobese women who are long-term users of estrogen-replacement therapy. J Gerontol A Biol Sci Med Sci. 2003; 58: M436-M440.
58. William J Boyle, W Scott Simonet, David L Lacey. Osteoclast differentiation and activation. Nature. 2003; 423: 337-342.
59. Clarke BL, Khosla S. Physiology of bone loss. Radiol Clin North Am. 2010; 48: 483-495.
60. Sapir-Koren R, Livshits G. Is interaction between age-dependent decline in mechanical stimulation and osteocyte-estrogen receptor levels the culprit for postmenopausal-impaired bone formation? Osteoporos Int. 2013; 24: 1771-1789.
61. Maltais ML, Desroches J, Dionne IJ. Changes in muscle mass and strength after menopause. J Musculoskelet Neuronal Interact. 2009; 9: 186-197.
62. Davis SR, Castelo-Branco C, Chedraui P, et al. Understanding weight gain at menopause. Climacteric J Int Menopause Soc. 2012; 15: 419-429.
63. Barton M. Cholesterol and atherosclerosis: modulation by oestrogen. Curr Opin Lipidol. 2013; 24: 214-220.
64. El Khoudary SR, Shields KJ, Janssen I, et al. Cardiovascular Fat, Menopause, and Sex Hormones in Women: The SWAN Cardiovascular Fat Ancillary Study. J Clin Endocrinol Metab. 2015; 100: 3304-3312.
65. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. J Clin Endocrinol Metab. 2009; 94: 1104-1110.
66. Taddei S. Blood pressure through aging and menopause. Climacteric J Int Menopause Soc. 2009; 12: 36-40.
67. Kuczmarski AV, Shoemaker LN, Hobson JC, et al. Altered endothelial ETB receptor expression in postmenopausal women. Am J Physiol-Heart Circ Physiol. 2020; 319: H242-H427.
68. Hage FG, Oparil S. Ovarian hormones and vascular disease. Curr Opin Cardiol. 2013; 28: 411-416.
69. Abramson BL, Melvin RG. Cardiovascular Risk in Women: Focus on Hypertension. Can J Cardiol. 2014; 30: 553-559.

70. Rocca WA, Grossardt BR, Miller VM, et al. Premature menopause or early menopause and risk of ischemic stroke. Menopause. 2012; 19: 272-277.

71. Calleja-Agius J, Brincat M. The effect of menopause on the skin and other connective tissues. Gynecol Endocrinol. 2012; 28: 273-277.

72. Archer DF. Postmenopausal skin and estrogen. Gynecol Endocrinol. 2012; 28: 2-6.

73. Viscomi B, Muniz M, Sattler S. Managing Menopausal Skin Changes: A Narrative Review of Skin Quality Changes, Their Aesthetic Impact, and the Actual Role of Hormone Replacement Therapy in Improvement. J Cosmet Dermatol. 2025; 24: e70393.

74. Grishina I, Fenton A, Sankaran-Walters S. Gender differences, aging and hormonal status in mucosal injury and repair. Aging Dis. 2014; 5: 160-169.

75. Kamp E, Ashraf M, Musbahi E, et al. Menopause, skin and common dermatoses. Part 1: hair disorders. Clin Exp Dermatol. 2022; 47: 2110-2116.

76. Calleja-Agius J, Brincat M. The effect of menopause on the skin and other connective tissues. Gynecol Endocrinol. 2012; 28: 273-277.

77. Lephart ED, Naftolin F. Menopause and the Skin: Old Favorites and New Innovations in Cosmeceuticals for Estrogen-Deficient Skin. Dermatol Ther. 2021; 11: 53-69.

78. Kim YS, Kim TH, Park E, et al. Ezrin Expression and Activation in Hypertrophic and Keloid Scar. GREM. 2020; 1: 29-36.

79. Moreau KL, Hildreth KL. Vascular Aging across the Menopause Transition in Healthy Women. Adv Vasc Med. 2014; 204390.

80. Blume-Peytavi U, Atkin S, Gieler U, et al. Skin academy: hair, skin, hormones and menopause - current status/knowledge on the management of hair disorders in menopausal women. Eur J Dermatol. 2012; 22: 310-318.

81. Ali I, Wojnarowska F. Physiological changes in scalp, facial and body hair after the menopause: a cross-sectional population-based study of subjective changes. Br J Dermatol. 2011; 164: 508-513.

82. Cho L, Kaunitz AM, Faubion SS, et al. Rethinking Menopausal Hormone Therapy: For Whom, What, When and How long? Circulation. 2023; 147: 597-610.

83. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003; 349: 523-534.

84. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998; 280: 605-613.

85. The 2022 Hormone Therapy Position Statement of The North American Menopause Society. Menopause. 2022; 29: 767-794.

86. Compounded Bioidentical Menopausal Hormone Therapy: ACOG Clinical Consensus No. 6. Obstet Gynecol. 2023; 142: 1266-1273.

87. Cunningham RL, Galea LAM, Goulmamine S, et al. Advancing evidence-based regulation: Organization for the Study of Sex Differences and Society for Women's Health Research support FDA action on menopausal hormone therapy and encourage broader sex-informed drug label updates. Biol Sex Differ. 2026.

88. Gu Y, Han F, Xue M, et al. The benefits and risks of menopause hormone therapy for the cardiovascular system in postmenopausal women: a systematic review and meta-analysis. BMC Womens Health. 2024; 24: 60.

89. Zhang GQ, Chen JL, Luo Y, et al. Menopausal hormone therapy and women's health: An umbrella review. PLoS Med. 2021; 18: e1003731.

90. Rozenberg S, Di Pietrantonio V, Vandromme J, et al. Menopausal hormone therapy and breast cancer risk. Best Pract Res Clin Endocrinol Metab. 2021; 35: 101577.

91. Yoo TK, Han KD, Kim D, et al. Hormone Replacement Therapy, Breast Cancer Risk Factors, and Breast Cancer Risk: A Nationwide Population-Based Cohort. Cancer Epidemiol Biomark Prev. 2020; 29: 1341-1347.

92. Gu Y, Han F, Xue M, et al. The benefits and risks of menopause hormone therapy for the cardiovascular system in postmenopausal women: a systematic review and meta-analysis. BMC Womens Health. 2024; 24: 60.

93. Management of Osteoporosis in Postmenopausal Women: 2021 Position Statement. Guideline Central. 2025.

94. Amanda Daley, Helen Stokes-Lampard, Adèle Thomas, et al. Exercise for vasomotor menopausal symptoms. Cochrane Database Syst Rev. 2014.

95. Wong C, Yip B, Gao T, et al. Mindfulness-Based Stress Reduction (MBSR) or Psychoeducation for the Reduction of Menopausal Symptoms: A Randomized, Controlled Clinical Trial. Sci Rep. 2018; 8.

96. The 2023 non hormone therapy position statement of The North American Menopause Society. Menopause. 2023; 30: 573-590.

97. Freedman RR. Hot flashes: behavioral treatments, mechanisms, and relation to sleep. Am J Med. 2005; 118: 124-130.

98. Faubion SS, Larkin LC, Stuenkel CA, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. Menopause. 2018; 25: 596-608.

99. Pachman DR, Jones JM, Loprinzi CL. Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. Int J Womens Health. 2010; 2: 123-35.

100. Taku K, Melby MK, Kronenberg F, et al. Extracted or

synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. Menopause. 2012; 19: 776-790.

101. Messina M, Barnes S, Setchell KD. Perspective: Isoflavones-Intriguing Molecules but Much Remains to Be Learned about These Soybean Constituents. Adv Nutr Bethesda Md. 2025; 16: 100418.

102. Mei-Hua Huang, Jean Norris, Weijuan Han, et al. Development of an updated phytoestrogen database for use with the SWAN Food Frequency Questionnaire: intakes and food sources in a community-based, multiethnic cohort study. Nutr Cancer. 2013.

103. Fang K, Dong H, Wang D, et al. Soy isoflavones and glucose metabolism in menopausal women: A systematic review and meta-analysis of randomized controlled trials. Mol Nutr Food Res. 2016; 60: 1602-1614.

104. Tang ZR, Zhang R, Lian ZX, et al. Estrogen-Receptor Expression and Function in Female Reproductive Disease. Cells. 2019; 8: 1123.

105. Jiang Y, Gong P, Madak-Erdogan Z, et al. Mechanisms enforcing the estrogen receptor β selectivity of botanical estrogens. FASEB J. 2013; 27: 4406-4418.

106. McCarty MF. Isoflavones made simple - genistein's agonist activity for the beta-type estrogen receptor mediates their health benefits. Med Hypotheses. 2006; 66: 1093-1114.

107. Sekikawa A, Ihara M, Lopez O, et al. Effect of S-equol and Soy Isoflavones on Heart and Brain. Curr Cardiol Rev. 2019; 15: 114-135.

108. Schmidt M, Arjomand-Wölkart K, Birkhäuser MH, et al. Consensus: soy isoflavones as a first-line approach to the treatment of menopausal vasomotor complaints. Gynecol Endocrinol 2016; 32: 427-430.

109. Fujitani M, Mizushige T, Adhikari S, et al. Mechanism of Soy Isoflavone Daidzein-Induced Female-Specific Anorectic Effect. Metabolites. 2022; 12: 252.

110. Armin Zittermann, Julia Geppert, Sonja Baier, et al. Short-term effects of high soy supplementation on sex hormones, bone markers, and lipid parameters in young female adults. European Journal of Nutrition. 2004; 43: 100-108.

111. Safety of isoflavones from food supplements in menopausal women. EFSA. 2015.

112. Bernatoniene J, Kazlauskaite JA, Kopustinskiene DM. Pleiotropic Effects of Isoflavones in Inflammation and Chronic Degenerative Diseases. Int J Mol Sci. 2021; 22: 5656.

113. Chacko BK, Chandler RT, Mundhekar A, et al. Revealing anti-inflammatory mechanisms of soy isoflavones by flow: modulation of leukocyte-endothelial cell interactions. Am J Physiol Heart Circ Physiol. 2005; 289: H908-915.

114. Verdrengh M, Jonsson IM, Holmdahl R, et al. Genistein as an anti-inflammatory agent. Inflamm Res. 2003; 52: 341-346.

115. Mace TA, Ware MB, King SA, et al. Soy isoflavones and their metabolites modulate cytokine-induced natural killer cell function. Sci Rep. 2019; 9: 5068.

116. Ruiz-Larrea MB, Mohan AR, Paganga G, et al. Antioxidant activity of phytoestrogenic isoflavones. Free Radic Res. 1997; 26: 63-70.

117. Křížová L, Dadáková K, Kašparovská J, et al. Isoflavones. Mol Basel Switz. 2019; 24: 1076.

118. Ko KP. Isoflavones: chemistry, analysis, functions and effects on health and cancer. Asian Pac J Cancer Prev. 2014; 15: 7001-7010.

119. Ke Zhang, Jingwen Wang, Baojun Xu. Critical Review on Molecular Mechanisms for Genistein's Beneficial Effects on Health Through Oxidative Stress Reduction. Antioxidants. 2025; 14: 904.

120. Setchell KD. Absorption and metabolism of soy isoflavones-from food to dietary supplements and adults to infants. J Nutr. 2000; 130: 654S-655S.

121. Izumi T, Piskula MK, Osawa S, et al. Soy isoflavone aglycones are absorbed faster and in higher amounts than their glucosides in humans. J Nutr. 2000; 130: 1695-1699.

122. Munro IC, Harwood M, Hlywka JJ, et al. Soy isoflavones: a safety review. Nutr Rev. 2003; 61: 1-33.

123. Barnes S, Sfakianos J, Coward L, et al. Soy isoflavonoids and cancer prevention. Underlying biochemical and pharmacological issues. Adv Exp Med Biol. 1996; 401: 87-100.

124. Atkinson C, Frankenfeld CL, Lampe JW. Gut bacterial metabolism of the soy isoflavone daidzein: exploring the relevance to human health. Exp Biol Med Maywood NJ. 2005; 230: 155-170.

125. Setchell KDR, Faughnan MS, Avades T, et al. Comparing the pharmacokinetics of daidzein and genistein with the use of 13C-labeled tracers in premenopausal women. Am J Clin Nutr. 2003; 77: 411-419.

126. Wu J, Oka J, Ezaki J, et al. Possible role of equol status in the effects of isoflavone on bone and fat mass in postmenopausal Japanese women: a double-blind, randomized, controlled trial. Menopause. 2007; 14: 866-874.

127. Frankenfeld CL, Atkinson C, Thomas WK, et al. High concordance of daidzein-metabolizing phenotypes in individuals measured 1 to 3 years apart. Br J Nutr. 2005; 94: 873-876.

128. Franke AA, Lai JF, Halm BM, et al. Equol production changes over time in postmenopausal women. J Nutr Biochem. 2012; 23: 573-579.

129. Muthyala RS, Ju YH, Sheng S, et al. Equol a natural estrogenic metabolite from soy isoflavones: convenient preparation and resolution of R- and S-equols and their differing binding and biological activity through estrogen receptors alpha and beta. Bioorg Med Chem. 2004; 12: 1559-1567.

130. Lund TD, Munson DJ, Haldy ME, et al. Equol is a novel anti-androgen that inhibits prostate growth and hormone feedback. Biol Reprod. 2004; 70: 1188-1195.

131. Kelly GE, Joannou GE, Reeder AY, et al. The variable metabolic response to dietary isoflavones in humans. Proc Soc Exp Biol Med. 1995; 208: 40-43.

132. Favari C, Rinaldi de Alvarenga JF, Sánchez-Martínez L, et al. Factors driving the inter-individual variability in the metabolism and bioavailability of (poly)phenolic metabolites: A systematic review of human studies. Redox Biol. 2024; 71: 103095.

133. Aboushanab SA, Khedr SM, Gette IF, et al. Isoflavones derived from plant raw materials: bioavailability, anti-cancer, anti-aging potentials, and microbiome modulation. Crit Rev Food Sci Nutr. 2023; 63: 261-287.

134. Lu LJ, Anderson KE. Sex and long-term soy diets affect the metabolism and excretion of soy isoflavones in humans. Am J Clin Nutr. 1998; 68: 1500S-1504S.

135. Lu LJ, Grady JJ, Marshall MV, et al. Altered time course of urinary daidzein and genistein excretion during chronic soya diet in healthy male subjects. Nutr Cancer. 1995; 24: 311-323.

136. King RA, Bursill DB. Plasma and urinary kinetics of the isoflavones daidzein and genistein after a single soy meal in humans. Am J Clin Nutr. 1998; 67: 867-872.

137. Hargreaves DF, Potten CS, Harding C, et al. Two-Week Dietary Soy Supplementation Has an Estrogenic Effect on Normal Premenopausal Breast. J Clin Endocrinol Metab. 1999; 84: 4017-4024.

138. Boutas I, Kontogeorgi A, Dimitrakakis C, et al. Soy Isoflavones and Breast Cancer Risk: A Meta-analysis. In Vivo. 2022; 36: 556-562.

139. Morimoto Y, Maskarinec G, Park SY, et al. Dietary isoflavone intake is not statistically significantly associated with breast cancer risk in the Multiethnic Cohort. Br J Nutr. 2014; 112: 976-983.

140. Nishio K, Niwa Y, Toyoshima H, et al. Consumption of soy foods and the risk of breast cancer: findings from the Japan Collaborative Cohort (JACC) Study. Cancer Causes Control. 2007; 18: 801-808.

141. Wei Y, Lv J, Guo Y, et al. Soy intake and breast cancer risk: a prospective study of 300,000 Chinese women and a dose-response meta-analysis. Eur J Epidemiol. 2020; 35: 567-578.

142. Yamamoto S, Sobue T, Kobayashi M, et al. Soy, isoflavones, and breast cancer risk in Japan. J Natl Cancer Inst. 2003; 95: 906-913.

143. Baglia ML, Zheng W, Li H, et al. The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. Int J Cancer. 2016; 139: 742.

144. Messina M, Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid. 2006; 16: 249-258.

145. You L, Casanova M, Bartolucci EJ, et al. Combined effects of dietary phytoestrogen and synthetic endocrine-active compound on reproductive development in Sprague-Dawley rats: genistein and methoxychlor. Toxicol Sci. 2002; 66: 91-104.

146. Domínguez-López I, Yago-Aragón M, Salas-Huetos A, et al. Effects of Dietary Phytoestrogens on Hormones throughout a Human Lifespan: A Review. Nutrients. 2020; 12: 2456.

147. Li D, Dang DX, Xu S, et al. Soy isoflavones supplementation improves reproductive performance and serum antioxidant status of sows and the growth performance of their offspring. J Anim Physiol Anim Nutr. 2022; 106: 1268-1276.

148. Fasero M, Sanchez M, Baquedano L, et al. Management of menopausal hot flushes. Recommendations from the Spanish Menopause Society. Eur J Obstet Gynecol Reprod Biol X. 2025; 25: 100366.

149. Hooper L, Ryder JJ, Kurzer MS, et al. Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis. Hum Reprod Update. 2009; 15: 423-440.

150. Viscardi G, Back S, Ahmed A, et al. Effect of Soy Isoflavones on Measures of Estrogenicity: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Adv Nutr. 2024; 16: 100327.

151. Taku K, Melby MK, Kronenberg F, et al. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. Menopause. 2012; 19: 776-790.

152. Chen MN, Lin CC, Liu CF. Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. Climacteric. 2015; 18: 260-269.

153. Hooper L, Ryder JJ, Kurzer MS, et al. Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis. Hum Reprod Update. 2009; 15: 423-440.

154. Howes LG, Howes JB, Knight DC. Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. Maturitas. 2006; 55: 203-211.

155. Thomas A, Ismail R, Taylor-Swanson L, et al. Effects of Isoflavones and Amino Acid Therapies for Hot Flashes and Co-occurring Symptoms during the Menopausal Transition and Early Post Menopause: A Systematic Review. Maturitas. 2014; 78: 263-276.

156. De Franciscis P, Colacurci N, Riemma G, et al. A Nutraceutical Approach to Menopausal Complaints. Med Kaunas Lith. 2019; 55: 544.

157. Cancellieri F, De Leo V, Genazzani AD, et al. Efficacy on menopausal neurovegetative symptoms and some plasma lipids blood levels of an herbal product containing isoflavones and other plant extracts. Maturitas. 2007; 56: 249-256.

158. Cheng G, Wilczek B, Warner M, et al. Isoflavone treatment for acute menopausal symptoms. Menopause. 2007; 14: 468-473.

159. Welty FK, Lee KS, Lew NS, et al. The association between soy nut consumption and decreased menopausal symptoms. J Womens Health. 2007; 16: 361-369.

160. Kahleova H, Znayenko-Miller T, Holubkov R, et al. Isoflavones and changes in body weight and severe hot flashes in postmenopausal women: A secondary analysis of a randomized clinical trial. Maturitas. 2025; 200.

161. Mbu RE, Abauleth YR, Koffi A, et al. Effect of daily supplementation of soy isoflavones on hot flashes and night sweats in African menopausal women. Open J Obstet Gynecol. 2014; 4: 42-46.

162. Roberts H, Lethaby A. Phytoestrogens for menopausal vasomotor symptoms: a Cochrane review summary. Maturitas. 2014; 78: 79-81.

163. Li L, Lv Y, Xu L, et al. Quantitative efficacy of soy isoflavones on menopausal hot flashes. Br J Clin Pharmacol. 2015; 79: 593-604.

164. Hachul H, Brandão LC, D'Almeida V, et al. Isoflavones decrease insomnia in postmenopause. Menopause. 2011; 18: 178-184.

165. De Franciscis P, Conte A, Schiattarella A, et al. Non-hormonal Treatments For Menopausal Symptoms and Sleep Disturbances: A Comparison Between Purified Pollen Extracts and Soy Isoflavones. Curr Pharm Des. 2020; 26: 4509-4514.

166. Rattanatantikul T, Maiprasert M, Sugkraroek P, et al. Efficacy and Safety of Nutraceutical on Menopausal Symptoms in Post-Menopausal Women: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Diet Suppl. 2022; 19: 168-183.

167. Cui Y, Niu K, Huang C, et al. Relationship between daily isoflavone intake and sleep in Japanese adults: a cross-sectional study. Nutr J. 2015; 14: 127.

168. Cao Y, Taylor AW, Zhen S, et al. Soy Isoflavone Intake and Sleep Parameters over 5 Years among Chinese Adults: Longitudinal Analysis from the Jiangsu Nutrition Study. J Acad Nutr Diet. 2017; 117: 536-544.e2.

169. Cheng PF, Chen JJ, Zhou XY, et al. Do soy isoflavones improve cognitive function in postmenopausal women? A meta-analysis. Menopause. 2015; 22: 198-206.

170. Cui C, Birru RL, Snitz BE, et al. Effects of soy isoflavones on cognitive function: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2020; 78: 134-144.

171. Maki PM. Hormone therapy and cognitive function: is there a critical period for benefit? Neuroscience. 2006; 138: 1027-1030.

172. Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. JAMA. 2004; 292: 65-74.

173. File SE, Jarrett N, Fluck E, et al. Eating soya improves human memory. Psychopharmacology (Berl). 2001; 157: 430-436.

174. Duffy R, Wiseman H, File SE. Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. Pharmacol Biochem Behav. 2003; 75: 721-729.

175. Henry-Vitrac C, Berbille H, Merillon JM, et al. Soy isoflavones as potential inhibitors of Alzheimer ß-amyloid fibril aggregation in vitro. Food Res Int. 2010; 43: 2176-2178.

176. Bonet-Costa V, Herranz-Pérez V, Blanco-Gandía M, et al. Clearing Amyloid-β through PPARγ/ApoE Activation by Genistein is a Treatment of Experimental Alzheimer's Disease. J Alzheimers Dis. 2016; 51: 701-711.

177. Wang Y, Cai B, Shao J, et al. Genistein suppresses the mitochondrial apoptotic pathway in hippocampal neurons in rats with Alzheimer's disease. Neural Regen Res. 2016; 11: 1153-1158.

178. Mirahmadi SMS, Shahmohammadi A, Rousta AM, et al. Soy isoflavone genistein attenuates lipopolysaccharide-induced cognitive impairments in the rat via exerting anti-oxidative and anti-inflammatory effects. Cytokine. 2018; 104: 151-159.

179. Wilkins HM, Mahnken JD, Welch P, et al. A Mitochondrial Biomarker-Based Study of S-Equol in Alzheimer's Disease Subjects: Results of a Single-Arm, Pilot Trial. J Alzheimers Dis. 2017; 59: 291-300.

180. Setchell KDR, Brown NM, Lydeking-Olsen E. The Clinical Importance of the Metabolite Equol—A Clue to the Effectiveness of Soy and Its Isoflavones. J Nutr. 2002; 132: 3577-3584.

181. González M, Cabrera-Socorro A, Pérez-García CG, et al. Distribution patterns of estrogen receptor alpha and beta in the human cortex and hippocampus during development and adulthood. J Comp Neurol. 2007; 503: 790-802.

182. Morito K, Hirose T, Kinjo J, et al. Interaction of phytoestrogens with estrogen receptors alpha and beta. Biol Pharm Bull. 2001; 24: 351-356.

183. Messina M. Soy and Health Update: Evaluation of the Clinical and Epidemiologic Literature. Nutrients. 2016; 8: 754.

184. Messina M, Gleason C. Evaluation of the potential antidepressant effects of soybean isoflavones. Menopause. 2016; 23: 1348-1360.

185. Asuka Hirose, Masakazu Terauchi, Mihoko Akiyoshi, et al. Low-dose isoflavone aglycone alleviates psychological symptoms of menopause in Japanese women: a randomized, double-blind, placebo-controlled study. Arch Gynecol Obstet. 2016; 293: 609-615.

186. Estrella REN, Landa AI, Lafuente JV, et al. Effects of antidepressants and soybean association in depressive menopausal women. Acta Pol Pharm. 2014; 71: 323-327.

187. Atteritano M, Mazzaferro S, Bitto A, et al. Genistein effects on quality of life and depression symptoms in osteopenic postmenopausal women: a 2-year randomized, double-blind, controlled study. Osteoporos Int. 2014; 25: 1123-1129.

188. Wang H, Nie Y, Luo Y, et al. Daidzein alleviates chronic restraint stress-induced depression-like behavior by regulating neuroinflammation and synaptic plasticity via microbiota-gut-brain axis. Phytomedicine. 2025; 148: 157394.

189. McLaren S, Seidler K, Neil J. Investigating the Role of 17β-Estradiol on the Serotonergic System, Targeting Soy Isoflavones as a Strategy to Reduce Menopausal Depression: A Mechanistic Review. J Am Nutr Assoc. 2024; 43: 221-235.

190. Gebhart JB, Rickard DJ, Barrett TJ, et al. Expression of estrogen receptor isoforms α and β messenger RNA in vaginal tissue of premenopausal and postmenopausal women. Am J Obstet Gynecol. 2001; 185: 1325-1331.

191. Chen LR, Ko NY, Chen KH. Isoflavone Supplements for Menopausal Women: A Systematic Review. Nutrients. 2019; 11: 2649.

192. Waetjen LE, Leung K, Crawford SL, et al. The Relationship Between Dietary Phytoestrogens and Development of Urinary Incontinence in Midlife Women. Menopause. 2013; 20: 428-436.

193. Lima SMRR, Bernardo BFA, Yamada SS, et al. Effects of Glycine max (L.) Merr. soy isoflavone vaginal gel on epithelium morphology and estrogen receptor expression in postmenopausal women: a 12-week, randomized, double-blind, placebo-controlled trial. Maturitas. 2014; 78: 205-211.

194. Dizavandi FR, Ghazanfarpour M, Roozbeh N, et al. An overview of the phytoestrogen effect on vaginal health and dyspareunia in peri- and post-menopausal women. Post Reprod Health. 2019; 25: 11-20.

195. Ghazanfarpour M, Latifnejad Roudsari R, Treglia G, et al. Topical administration of isoflavones for treatment of vaginal symptoms in postmenopausal women: A systematic review of randomised controlled trials. J Obstet Gynaecol. 2015; 35: 783-787.

196. Yang IH, Lin IE, Chen TC, et al. Synthesis, characterization, and evaluation of BDDE crosslinked chitosan-TGA hydrogel encapsulated with genistein for vaginal atrophy. Carbohydr Polym. 2021; 260: 117832.

197. Lima SMRR, Honorato JV, Silva MALG. Glycine Max (L.) Merr isoflavone gel improves vaginal vascularization in postmenopausal women. Climacteric. 2020; 23: 505-510.

198. Carmignani LO, Pedro AO, Montemor EB, et al. Effects of a soy-based dietary supplement compared with low-dose hormone therapy on the urogenital system: a randomized, double-blind, controlled clinical trial. Menopause. 2015; 22: 741-749.

199. Maranon J. Clinical Study: Effect of Supplementation with High Genistein Soybean Isoflavones and Pumpkin Standardized Extract on Urinary Incontinence in Western Perimenopausal Women. J Gynecol Womens Health. 2017; 4.

200. https://www.tandfonline.com/doi/abs/10.3109/09513590.2016.1150635

201. Caruso S, Cianci S, Fava V, et al. Vaginal health of postmenopausal women on nutraceutical containing equol. Menopause. 2018; 25: 430-435

202. Hooshiar SH, Tobeiha M, Jafarnejad S. Soy Isoflavones and Bone Health: Focus on the RANKL/RANK/OPG Pathway. BioMed Res Int. 2022; 8862278

203. Hooshiar SH, Tobeiha M, Jafarnejad S. Soy Isoflavones and Bone Health: Focus on the RANKL/RANK/OPG Pathway. BioMed Res Int. 2022; 8862278.

204. Akhlaghi M, Ghasemi Nasab M, Riasatian M, et al. Soy isoflavones prevent bone resorption and loss, a systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2020; 60: 2327-2341

205. Ratchanon Inpan, Mingkwan Na Takuathung, Wannachai Sakuludomkan, et al. Isoflavone intervention and its impact on bone mineral density in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Osteoporos Int. 2024; 35: 413-430

206. Maranon J, de los Santos L, Lozano C, et al. The Phytochemical Society of North America. In: Solgen 40, the high Genistin/Genistein soy concentrate prevents bone mineral loss during menopause in a dose concentrate manner preventing the oxidized bone microenvironment. University of Illinois at Urbana-Champaign; 2015

207. Sathyapalan T, Aye M, Rigby AS, et al. Soy Reduces Bone Turnover Markers in Women During Early Menopause: A Randomized Controlled Trial. J Bone Miner Res. 2017; 32: 157-164

208. Walton C, Godsland IF, Proudler AJ, et al. The effects of the menopause on insulin sensitivity, secretion and elimination in non-obese, healthy women. Eur J Clin Invest. 1993; 23: 466-473

209. Llaneza P, González C, Fernández-Iñarrea J, et al. Soy isoflavones improve insulin sensitivity without changing serum leptin among postmenopausal women. Climacteric J Int Menopause Soc. 2012; 15: 611-620.

210. Villa P, Costantini B, Suriano R, et al. The differential effect of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women: relationship with the metabolic status. J Clin Endocrinol Metab. 2009; 94: 552-52.

211. Bakhtiary A, Yassin Z, Hanachi P, et al. Evaluation of the Oxidative Stress and Glycemic Control Status in Response to Soy in Older Women with the Metabolic Syndrome. 2011; 13

212. Llaneza P, Gonzalez C, Fernandez-Iñarrea J, et al. Soy isoflavones, Mediterranean diet, and physical exercise in postmenopausal women with insulin resistance. Menopause. 2010; 17: 372-378.

213. Han KK, Soares JM, Haidar MA, et al. Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. Obstet Gynecol. 2002; 99: 389-394.

214. Aubertin-Leheudre M, Lord C, Khalil A, et al. Effect of 6 months of exercise and isoflavone supplementation on clinical cardiovascular risk factors in obese postmenopausal women: a randomized, double-blind study. Menopause. 2007; 14: 624-629.

215. Ho SC, Chen Y ming, Ho SSS, et al. Soy isoflavone supplementation and fasting serum glucose and lipid profile among postmenopausal Chinese women: A double-blind, randomized, placebo-controlled trial. Menopause. 2007; 14: 905.

216. Jayagopal V, Albertazzi P, Kilpatrick ES, et al. Beneficial Effects of Soy Phytoestrogen Intake in Postmenopausal Women With Type 2 Diabetes. Diabetes Care. 2002; 25: 1709-1714.

217. Jayagopal V, Albertazzi P, Kilpatrick ES, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care. 2002; 25: 1709-1714.

218. Liu Z min, Chen Y ming, Ho SC, et al. Effects of soy protein and isoflavones on glycemic control and insulin sensitivity: a 6-mo double-blind, randomized, placebo-controlled trial in postmenopausal Chinese women with prediabetes or untreated early diabetes1234. Am J Clin Nutr. 2010; 91: 1394-1401.

219. Liu Z m, Ho SC, Chen Ym, et al. A mild favorable effect of soy protein with isoflavones on body composition-a 6-month double-blind randomized placebo-controlled trial among Chinese postmenopausal women. Int J Obes. 2010; 34: 309-318.

220. Imai S. Soybean and Processed Soy Foods Ingredients, and Their Role in Cardiometabolic Risk Prevention. Recent Pat Food Nutr Agric. 2015; 7: 75-82.

221. Yamagata K. Soy Isoflavones Inhibit Endothelial Cell Dysfunction and Prevent Cardiovascular Disease. J Cardiovasc Pharmacol. 2019; 74: 201.

222. Reverri EJ, LaSalle CD, Franke AA, et al. Soy provides modest benefits on endothelial function without affecting inflammatory biomarkers in adults at cardiometabolic risk. Mol Nutr Food Res. 2015; 59: 323-333.

223. Yan Tang, Shuangyue Li, Ping Zhang, et al. Soy Isoflavone Protects Myocardial Ischemia/Reperfusion Injury through Increasing Endothelial Nitric Oxide Synthase and Decreasing Oxidative Stress in Ovariectomized Rats. Oxid Med Cell Longev. 2016; 5057405.

224. Ohkura Y, Obayashi S, Yamada K, et al. S-equol Partially Restored Endothelial Nitric Oxide Production in Isoflavone-deficient Ovariectomized Rats. J Cardiovasc Pharmacol. 2015; 65: 500-507.

225. Xu JW, Ikeda K, Yamori Y. Genistein inhibits expressions of NADPH oxidase p22phox and angiotensin II type 1 receptor in aortic endothelial cells from stroke-prone spontaneously hypertensive rats. Hypertens Res. 2004; 27: 675-683.

226. Li Y, Zhang H. Soybean isoflavones ameliorate ischemic cardiomyopathy by activating Nrf2-mediated antioxidant responses. Food Funct. 2017; 8: 2935-2944.

227. Zhang H, Zhao Z, Pang X, et al. Genistein Protects Against Ox-LDL-Induced Inflammation Through MicroRNA-155/SOCS1-Mediated Repression of NF-κB Signaling Pathway in HUVECs. Inflammation. 2017; 40: 1450-1459.

228. Hall WL, Formanuik NL, Harnpanich D, et al. A meal enriched with soy isoflavones increases nitric oxide-mediated vasodilation in healthy postmenopausal women. J Nutr. 2008; 138: 1288-1292.

229. Hall WL, Vafeiadou K, Hallund J, et al. Soy-isoflavone-enriched foods and inflammatory biomarkers of cardiovascular disease risk in postmenopausal women: interactions with genotype and equol production. Am J Clin Nutr. 2005; 82: 1260-1268.

230. Wójciak M, Drozdowski P, Skalska-Kamińska A, et al. Protective, Anti-Inflammatory, and Anti-Aging Effects of Soy Isoflavones on Skin Cells: An Overview of In Vitro and In Vivo Studies. Mol Basel Switz. 2024; 29: 5790.

231. Magdalena Wójciak, Piotr Drozdowski, Agnieszka Skalska-Kamińska, et al. Protective, Anti-Inflammatory, and Anti-Aging Effects of Soy Isoflavones on Skin Cells: An Overview of In Vitro and In Vivo Studies. Molecules. 2024; 29: 5790.

232. Chiang HS, Wu WB, Fang JY, et al. UVB-Protective Effects of Isoflavone Extracts from Soybean Cake in Human Keratinocytes. Int J Mol Sci. 2007; 8: 651-661.

233. Li J, Li J, Yue Y, et al. Genistein suppresses tumor necrosis factor α-induced inflammation via modulating reactive oxygen species/Akt/nuclear factor κB and adenosine monophosphate-activated protein kinase signal pathways in human synoviocyte MH7A cells. Drug Des Devel Ther. 2014; 8: 315-323.

234. Wang A, Wei J, Lu C, et al. Genistein suppresses psoriasis-related inflammation through a STAT3-NF-κB-dependent mechanism in keratinocytes. Int Immunopharmacol. 2019; 69: 270-278.

235. Li HJ, Wu NL, Lee GA, et al. The Therapeutic Potential and Molecular Mechanism of Isoflavone Extract against Psoriasis. Sci Rep. 2018; 8: 6335.

236. Chiu TM, Huang CC, Lin TJ, et al. In vitro and in vivo anti-photoaging effects of an isoflavone extract from soybean cake. J Ethnopharmacol. 2009; 126: 108-113.

237. Savoia P, Raina G, Camillo L, et al. Anti-oxidative effects of 17 β-estradiol and genistein in human skin fibroblasts and keratinocytes. J Dermatol Sci. 2018; 92: 62-77.

238. Irrera N, Pizzino G, D'Anna R, et al. Dietary Management of Skin Health: The Role of Genistein. Nutrients. 2017; 9: 622.

239. Emmerson E, Campbell L, Ashcroft GS, et al. The phytoestrogen genistein promotes wound healing by multiple independent mechanisms. Mol Cell Endocrinol. 2010; 321: 184-193.

240. Izumi T, Saito M, Obata A, et al. Oral intake of soy isoflavone aglycone improves the aged skin of adult women. J Nutr Sci Vitaminol (Tokyo). 2007; 53: 57-62.

241. Skovgaard GRL, Jensen AS, Sigler ML. Effect of a novel dietary supplement on skin aging in post-menopausal women. Eur J Clin Nutr. 2006; 60: 1201-1206.

242. Yamanaka K, Xu B, Suganuma I, et al. Dienogest inhibits aromatase and cyclooxygenase-2 expression and

prostaglandin E_2 production in human endometriotic stromal cells in spheroid culture. Fertil Steril. 2012; 97: 477-482.

243. Sabetian S, Dialameh PA, Tanideh N, et al. Potential therapeutic properties of broccoli extract and soy isoflavones on improvement endometriosis and involved oxidative parameters. Horm Mol Biol Clin Investig. 2024; 45: 131-137.

244. Sabetian S, Namavar Jahromi B, Vakili S, et al. Potential Effects of Soy Isoflavones and Broccoli Extract on Oxidative Stress, Autophagy, and Apoptosis Gene Markers in Endometriosis. Int J Fertil Steril. 2024; 18: 384-390.

245. Takaoka O, Mori T, Ito F, et al. Daidzein-rich isoflavone aglycones inhibit cell growth and inflammation in endometriosis. J Steroid Biochem Mol Biol. 2018; 181: 125-132.

246. Yavuz E, Oktem M, Esinler I, et al. Genistein causes regression of endometriotic implants in the rat model. Fertil Steril. 2007; 88: 1129-1134.

247. Vanegas JC, Afeiche MC, Gaskins AJ, et al. Soy food intake and treatment outcomes of women undergoing assisted reproductive technology. Fertil Steril. 2015; 103: 749-755.e2.

248. Diamanti-Kandarakis E, Dunaif A. Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications. Endocr Rev. 2012; 33: 981-1030.

249. Jamilian M, Asemi Z. The Effects of Soy Isoflavones on Metabolic Status of Patients With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2016; 101: 3386-3394.

250. Romualdi D, Costantini B, Campagna G, et al. Is there a role for soy isoflavones in the therapeutic approach to polycystic ovary syndrome? Results from a pilot study. Fertil Steril. 2008; 90: 1826-1833.

251. Ma X, Li X, Ma L, et al. Soy isoflavones alleviate polycystic ovary syndrome in rats by regulating NF- κB signaling pathway. Bioengineered. 2021; 12: 7204-7212.

252. Weickert MO, Reimann M, Otto B, et al. Soy isoflavones increase preprandial peptide YY (PYY), but have no effect on ghrelin and body weight in healthy postmenopausal women. J Negat Results Biomed. 2006; 5: 11.

253. Fuchs D, Vafeiadou K, Hall WL, et al. Proteomic biomarkers of peripheral blood mononuclear cells obtained from postmenopausal women undergoing an intervention with soy isoflavones. Am J Clin Nutr. 2007; 86: 1369-1375.

254. Santoro N. Perimenopause: From Research to Practice. J Womens Health. 2002; 25: 332-339.

255. https://www.who.int/news-room/fact-sheets/detail/menopause

256. Kirchengast S. Menopause in a globalized world - A systematic literature review focussing on the challenge of health problems associated with menopausal transition among women with a migration background. Maturitas. 2024.