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Review Article

Soy isoflavones in postmenopausal women: a review of current evidence

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Abstract: In human history, soy has been a predominant dietary content consumed for centuries. Isoflavones from soy predominantly Genistein and daidzein are non-steroidal compounds structurally similar to estradiol-17β that act as a selective estrogen receptor modulator. Besides having estrogenic activity, isoflavones have non-hormonal effects such as inhibition of aromatase activity, downregulation of protein tyrosine kinases, and modulation of gene expression. In postmenopausal women, current meta-analytic evidence indicates that soy isoflavones are effective in improving bone mineral density and reducing the symptoms of menopause predominantly hot flashes, they improve oxidative stress, glycemia, and lipid abnormalities. These effects are essential in postmenopausal women in terms of their cardiovascular risk. In addition, soy isoflavones are shown to reduce the risk of breast cancer and its recurrence. This indicates potential benefits in other hormone-dependent malignancies. In terms of safety, no long-term human studies are available and short-term evidence indicates they have an acceptable safety profile as that of a placebo. Though some evidence indicates soy isoflavones are as effective as hormone replacement therapy, they may not be considered an alternative. In conclusion, the current evidence indicates that in postmenopausal women soy isoflavones improve bone mass and provide effective relief of hot flashes. Antioxidant, lipid-lowering, and breast cancer-protective effects can provide additional benefits in this high-risk women population.

Keywords: Phytoestrogens, soy isoflavones, genistein, daidzein, postmenopausal women, osteoporosis

Introduction

Soy foods, the rich source of isoflavones, have been the topic of a vast amount of clinical research for more than two decades. Isoflavones (flavones and coumestans) are the phytoestrogens present abundantly in the human diet, soy being the richest source [1]. A remarkable increase in the soy consumption occurred in the last decade of the 20th century. This is probably due to the belief that soy foods offer various health benefits besides being rich in proteins and low in saturated fats. Soy isoflavone is a non-steroidal compound structurally similar to oestradiol-17β that acts as a selective estrogen receptor modulator [2]. As a result of this, there have been numerous investigations to study their clinical importance in low estrogen states such as menopause, estrogen-dependent breast cancer, cystic ovaries, endometriosis, etc. This area of research gained immense popularity to seek natural alternatives to conventional hormonal therapy with the motive to avoid its adverse effects such as thromboembolism, uterine hyperplasia, uterine cancer, increased risk of breast, ovarian, and endometrial cancers, coronary heart disease, and stroke [3]. These non-steroidal isophenolic structures possess anti-oxidant and anti-inflammatory properties, as well as inhibit cancer cell proliferation. These properties have been explored in the prevention of cardiovascular diseases and cancer [4]. Given the abundance of emerging evidence, it is essential to update on current evidence. Hence in this review, we present an overview of the history, development, and potential applications of soy isoflavones in the postmenopausal women and related conditions.

History and development of soy isoflavones

Soyfoods, originally derived from soybeans are a rich source of high-quality proteins and low in saturated fats. They have been consumed by the Asian populations for centuries as. The biological effects of isoflavones first came to the light in clinical research in the 1940s because of breeding problems experienced by female sheep grazing on a type of clover that was rich in isoflavones [5-7]. Later in the 1960s, the soybean constituents were firmly established as phytoestrogens due to their relative binding affinities for estrogen receptors (ER) [8, 9]. However, it was only after the 1990s, that significant attention was drawn by soyfoods due to their potential for disease prevention. Subsequently, after the 1990s, isoflavones and soyfoods were investigated for their ability to alleviate hot flashes and inhibit bone loss in postmenopausal women. From 1995 onwards, soy protein was also investigated worldwide for its ability to lower cholesterol levels. Around the same time, research also began to study isoflavones as the potential alternatives to conventional hormone replacement therapy (HRT) [1]. In 2002, it was suggested that soy intake offers more benefits in individuals harboring intestinal bacteria that can convert soy isoflavone daidzein into the isoflavone equol [1].

In soybeans, genistein and daidzein are the predominant forms of isoflavones. Conjugated with sugars, they form malonylglucosides, acetylglucosides, and glycosides, that lead to differing compositions among foods. Most soy food products contain conjugated forms of isoflavones. Food processing has a significant effect on isoflavone content and composition. Soy foods prepared from processed soy may contain nearly 1.0-1.5 mg of isoflavones per gram of protein. Consumption of the whole soyfoods may have higher isoflavone amounts (3.0-3.5 mg/g) [10].

Mechanistic overview of soy-isoflavones

Physiologically relevant amounts of isoflavones are present uniquely in soybean-derived products. The soybean constitutes of 12 different isoflavone isomers. Genistein and daidzein account for 90% of the total soybean isoflavone content, with genistein accounting for 60%. Genistein has been widely studied for the beneficial effects of isoflavones [11].

Isoflavones activate both estrogens α (ERα) and estrogen β (ERβ) receptors by competitive binding. However, they appear to be tissue-selective because of their preferential binding to and activation of ERβ in comparison to ERα. The similarities of genistein and daidzein with estrogen at the molecular level allow them to mimic the actions of estrogen and also act as antagonists of estrogen at times [12]. Isoflavones have also been known to affect the synthesis as well as the metabolism of endogenous hormones.

The key elements that contribute to the estrogen-like effects of isoflavones are low molecular weight, structural ring similar to estrogen, and similar distance between two hydroxyl groups at the nucleus of isoflavones as that of estrogen, and optimal hydroxylation process. Isoflavones also modulate the concentration of endogenous estrogen and affect the synthesis of sex hormones by binding or stimulating the synthesis of sex hormone-binding globulin. Isoflavones are present in soyfoods as conjugates as well as aglycones and are separated from other components of foods by hydrolytic enzymes of gut bacteria. Daidzein and genistein are further metabolized to equol and p-ethylphenol respectively [12].

The main molecular targets of genistein are estrogen receptors, tyrosine kinases, and topoisomerase-II thereby causing inhibition of DNA topoisomerase II activity, regulation of cell cycle checkpoints, and antiangiogenic and antioxidant activity. Furthermore, it has also been found that isoflavones possess several non-hormonal effects. These include inhibition of aromatase activity, downregulation of protein tyrosine kinases, and modulation of gene expression. However, the exact relevance of these actions remains unclear. **Figure 1** summarizes the important mechanisms of soy isoflavones. **Table 1** provides a mechanistic overview of isoflavones in different clinical conditions [10].

Systemic effects of soy isoflavones in postmenopausal women

Vasomotor symptoms such as hot flashes (HFs)

Epidemiology and etiopathogenesis in postmenopausal women: Hot flashes in postmenopausal women are characterized by a transient

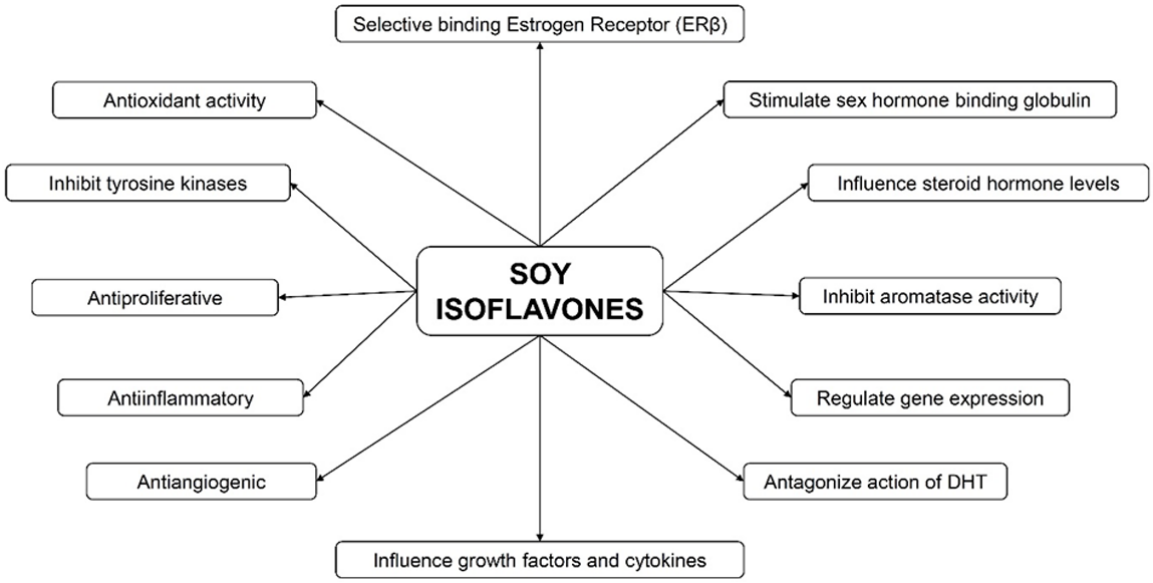

Figure 1. Important mechanisms of soy isoflavones.

Table 1. Mechanistic effects of isoflavones in different clinical conditions

Disorder/symptoms	Mechanism of action
Vasomotor symptoms of menopause such as hot flashes, night sweats	Bind to the estrogen receptors and activate endothelial nitric oxide synthase (eNOS) transcription, causing eNOS synthesis and nitric oxide production, which allows cutaneous heat dissipation by causing vasodilatation.
Osteoporosis	Increased bone formation by stimulation of osteoblastic activity via activation of estrogen receptors and promotion of insulin-like growth factor-I (IGF-I) production and reduction in the rate of bone resorption.
Cardiovascular effects	Reduction in LDL, triglycerides levels, reducing the risk and incidence of atherosclerosis and myocardial infarction.
Cancer	Inhibition of DNA topoisomerase II activity, regulation of cell cycle checkpoints, antiangiogenic and antioxidant activity, modulation of gene expression.
Diabetes mellitus	Improvement in the glycemic metabolism, reducing the insulin resistance.
Anti-oxidant effect	Improving 5HT metabolism, stabilization of MAO activity.

sensation of heat, sweating, flushing, and anxiety lasting for 1-5 minutes. HFs constitute one of the most common symptoms in postmenopausal women affecting 85% of them. The mean duration of HFs in postmenopausal women varies from 4 years to 8 years [13]. Nearly 25% of women continue to suffer from HFs after five years of menopause while one-third of them continue to experience them even after 10 years of attaining menopause [14]. Worldwide prevalence of HFs indicates the highest frequency in Turkish women (97%), followed by Australian women (83%), European (76%), North American (58.8%), and South American (47%) while 45% of Asian women suffer from HFs [15]. The underlying cause of HFs in postmenopausal women is an abnormality of hypothalamic thermoregulatory mechanisms; one of the contributing factors to this is an estrogen deficiency. However, the exact role of estrogen deficiency remains to be elucidated, as studies have not shown any correlation between the serum estrogen levels and frequency as well as the severity of HFs. Moreover, a potential role of pituitary hormones, gonadotropins, anti-Mullerian hormones, serotonin, and endorphin levels have also been suggested as possible causative factors of HFs in postmenopausal women [13].

Mechanism of soy isoflavones in reducing hot flashes: Soy isoflavones act by competitively inhibiting the enzyme 17-hydroxysteroid oxidoreductase (type 1). This enzyme converts the

relatively inactive estrone to the much more potent estradiol. Soy isoflavones bind to the estrogen receptors and activate endothelial nitric oxide synthase (eNOS) transcription, leading to eNOS synthesis and nitric oxide (NO) production. The increased production of NO allows cutaneous heat dissipation by causing vasodilatation. Through this mechanism, isoflavones help to alleviate vasomotor symptoms [16].

A large area of research is devoted to determining the efficacy of soy isoflavones in alleviating hot flashes in postmenopausal women. We here briefly discuss the evidence of soy isoflavones in HF. Ahsan M et al. (2017) [17] in a prospective, observational study evaluated the effect of 100 mg soy supplementation on the menopausal rating scale in perimenopausal and postmenopausal women after 12 weeks of treatment. The study showed significant improvements in total scores in both groups with the most remarkable improvements seen in the scores of hot flashes. Jacobs et al. (2009) [18] in a systematic review of studies including 17 randomized, placebo-controlled trials that investigated the effect of soy isoflavones on hot flashes. They reported an inconsistent reduction in hot flashes. Meta-analysis was not done in this review as the studies were highly heterogeneous and qualitatively deficient. However, in 2010, Bolanos et al. [19] in their meta-analysis included placebo-controlled randomized controlled trials (RCTs) and reported an effective reduction in vasomotor symptoms with soy isoflavones therapy compared to placebo. A Cochrane systematic review by Lethaby et al. (2013) [20] observed a significant reduction in the frequency of hot flashes from the use of soy extracts as compared with a placebo. Taku et al. (2012) [21] in a systematic review of 19 trials evaluating the efficacy of extract or synthesized soybean isoflavones reported that soy isoflavone supplements significantly reduced the frequency and severity of hot flashes. In a systematic review of 17 randomized controlled trials by Thomas et al. (2014) [22], it was reported that isoflavone significantly improved hot flashes and co-occurring symptoms in the perimenopausal as well as postmenopausal period.

In the meta-analysis by Chen et al. (2015) [23] of 15 studies evaluating the efficacy of phytoestrogens in reducing hot flashes, authors reported outcomes only regarding isoflavones and not the other phytoestrogens. The follow-up period was 3 to 12 months. Out of 15 studies, ten reported a significant reduction in the frequency of hot flashes in the isoflavone group when compared with the placebo group. No significant differences were observed in terms of side effects between the isoflavone and placebo groups. Similarly, Li et al. (2015) [24] in a meta-analysis that included 16 studies reported a slow and slight efficacy of soy isoflavones in alleviating menopausal hot flashes. The duration of studies included ranged from four weeks to two years, with a median of 12 weeks. The maximum dose of isoflavones in these studies was 200 mg/day. Despite the positive effect of isoflavones, the authors emphasized that the effects took a long time to appear. A study reported that isoflavones required 13.4 weeks to develop a proven efficacy on hot flashes, in contrast to estradiol which took 3.09 weeks. It suggests that soy isoflavone treatment for 12 weeks or more may be necessary to exert a beneficial effect. Crisafulli et al. (2004) [25] studied the effect of genistein, menopausal hormone therapy (MHT), and placebo on hot flashes. After 12 weeks of treatment, there was a 22% daily reduction in hot flashes in the genistein group and a 53% reduction in hot flashes in the MHT group when compared with placebo. Another study by Tranche S et al. (2016) [26] involved 147 women in the peri- and post-menopausal phase. Soy milk (50 mg isoflavones) for 12 weeks resulted in a significant reduction in vasomotor symptoms along with the improved quality of life [26].

Besides these discussed studies and reviews, a few more meta-analyses [27-31] studying the role of soy isoflavones in reducing menopausal symptoms have been summarized in **Table 2**. This strong body of evidence suggests soy isoflavones have a significant effect on HFs in postmenopausal women. Thus, soy isoflavones can be considered either as a first choice for alleviating the hot flashes or as a safe alternative to MHT and other drugs in postmenopausal women.

Effect on bone mineral density (effect on osteoporosis)

Epidemiology and etiopathogenesis in postmenopausal women: Globally, postmenopausal osteoporosis has been identified as a perva-

Table 2. Recent evidence with isoflavones in the treatment of hot flashes

Authors	Type of study	Number of participants	Dose and type of isoflavone	Results
Daily et al. (2019) [27]	Metanalysis of 5 RCTs	728 postmenopausal women	Soy isoflavones 33-200 mg/day and equol 10 mg/day	Soy isoflavones and equol cause a significant reduction in menopausal symptoms than placebo
Sarri et al. (2017) [28]	Systematic review and meta-analysis of 47 RCTs	8326 menopausal women	Isoflavones and black cohosh compared with placebo and oral/transdermal hormonal therapy and SSRIs/SNRIs	Isoflavones and black cohosh were effective when compared to placebo but provided no beneficial effect when compared with oral/transdermal therapy
Li et al. (2016) [29]	Metaanalysis of 39 RCTs	A median of 200 women (age not mentioned) per RCT	Soy isoflavones 30-200 mg/day studies against SSRIs/SNRIs, clonidine, gabapentin (mean study duration 12 weeks)	Mild and slow relief of hot flashes in women when compared with other drugs
Franco et al. (2016) [30]	Systematic review and meta-analysis of 62 studies, 36 of which involved phytoestrogens	3762 menopausal women (median age: 53.2 years)	Soy isoflavones, red clover isoflavones and other phytoestrogens (follow-up: 12 weeks)	Soy isoflavones were associated with significant reduction in daily hot flashes and vaginal dryness score
Nelson et al. (2006) [31]	Systematic review and meta-analysis	17 RCTs	30-135 mg/day isoflavones (aglycone equivalents)	Decrease in number of daily hot flashes and reduced severity of hot flashes

sive health problem in women. Hip fracture, the most disabling consequence of osteoporosis, is associated with a death rate of 10-24% within a year of the fracture [32]. In Indian women, an average age of natural menopause is 46.7 years whereas the life expectancy is 70.3 years. It Low bone mass affected more than 40% of women from the age of 40 years and increases to more than 80% by the age of 65 years [33]. Postmenopausal women are susceptible to primary osteoporosis since osteoporosis is closely related to estrogen deficiency. During the menopausal transition period, the drop of estrogen leads to increased bone resorption than bone formation, resulting in osteoporosis. The major health consequence of osteoporosis is the occurrence of osteoporotic fractures.

Mechanism of soy isoflavones: Soy isoflavones along with other phytoestrogens have been studied extensively for their beneficial effect in maintaining good bone health in terms of bone mineral density, bone mass, and bone structure in postmenopausal women. The mechanism of action of isoflavones in postmenopausal osteoporosis has not been completely understood. However, it has been proposed that they reduce the rate of bone resorption as well as increase the rate of bone formation. The increased bone formation is probably due to the stimulation of osteoblastic activity mainly via activation of estrogen receptors and promotion of insulin-like growth factor-I (IGF-I) production [34]. Various mechanisms through which soy isoflavones impact bone health are summarized below [35].

• Antiresorptive and bone-sparing agent in preventing osteoporosis - directly regulating gene expression of target ERs in human osteoblastic cells.

• Reduces TNF-α-induced interleukin-6 and prostaglandin E2 levels - promotes the function of osteoblasts.

• Antioxidant effects, induction of cell differentiation and apoptosis, and inhibition of tyrosine kinase and topoisomerases-contribute to the prevention of bone loss.

• Regulation of bone-related genes participating in bone remodeling.

• Promotes calcium absorption.

Clinical studies with effect on postmenopausal osteoporosis: A vast amount of research has been conducted to assess the impact of soy isoflavones on bone health. We discuss the meta-analytic evidence about the same.

Abdi et al. (2016) [36] in a systematic review of 23 RCTs concluded that isoflavones exerted a little influence over bone mineral density during menopause. However, not all the studies included in this review observed the same effect. These contradictory findings could be due to the variable duration of the therapy, the type of isoflavone used, and its dose. The authors also reported that, of the various isoflavones that are available, genistein alone or in combination with daidzein, improved bone density and bone turnover more effectively. Sansai et al. (2020)

Table 3. Meta-analyses assessing the effect of soy isoflavones on bone health

Authors	Number of RCTs	Number of participants	Dose and type of isoflavone	Results
Taku et al. (Lumbar spine BMD) [41]	11 RCTs	1240 menopausal and postmenopausal women	Average 82 (47-150) mg soy isoflavones (aglycone equivalent) for 6-12 months	Significant improvement in lumbar spine BMD as compared to control group (P<0.001)
Taku et al. (femoral neck BMD) [41]	7 RCTs	868 postmenopausal women	Average 82 (47-150) mg soy isoflavones (aglycone equivalent) for 6-12 months	Significant improvement in BMD (P<0.001)
Taku et al. (Total Hip BMD) [41]	5 RCTs	420 postmenopausal women	Average 82 (47-150) mg soy isoflavones (aglycone equivalent) for 6-12 months	No significant improvement in BMD compared to control (P≥0.1)
Liu et al. (lumbar spine BMD) [42]	10 RCTs	896 (pre- and post-menopausal women)	40-200 mg/day soy isoflavone vs control	Significant improvement in lumbar spine BMD compared to control group (P<0.001)
Liu et al. (Total hip BMD) [42]	5 RCTs	494 postmenopausal women	40-99 mg/day soy isoflavone vs control	No significant improvement in BMD compared to control (P=0.92)
Liu et al. (femoral neck BMD) [42]	6 RCTs	536 pre- and post-menopausal women	40-200 mg/day isoflavone vs control	Significant improvement in BMD compared to control (P=0.003)
Ma et al. (lumbar spine BMD) [43]	10 RCTs	612 peri- and post-menopausal women	4.4-150 mg/day soy isoflavone vs control for 3-24 months	Significant improvement in BMD (P=0.01)

[37] in a meta-analysis of 63 controlled trials, including 6427 postmenopausal women concluded that isoflavones improve bone density at the lumbar spine, femoral neck, and the distal radius in postmenopausal women. These beneficial results were associated with 54 mg/day of genistein and 600 mg/day of synthetic isoflavone ipriflavone. Lambert et al. (2017) [38] in a meta-analysis of 26 trials involving 2652 postmenopausal women supported that the isoflavones moderately attenuate bone resorption in women with low estrogen levels, mainly at the level of the lumbar spine and the femoral neck. Akhlaghi et al. (2020) [39], in another meta-analysis, included 52 controlled trials with 5313 postmenopausal women, reported that soy isoflavones have beneficial effects on bone mineral density in the femur neck, lumbar spine, and hip, regardless of body weight or ethnicity.

Tit et al. (2018) [40] evaluated the efficacy of soy isoflavones in the prevention of postmenopausal osteoporosis as compared to low dose MHT They assessed the BMD and urinary deoxypyridinoline (D-pyr) levels in 325 postmenopausal women over twelve months. Compared to the control group, both therapies exerted beneficial effects on bone metabolism leading to a significant decrease in bone resorption. However, there was no significant difference between the efficacy of MHT and soy isoflavones in terms of the effects on BMD and bone resorption.

Few more RCTs and meta-analyses studying the role of soy isoflavones in improving bone health at various sites have been discussed in **Table 3**. Current scientific evidence supports that soy isoflavones are beneficial in improving bone health. Also, they help in the prevention and treatment of osteoporosis in postmenopausal women with a predominant effect on the lumbar spine followed by the femoral neck. Further large-scale RCTs are warranted to understand the site-specific effect (axial and appendicular skeleton) of soy isoflavones.

Effect on female urogenital tract

Evidence indicates that phytoestrogens may exert an effect on the human menstrual cycle. In premenopausal women, soy isoflavones may lead to unchanged follicular phase length, midcycle luteinizing hormone (LH), and follicle-stimulating hormone (FSH); increased, unchanged, or decreased estradiol; decreased dehydroepiandrosterone sulfate, and decreased or unchanged luteal phase progesterone. The effect on endometrial thickness (ET) has been variable. A metanalysis of 23 RCTs found that a daily dose of >54 mg could decrease the ET by 0.26 mm. It was affected differently in different populations with a significant decrease observed in North American studies (0.23 mm), but a non-significant increase in Asian studies (0.23 mm) [44]. Another meta-analysis of 25 studies identified that compared to the control arm, soy isoflavones improve the vaginal sym-

ptoms in postmenopausal women. However, they observed vast heterogeneity in the studies [45]. In assessing the effects of phytoestrogens on sexual function in menopausal women, Najafi and Ghazanfarpour in their meta-analysis reported that maritime pine bark, *T. foenum-graecum* L., and *F. vulgare* can improve the sexual dysfunctions whereas other phytoestrogens such as soy, red clover, genistein, and flaxseed showed no promising effects on sexual dysfunction [46].

Pelvic floor disorders such as urinary incontinence (UI), fecal incontinence, and pelvic organ prolapse are not uncommon in women. Evidence indicates phytoestrogens can improve UI and pelvic organ prolapse [47]. With soy isoflavones, some studies indicate their potential benefit in conditions such as UI [48, 49], while others find no benefit [50]. These differences call for further evaluation in a large RCT to establish the effects of soy isoflavones in pelvic floor disorders, especially in postmenopausal women.

Other endocrine effects

Type 2 diabetes and metabolic syndrome: Isoflavones' action on Peroxisome proliferator-activated receptors (PPARs), can be helpful in diabetes. Isoflavones such as genistein, daidzein, formononetin, and biochanin A activate PPAR-gamma which regulates insulin sensitivity and blood glucose homeostasis. By their antioxidant effects, isoflavones may activate the adenosine monophosphate-activated protein kinase (AMPK) thereby modulating the energy metabolism. Multiple other mechanisms may also contribute to the regulation of glucose homeostasis which has been reviewed elsewhere [51]. Inhibition of glucosidase has also been suggested to be a possible mechanism [52]. However, the exact mechanisms that contribute to beneficial effects in patients with diabetes remain unclear [53].

Multiple clinical studies have evaluated soy isoflavones in type 2 diabetes. Among postmenopausal women with type 2 diabetes, Jayagopol et al. [54] conducted a double-blind, placebo-controlled cross-over study. Short-term supplementation of soy protein (30 g/day) reduced insulin resistance and improved glycemic control. A pooled analysis from three United States cohort studies identified that consumption of low- to moderate-amounts of soy foods modestly lowered the risk of type 2 diabetes in both men and women [55]. In a randomized cross-over trial in 42 postmenopausal women with metabolic syndrome, short-term soy-nut consumption improved glycemic control and lipid profiles [56]. However, some studies did not identify any benefits on glycemic profiles in postmenopausal women [57]. It necessitates a large RCT to confirm potential glycemic benefits with soy isoflavones.

Effect on thyroid function: There were concerns raised that the use of soy isoflavones may affect thyroid function and reduce the absorption of synthetic thyroid hormone supplements. However, evidence from the review of 14 trials [58] and a meta-analysis of 18 studies [59] reported no effect of soy supplementation on thyroid hormones.

Soy isoflavones and cardiovascular effects

Estrogen deficiency leads to vasoconstriction in the wall of arteries and an accelerated increase of low-density lipoproteins. These changes contribute to the increased risk of cardiovascular diseases, disturbed sleep patterns, mood swings, vasomotor symptoms, and generally lower quality of life. Soy isoflavones have gained considerable attention for their potential role in improving various risk factors for cardiovascular disease [60].

Clinical studies with effects on specific CV risk parameters: Multiple studies and metanalyses have been conducted to assess the effect on CV risk parameters. Perna et al. (2016) [61] in a systematic review involving 1307 menopausal women suggested that daily consumption of 20 mg to 100 mg/day of soy isoflavones, reduces the plasma concentrations of total cholesterol and triglycerides, along with the reduction in markers of oxidative stress such as nitric oxide and malonaldehyde thereby reducing the cardiovascular risk. Yan et al. (2017) [62] in their meta-analysis of 17 prospective as well as case-control studies involving 508,841 participants and 17,269 CV disease events, reported that the consumption of soy foods, but not that of isoflavones, was associated with a lower risk of coronary heart disease and stroke. This finding suggests that other constituents, such as fiber in soy foods, may contribute to providing beneficial effects. Another meta-analysis by

Table 4. Evidence on the effect of soy isoflavones on cardiovascular risk parameters

Authors	Type of study	Number of participants	Dose and type of isoflavone	Results
Rienks et al. (2017) [66]	Meta-analysis of three prospective studies	68,748 (Age: 40-70 years)	Not mentioned Follow up for 10 years	Isoflavones decreased the risk of coronary heart disease and acute coronary syndrome
Kim et al. (2017) [67]	Meta-analysis of 15 prospective studies	-	-	High flavonoids intake reduced the risk of CVD and all-cause mortality
Nachvak S et al. (2019) [68]	Meta-analysis of 23 prospective studies	3,30,826	Not mentioned	Inverse association between soy consumption and CV disorders. Decreased risk of mortality from ischemic heart diseases
Chalvon-Demersay et al. (2017) [69]	Meta-analysis of 17 RCTs	337 healthy, diabetic or hypercholesterolemic individuals (Age: 18-74 years) 406 healthy, postmenopausal or obese participants (Age: 50-79 years)	Isoflavones 3 to 102 mg/day Intervention period: 4-208 weeks Isoflavones 60 to 135 mg/day Intervention period: 3-12 months	Reduction in total cholesterol and LDL cholesterol Changes in systolic or diastolic blood pressure

Simental M et al. (2018) [63] reported that soy isoflavones do not affect plasma concentrations of lipoprotein (a) (Lp[a]), a type of low-density lipoprotein (LDL) associated with increased cardiovascular risk due to its pro-thrombotic and atherogenic properties. Abshirini et al. (2020) [64] in the review of RCTs involving 802 postmenopausal women, studied the effect of soy protein supplementation (isoflavone intake ranging from 49.3 to 118 mg/day) on endothelial function. The study reported that soy isoflavones being modulators of estrogen receptors, modified the adhesion molecules by binding to the vascular epithelial receptors. Soy isoflavones also increase nitric oxide production and thereby increasing arterial compliance. Man et al. (2020) [65] in a systematic review and meta-analysis, revealed that supplementation of soy isoflavones effectively reduces arterial stiffness, thereby contributing to the reduction in the risk of coronary heart disease, stroke, hypertension, or heart failure.

Additional studies and meta-analyses are summarized in **Table 4**. Evidence from various RCTs and their meta-analyses indicates that soy isoflavones potentially reduce cholesterol levels as well as reduce the risk of CV events and mortality. The effects may be more profound in women than in men. However, further research is necessary to establish gender-related differences in reducing major CV events by soy isoflavones.

Effect on cancer risk and treatment

Isoflavones because of their similarity with estradiol may reduce the risk of cancers. Being estrogen receptor modulators, they exert estrogenic or antiestrogenic actions, based on the cell type and the binding to the type of estrogen receptors. Isoflavones inhibit cell proliferation and stimulate apoptosis. Furthermore, isoflavones can inhibit aromatase activity, the enzyme that converts androgen to estrogen. It is also important to mention that isoflavones could act as potential anticancer compounds due to their antioxidant role in malignant cell proliferation and differentiation.

Nachvack et al. (2019) [68] in a systematic review and a meta-analysis of 23 prospective studies involving 3,30,826 participants observed that soy isoflavone consumption was inversely associated with cancer deaths. Moreover, a higher intake of soy was associated with decreased risk of mortality from gastric, colorectal, and lung cancers as well as ischemic cardiovascular diseases. Indeed, a 10-mg/day increase in intake of soy isoflavones was associated with a 7% and 9% decreased risk of mortality from all cancers and breast cancer respectively. The study also reported that an increase in 5 gm/day of soy protein consumption was associated with a 12% reduction in breast cancer death. Micek et al. (2020) [70] in a systematic review and meta-analysis of 28 studies on breast, lung, prostate, colorectal cancer, and glioma studied the association between isoflavone intake (<62.7 mg/day) and cancer mortality and its recurrence. A significant inverse association was reported between isoflavone intake, overall mortality and recurrence of breast cancer. The correlation between isoflavone intake and the risk of breast cancer was studied in a meta-analysis, by Zhao

et al. (2019) [71] which included 16 prospective studies involving 11,169 breast cancer cases and 648,913 participants. The study reported that a moderate intake of soy isoflavones did not reduce the breast cancer risk. However; a significant reduction was seen when the intake was high. Limitations of these prospective studies were the small sample size of the study population and the lack of proper definition of high, moderate, and low isoflavone intake. Thus, soy isoflavones have the potential to lower breast cancer risk and possibly reduce recurrences. The effect on other cancer types needs further evaluation in prospective studies.

India-specific evidence

Multiple Indian studies have assessed the effect of soy isoflavones. Husain and Bhatnagar [72] in a randomized controlled study, evaluated the effect of soy flour supplementation (containing 52.62 mg isoflavones) for 16 weeks in 30 postmenopausal women. It was associated with a significant increase in alkaline phosphatase, estrone, estradiol, and fat-free mass ($P< 0.05$) and a significant ($P<0.05$) decrease in the waist-hip ratio in the treatment group compared to the control group stating that soy isoflavones can have a beneficial effect in enhancing the bone formation and increasing muscle mass in osteoporotic postmenopausal women. Bharathi and Baby (2017) [73] evaluated the efficacy of 60 mg of soy isoflavones supplementation along with 500 mg of calcium plus 250 IU of vitamin D and a glass of milk (200 ml) in minimizing the risk of osteoporosis and maintaining bone health as compared to control group with no supplementation. The results of the study indicated a significant rise ($P<0.01$) in serum estradiol levels when the women were supplemented with soy isoflavones capsule supplementation along with calcium and Vitamin D for six months. In the control group, serum estradiol levels declined continuously. Soy isoflavones also significantly enhanced the bone mass and strength as observed by the shift in BMD T-score from osteoporotic condition to osteopenic condition. Ahsan and colleagues [17] reported significant improvements in total scores on the Menopausal Rating Scale in perimenopausal and postmenopausal women. Most significant improvements were reported in the scores of hot flashes. In another randomized study, Mittal et al. [74] evaluated the antioxidant effect of isoflavones in oophorectomized women. Compared to placebo, 12 weeks of treatment with 75 mg/day isoflavones tablet showed significant improvements in lipid peroxidation, catalase, superoxide dismutase, and glutathione peroxidase. This antioxidant activity probably explains the positive effects on CV risk. In assessing the menopausal symptom score, there was a significant reduction from baseline with isoflavones with significant improvement in urogenital symptoms. There was no significant effect on free T3 levels with isoflavone treatment [75].

Safety profile of soy isoflavones

As isoflavones share structural similarities to endogenous estrogen, there are concerns about some potential adverse effects of their consumption. The current evidence indicates that the consumption of isoflavones is safe and has no short-term adverse effects. Long-term studies on humans are lacking and therefore long-term safety needs to be established. Most of the adverse effects are reported from animal studies [76]. Recent RCT from India reported discontinuation of isoflavones for the reason of disturbed sleep, anxiety, and restlessness. The rates of discontinuation were similar to those observed in the placebo group [75]. An in-depth safety review by Munro et al. reports that dietary intervention studies using similar or higher doses of soy isoflavones are well tolerated by humans and are without reported adverse effects [77].

Ongoing research

Soy isoflavones are currently under investigation for asthma (NCT00277446), chronic pancreatitis (NCT02577640), prostate adenocarcinoma (NCT00078923, NCT00765479), non-small cell lung cancer (NCT01958372), major depression (NCT00042380). It is also under evaluation for gestational diabetes (NCT02806739).

Conclusion

In postmenopausal women, current evidence indicates that soy isoflavones, in daily dose varying from 30 to 200 mg, improve bone health and reduce the incidence of osteoporotic fractures. Isoflavones effectively provide

symptomatic relief in postmenopausal hot flashes as indicated in multiple meta-analyses of RCTs. Current evidence does indicate that they are safe for human use in the short term. However, long-term studies in humans are lacking and therefore caution is advised when used for the long-term. In addition to osteogenic and menopausal symptoms effects, soy isoflavones have shown to be effective in reducing the risk of breast cancer and its recurrences. It suggests the promising potential in gynecological and other cancers. The two major isoflavones, genistein, and daidzein have potential anticancer effects. Besides these effects, isoflavones improve oxidative stress and improve glycemic and lipid profiles that can help improve the metabolic profiles and cardiovascular risk in postmenopausal women. Ongoing research with soy isoflavones will further establish their possible benefits in different cancers and other chronic disorders. In summary, for postmenopausal women who are at risk of multiple health conditions such as osteoporotic fracture, and high CV risk, soy isoflavones offer a multitude of health benefits, and thus, we advise using soy supplements in postmenopausal women.

Disclosure of conflict of interest

Aaditi Phadke and Amit Qamra are salaried employees of Macleods Pharmaceuticals Ltd., Mumbai, India. Other authors declare no conflict of interest.

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