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Menopausal Symptoms: From Soy Isoflavones to Combined Soy-Exercise Interventions

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Abstract

Diet and physical activity affect menopausal symptoms. We aimed to review recent evidence based on clinical trials and meta-analysis on the effect of soy isoflavones on menopausal symptoms and the potential synergistic effect of soy consumption and exercise on menopausal women. Many studies have investigated the effect of soy isoflavones on menopausal symptoms and the data indicates that equol status is the main determinant for efficacy. Despite this, it is well known that exercise changes microbiota composition. Only one study has investigated the combined intervention with soy and exercise and reported that soy extract did not improve the positive impact of mixed exercise training. Moreover, soy proteins have anti-nutrient effects on iron and zinc, and negatively influence protein digestibility. In conclusion, although isoflavones could improve menopausal symptoms in equol-producers, postmenopausal women doing exercise should avoid high soy consumption. Furthermore, a recent prospective study has suggested caution against the use of supplements containing soy isoflavones in women with a family history of breast cancer.

Keywords: Equol; Nutraceuticals; Nutrition; Sport

Introduction

Diet and physical activity affect menopausal symptoms and quality of life **[1-3]**. A recent meta-analysis reported no significant association between a high intake of soy products and all-cause, cardiovascular diseases (CVD), and cancer mortality **[4]**. The Food and Drug Administration recently proposed to revoke the authorized health claim related to soy proteins and coronary heart disease (CHD) **[5].**

Data from meta-analysis reported that the ingestion of ≥ 25 g of soy protein per day has blood pressure-lowering effects **[6]**, whereas in non-Asian postmenopausal women a greater reduction in body weight was observed in the lower dose subgroup (dose <100 mg) **[7]** and a relationship exists between the production of equal and CHD risk factors **[8].**

On the other hand, following a request from the European Commission, in 2012 the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was invited to provide a

scientific opinion on health claims under Article 13 of Regulation (EC) no. 1924/2006 in the framework of further assessments concerning soy isoflavones and the reduction of vasomotor symptoms associated with menopause (European Food Safety Authority, 2012) **[9]**. On the basis of data presented, the Panel concluded that the evidence provided was insufficient to establish a cause-and-effect relationship both between the consumption of soy isoflavones and reduction of vasomotor symptoms associated with menopause.

Similarly, a meta-analysis concluded that evidence was insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms **[2]**, but it is well known that sport changes microbiota composition [10-16], potentially affecting soy efficacy. We aimed to review recent evidence based on clinical trials and meta-analysis on the effect of soy isoflavones on menopausal symptoms and the potential synergistic effect of soy consumption and exercise in menopausal women, in order to study at best the correlation between the food use of soy isoflavones in the treatment of menopause in women worldwide.

Soy Isoflavones and Equol Production

Soy isoflavones (genistein, daidzein and glycitein) are bioactive compounds with slightly estrogenic properties and often referred to as phytoestrogens **[3]**. These are present in significant quantities (up to 4-5 mg g-1 on a dry basis) in legumes, mainly soy, green beans, mung beans **[3]**. In cereals (raw materials) they are mainly present as glycosides, which are poorly absorbed by consumption. The main metabolite of soy isoflavones is equol, produced through digestion by the bacterial flora, and is thought to be the most responsible for the isoflavone activity **[17]**. After soy intake, a biphasic model is found in the absorption of soy isoflavones in plasma and urine, which appears to be due to the absorption in the small intestine (about 10%) during the first 2 hours after the intake and to that in the large intestine (about 90%) 4-6 hours after taking. The bioavailability of isoflavones is also influenced by intestinal bacteria and treatment with oral antibiotics. While daidzein and genistein begin to be absorbed a few minutes after intake, the equol appears in plasma only at least 8 hours after taking soy, due to the required transit time of daidzein to colon, where the conversion of daidzein to equol occurs thanks to the intestinal microbiota **[17]**.

Phytoestrogens, found in the diet as glucoconiugates (daidzin, genistin), are hydrolysed in the intestine in the active aglycon forms (daidzein and genistein) by the action of UDP-glucuronosyltransferase, which is secreted by intestinal bacteria [**18]**. Genistein and daidzein are also produced by the demethylation of their precursors, respectively biocanin A and formononetin. The aglycones are absorbed from the intestinal tract towards the liver, where they are mainly conjugated with glucuronic acid and sulfates. Some of the conjugated aglycones are excreted in the bile, where they are hydrolysed, and some of the unconjugated aglycones are excreted in the faeces, whereas some of them are reabsorbed in the liver through the enterohepatic circulation. In the blood, isoflavones are metabolised mainly in equol and O-desmethylangolensin, which are excreted in the urine **[18]**. The synthesis of equol unfolds in three key reactions: the hydrolysis starts in the small intestine with the release of the aglycone. This is a fundamental step because the aglycone fails to cross the enterocyte and hydrolysis takes place thanks to the intestinal microbial flora that produces good quantities of β-glucosidase. During the intermediate passage the metabolite dehydrodadzein is produced to then give S - (-) equol. The latter turns out to be more bioavailable and bioactive than its starting compounds; in particular, they have a greater estrogenic strength thanks to the better interaction with the receptor, so that it competes with the endogenous compound for binding to the receptor. After the first studies, it was noticed that not all healthy adults produced equol after the dietary intake of soy isoflavones, so the term "producers of equol" was coined **[19]**. Subsequent studies have shown that only 20-30% of the western population is able to produce it metabolically. This datum clashes strongly with similar studies carried out in the East (Japan, China and Korea) and in Western vegetarians, in which it appears instead that around 50 - 60% of the population produces equol. The major factor that regulates the production of equol is the presence in the intestinal microbial flora of specific bacteria equipped with the right β-glucosidase **[19]**.

Estrogenic Activity of Isoflavones

The estrogen beta receptor (ERβ) is one of the two key receptors (ERα, ERβ) that facilitate the biological actions of 17β-estradiol (E2). ERβ is widely expressed in many tissues and its expression is reduced or lost during the progression of many tumours **[20]**. Natural ERβ ligands have been suggested for cancer treatment and prevention. Natural ERβ agonists preferentially activate ERβ signalling and also up regulated ERβ expression. A meta-analysis included 47 studies (11 pre-, 35 post- and 1 perimenopausal women) and indicated that consumption of soy or isoflavones did not affect the levels of estradiol, estrone or sex hormone binding globulin (SHBG), but significantly reduced those of follicle stimulating hormone (FSH) and luteinizing hormone (LH) (20%) [**21]**. In postmenopausal women there were no statistically significant effects on estradiol, estrone, SHBG, FSH or LH, although there was a statistically non-significant increase in total estradiol with soy or isoflavones (14 %,). Cases of endometriosis have been reported **[22, 23]** and case reports documented following the ingestion of soy-based products in men: gynecomastia and erectile dysfunction in a 60-year-old man concomitantly with levels 4 times higher than the standard of estrone and estradiol, reversible after stopping consumption of soy milk **[24]**, hypogonadism and erectile dysfunction in a 19-year-old vegan man (with a high intake of soy-based products), with a reduction in testosterone levels

that are reversible following diet interruption **[25]**. On the contrary, exercise improved reproductive hormone levels by increasing serum testosterone in obese men **[26]**, and affected the hypothalamus-pituitary-adrenal axis activity in postmenopausal women on hormone replacement therapy (HRT) **[27]**.

Effect of Soy Isoflavones on Menopausal Symptoms

(Table 1) and **(Table 2)** include selected randomized placebo controlled trials **[28-39]** and meta-analysis **[40-46],** respectively, investigating the effect of soy on menopausal symptoms. A literature search has been carried out on PubMed with the terms: "Soy isoflavones, menopause". 278 clinical trials have been identified starting from 644 references. Based on the abstracts, 12 clinical trials which studied the effect of soy-based foods, nutraceuticals and supplements, and soy isoflavones on menopausal symptoms were selected. With the same criterion, 7 of the 23 identified meta-analysis were selected. The population is heterogeneous, since studies on western and eastern women have been selected, as well as number of volunteers.

Ref.	Treatment	Duration	N°	Outcomes
[28]	80-120 mg soy isoflavones	24 months	403 postmenopausal	general symptomatology ↔
[29]	60 mg soy isoflavones	6 months	1682 postmenopausal	vasomotor symptoms ↓
[30]	90 mg soy isoflavones (to HRT and placebo)	16 weeks	60 postmenopausal	vaginal dryness ↓
[31]	100 mg soy isoflavones	3 months	50 with depression	vasomotor symptoms ↓
[32]	66, 100, 200 mg isoflavone capsules	12 weeks	130 peri and postmenopausal	vasomotor symptoms ↓
[33]	80 mg soy isoflavone tablet	12 weeks	180 (40/65 age)	vasomotor symptoms ↓
[34]	33 g soybean in the form of biscuits (54 mg isoflavones)	8 weeks	61 iranian postmenopausal	vasomotor symptoms ↓
[35]	10, 20, 40 mg S-equol/day or soy isoflavones	8 weeks	102 American postmenopausal (45/65 age)	vasomotor symptoms ↓
[36]	40 g of soy flour (whole soy group), 40 g of low-fat milk powder + 63 mg of daidzein (daidzein group)	6 months	270 Chinese postmenopausal	general symptomatology↔
[37]	60 mg wheat germ isoflavone capsules	6 months	50 non-Asian postmenopausal with contraindications to HRT	vasomotor symptoms ↓ general symptomatology↓
[38]	Soy milk (50 mg isoflavones)	12 weeks	147 Spanish peri and postmenopausal	vasomotor symptoms ↓
[39]	35 or 70 mg of soy extract	24 weeks	130 Taiwanese menopausal	vasomotor symptoms ↓
HRT: hormone replacement therapy				

Table 1: Randomized placebo controlled trials.

Soy has been administered in multiple ways in these studies, as real foods (biscuits, milk, germ and soy flour with isoflavone titre) or as supplements, in the form of tablets and pills, with isoflavone titre. The duration of the studies is also varied and ranges from 8 weeks to 24 months as well as dosages. These studies show a wide heterogeneity of results. Only in two trials was no improvement in symptoms observed **[28, 36]**. Amato et al. have studied a large sample of menopausal women for at least 5 years, and have hypothesized that the poor result obtained could be attributed to this and that in perimenopausal or recently menopausal women there could be greater benefits **[28]**. Regarding vasomotor symptoms, almost all the studies taken into consideration seem to give positive results in the response of women treated with isoflavones. However, it must bear in mind that this datum can be modified by the fact of being able or not to produce equol starting from the isoflavones, and that the Oriental women tend to be producers of equol in the highest percentage. In fact, from these studies we note that in Western women there is often a failure of the soy phytoestrogen therapy.

The relationship between efficacy and equol production is partly confirmed by the results of Jenks et al. who compared the effect of equol to that of daidzein in menopausal women, dividing the subjects into the following treatment groups: 10 (n = 24), 20 (n = 27), or 40 (n = 25) mg S - equol/day or soy isoflavones (n = 26). After 8 weeks of treatment the reduction in hot flushes was The relationship between efficacy and equol production is partly confirmed by the results of Jenks et al. who compared the effect of equol to that of daidzein in menopausal women, dividing the subjects into the following treatment groups: 10 (n = 24), 20 (n = 27), or 40 (n = 25) mg S - equol/day or soy isoflavones (n = 26). After 8 weeks of treatment the reduction in hot flushes was higher for doses of 20 and 40 mg/d S-equol compared to treatment with isoflavones, but especially in women who had a frequency > 8/d at baseline **[35]**.

More than half of the studies deal with symptomatology in general (which is the most important aspect to consider to improve the quality of life of menopausal women) and most of them give positive results. Finally, no side effects due to the use of these substances have been highlighted.

Many of the selected studies report a good result on vasomotor symptoms **[31, 33, 37]** or on other symptoms, such as mood development **[31]**, vaginal dryness **[30]** or urogenital symptoms **[38].**

A multicentre study, which involved more than a thousand women, analysed whether the time (morning/evening) of administering a compound containing 60 mg of dry soybean extract (glycine max) with 40% of total isoflavones, primula oil and α-tocopherol, modifies the effect on the climacteric syndrome **[29]**. Both times of administration improved climacteric symptoms after 3 and 6 months of treatment.

With regard to the dose and frequency of administration, menopausal women (without menstruation in the last 3 months) and postmenopausal women (≥ 12 months of amenorrhea) with an average of five or more moderate/severe hot flushes per day were divided into groups of treatment with different total isoflavone doses and dosage frequency, separately in producers of equol and non-producers **[32]**. Participants recorded the daily frequency and severity of hot flushes. The comparative analysis indicates the scores daily intensity of hot flush (sum of hot flashes weighted by gravity) based on total daily dose and dosage frequency. These flushing scores were lower in women selected for the highest total daily dose (100-200 mg) and for those with the highest dosage frequency (twice a day and three times a day), with greater benefit on scores at night compared to daytime scores. The differences in dose and frequency were slightly greater in the producers of equol than in the non-producers.

The first meta-analysis **(Table 2)** that evaluated the effect of soy isoflavones on menopausal symptoms dates back to 2006 and had not observed a significant reduction in the frequency of hot flushes, also in view of the low quality of the studies [40]. A high heterogeneity of the studies that makes it difficult to reach conclusive results has been reported by a meta-analysis of 2010 **[41]**.

Subsequently, other meta-analysis were conducted. Measuring the effectiveness of extracted or synthesized soy isoflavones in the alleviation of hot flushes in perimenopausal and postmenopausal women was the goal of a 2012 meta-analysis **[42]**. 17 studies were selected which revealed that the ingestion of soy isoflavones (on average 54 mg, aglycon equivalents) for 6 weeks to 12 months significantly reduced the frequency (combined model of fixed and random effects) of flushes by 20.6%. A meta-analysis of 2015 included RCT with these criteria: perimenopausal or postmenopausal women with menopausal symptoms, intervention with a phytoestrogen (oral) **[43]**. Outcome measures included the frequency of daily hot flushes and the likelihood of side effects. Of 543 potentially relevant studies identified, 15 RCTs were included that meet the inclusion criteria. The average age of the subjects ranged from 49 to 58.3 and from 48 to 60.1 years, respectively, in the groups treated with placebo and phytoestrogens. The number of participants ranged from 30 to 252 and the intervention periods ranged from 3 to 12 months. Meta-analysis of the ten studies that reported data on hot flushes indicated that phytoestrogens cause a significant reduction in the frequency of hot flushes compared to placebo (aggregate average difference 0.89, p 0.005). The subsequently, other meta-analysis were conducted. Measuring the effectiveness of extracted or synthesized soy isoflavones in the alleviation of hot flushes in perimenopausal and

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Ref.	Treatment	Duration	N°	Outcomes
[40]	soy isoflavone extracts (50-600 mg/d)	4 weeks-1 year	17 trials on isoflavone extracts	hot flushes ↔
[41]	33,3-134,4 mg/d of soy supplement	12 weeks	19 studies	vasomotor symptoms ↓
[42]	30-135 mg/d of isoflavones (aglycone equivalents)	6 weeks-1 year	17 trials on soybean isoflavones	hot flush frequency and severity↓
[43]	5-80 mg/d of isoflavones	3-12 months	15 RCT 30-252 participants	hot flush frequency ↓
[44]	30-200 mg/d of soy isoflavones	4 weeks-1 year	16 studies 1710 subjects	hot flush frequency ↓
[45]		4-96 weeks	24-236	hot flushes ↓
[46]	6,5-160 mg/d	4 weeks-2 years	6653	hot flush frequency ↓ vaginal dryness ↓ night sweats ↔
RCT: randomized controlled trial				

Table 2: Meta-analysis.

Combined Soy and Exercise Intervention

Only Fontvieille et al. **[47]** verified the efficacy of phytoestrogen supplementation (PHY: each capsule contained 325 mg of soy extract with 17.5 mg of isoflavones for a 70-mg daily dose of 44 mg of daidzein, 16 mg of glycitein and 10 mg of genistein) combined with exercise (EXT) on improving climacteric symptoms in postmenopausal women, compared with EX plus placebo (PL). The 12-month exercise program consisted of three non-consecutive sessions (1 h each) per week of combined exercise, which means combination of aerobic (30 min) and resistance (30 min) exercises. Climacteric symptoms were assessed using the Kupperman Index questionnaire, including 11 symptoms: hot flushes, night sweats, insomnia, nervousness, melancholy, dizziness, asthenia, arthralgia, headache, palpitation and vaginal dryness. After 1 year of intervention, while the EX + PL group showed improvements in the total score of menopausal symptoms and hot flushes, the combination with phytoestrogens prevented positive effects in the long term in overweight postmenopausal women. The results of this study did not support the usefulness of phytoestrogen supplementation in the long term when exercise is performed on a regular basis and suggested that adding phytoestrogens may interfere with exercise training adaptations as beneficial impacts were observed in the EX + PL group only. Authors **[47]** suggested that exercise (activating ERα) and phytoestrogens (activating ER β) may induce opposite effects in the long term.

Similarly, a 2-year intervention with EX (resistance training 2 days/week and walking 4 days/week) with or without isoflavone supplementation (Iso: 165 mg/d, 105 mg/d aglycone equivalent) in postmenopausal women provided with calcium and vitamin D, suggested that these two interventions interfere with each other when combined **[48]**. Authors found a significant interaction for total hip bone mineral density (BMD) and ExIso had a greater rate of decrease than either the Ex or Iso groups alone **[48]**. Moreover, in a 6-month intervention (isoflavones 70 mg/day + resistance and aerobic training, isoflavones or exercise alone), exercise improved muscle strength in sedentary postmenopausal women, whereas isoflavones, irrespective of exercise, did not produce changes [49]. On the contrary, Shenoy et al. **[50]** observed, in osteopenic/osteoporotic postmenopausal women, that a combined intervention with soy plus resistance exercises improved bone and/or muscle strength more than soy or exercise alone. Wu et al. **[51]** suggested that the preventive effects of isoflavones on BMD in postmenopausal women depend on the individual's intestinal flora for equol production.

On the other hand, in postmenopausal women, soy milk consumption for 28 days did not inhibit the expression of inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6) and proteolytic genes (calpain 1, calpain 2, ubiquitin, E2, atrogin-1, muRF-1) that were assessed in muscle biopsies and did not attenuate the eccentric exercise-induced up-regulation in the proteolytic genes **[52, 53]**. When non-obese postmenopausal women performed 30 sessions of combined exercises (aerobic plus resistance) over ten weeks and consumed 100 mg of isoflavone supplementation or placebo, there were no differences in the changes (pre vs. post) between groups for any markers IL-6, superoxide dismutase (SOD), total antioxidant capacity (FRAP), and thiobarbituric acid reactive substances (TBARS) **[54]**. On the contrary, beneficial effects of physical activity are well known and supported by studies on in untrained adults with chronic spinal cord injury (SCI), forced by their impairment to be sedentary [55, 56]. Plasma levels of TNF-α and IL-6 were significantly decreased in SCI after the completion of a 12-week arm cranking exercise program of 3 sessions per week **[55]**, as well as lipid (malondialdehyde) and protein (carbonyl groups) oxidation markers, whereas total antioxidant status and erythrocyte glutathione peroxidase activity were significantly increased **[56]**.

Conclusions

In conclusion, the results on the efficacy of isoflavones on menopausal symptoms are conflicting. Despite the production of equol being a determining factor affected by microbiota composition, combined intervention with soy and exercise, known to change microbiota composition **[10-16]**, did not improve the positive impact of mixed exercise training. Moreover, inhibitors of iron (Fe) absorption include polyphenols, phytate and soy protein, and the latter also inhibit zinc (Zn) absorption **[57, 58, 59]**. Moreover, data from meta-analysis did not support that soy isoflavones increased BMD in menopausal women **[60]**, soy protein content negatively influenced protein digestibility and Ca bioaccessibility **[59]** and decreased heme Fe absorption **[61]**. From that, although isoflavones could improve menopausal symptoms in equol-producers, post-menopausal women doing exercise should avoid high soy consumption. Furthermore, a recent prospective study suggested caution against the use of supplements containing soy isoflavones in women with a family history of breast cancer and that the risk profile of soy supplements deserves further investigation **[62]**. A proposed alternative treatment is acupuncture, suggesting the involvement of the central nervous system transmission **[63-68]**, although its efficacy is still controversial.

Author Contributions

A.R. and P.A. equally contributed to research and selection of studies. All authors (A.R., P.A., I.P., M.P. and M.B.) wrote the paper.

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Conflicts of Interest

The authors declare no conflict of interest.

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