The Impact of Soy Isoflavone Supplementation on the Menopausal Symptoms in Perimenopausal and Postmenopausal Women

Shrutika Khapre, Ujjwala Deshmukh¹, Sheela Jain

Department of Obstetrics and Gynaecology, NKP Salve Institute of Medical Sciences and Lata Mangeshkar Hospital and Research Centre, ¹Dr. Deshmukh Shree Clinic Nursing Home, Nagpur, Maharashtra, India

Introduction: Approximately one-third of a woman’s life is spent in the menopausal phase. The unpleasant menopausal symptoms are unacceptable as a part of routine life. Indications of menopausal hormone therapy (MHT) are for alleviation of vasomotor symptoms, prevention of osteoporosis, and genitourinary symptoms associated with menopause. MHT is associated with an increased risk of breast cancer, cerebrovascular accidents, and coronary heart disease. Soy isoflavones have been extensively used as an alternative treatment in patients who cannot take MHT. The evidence of the efficacy of isoflavones in the literature is equivocal. Aim: The aim of the study was to evaluate the efficacy of soy isoflavone supplementation on menopausal symptoms in perimenopausal and postmenopausal women and to evaluate the effect on blood pressure (BP) and body mass index (BMI).

Materials and Methods: A questionnaire-based prospective observational study was undertaken involving 39 perimenopausal and 61 postmenopausal women, who were prescribed 40 mg soy isoflavone supplements twice daily for 12 weeks. Menopause Rating Scale questionnaire was given to the patients before starting soy isoflavone therapy and at the end of the treatment; BP and BMI were also noted. Results: The total score of both the groups was comparable at baseline. Among perimenopausal and postmenopausal women, the highest score was noted in symptoms of somatic domain. At the completion of our study, the total scores improved significantly by 38.6% and 33.3% in perimenopausal and postmenopausal women, respectively. The greatest improvement was seen in somatic subscale (42.5%) and psychological subscale (42.5%) and the least in urogenital subscale (16.1%) for perimenopausal women. For postmenopausal women, the greatest improvement was seen in psychological subscale (40.0%) and the least in urogenital subscale (14.2%).

Conclusion: Soy isoflavone supplementation is beneficial in both perimenopausal and postmenopausal women, more so in perimenopausal women. There is no beneficial effect of soy isoflavone supplementation on lowering systolic BP and BMI.

Keywords: Blood pressure, body mass index, menopausal hormone therapy, menopause, Menopause Rating Scale questionnaire, selective estrogen receptor modulator, soy isoflavones
Impact of soy isoflavone supplementation on the menopausal symptoms

Before menopause, when there are higher circulating levels of endogenous estrogen, isoflavones act as an estrogen agonist and thus effectively balance the estrogen metabolism in the body. Therefore, approximately one-third of a woman’s life is spent in the menopausal phase. Hormonal fluctuations culminating in the final menstrual period begin at least a decade earlier and continue for much longer and are characterized by reduced fertility, irregular menstrual cycles, vasomotor symptoms (VMS), sleep disturbances, emotional changes, osteoporosis, reduced metabolism, and vaginal dryness, which can have a large impact on a woman’s psychological health and well-being.

The menopausal symptoms vary with the phase of the menopausal transition, region, and ethnicity and show a greater interindividual variation.

 Isoflavone is a phytoestrogen and a nonsteroidal compound. Isoflavones are abundant in soybeans, beans, pulses, lentils, red clover, and alfalfa. The major dietary source of isoflavones in the most populations is soy. Soybeans are nutritious and healthy. It is an important source of proteins; contains polyunsaturated fats, fiber, and vitamins; and does not contain starch, saturated fats, and cholesterol. Soy extract products have been widely used as an alternative treatment, targeting menopausal symptoms in patients who cannot or have concerns related to and are unwilling to take menopausal hormone therapy (MHT). Isoflavone is a selective estrogen receptor (ER) modulator, with main constituents of genistein, daidzein, and glycitein. The studies of isoflavone intake in Western countries indicate an average daily isoflavone intake of approximately <3 mg, and Asian populations consuming a high soy diet or people consuming soy supplements have a daily intake of approximately 40 mg/day.

There are two types of ERs: ERα, which is present in the breast, uterus, and vagina, and ERβ, which is present in the bone, urogenital tract (bladder, urethra, vaginal mucosa, and levator ani), cardiovascular system, and brain. Conventional estrogens bind to both ERα and ERβ with the same affinity. Isoflavones bind weakly to ERα, but the affinity to ERβ is stronger (83-fold). The preferential binding of isoflavones to ER-β receptors is responsible for the beneficial effects, and a higher concentration of isoflavones required for cellular growth explains a fewer chances of adverse effects such as breast cancer. Before menopause, when there are higher circulating levels of endogenous estrogen, isoflavones act as an estrogen antagonist. Whereas, after menopause, when there is a low estrogen environment, isoflavones act as an estrogen agonist and thus effectively balance the estrogen metabolism in the body.

There has been a dramatic rise in the academic and clinical interests in isoflavones as an alternative to conventional MHT for menopause. Previous studies have shown high heterogeneity, making it difficult to conclude. Questions such as which active component of isoflavones provides estrogen-like benefits, which substances in soy, apart from isoflavones, exert beneficial effects, and whether synthetic isoflavones are superior to soy isoflavones remain unanswered. No study has suggested an upper limit of dose of isoflavone supplements. Although soy isoflavones are extensively used, scientific evidence for their efficacy in the management of menopausal symptoms among Indian women is mixed. We planned this study to evaluate the impact of soy isoflavone supplementation on the Menopause Rating Scale (MRS) scores among perimenopausal and postmenopausal Indian women.

Aims and objectives

Primary objective

The primary objective of this study was to study the effect of soy isoflavone supplementation on the menopausal symptoms (somatic, psychological, and urogenital symptoms) in perimenopausal and postmenopausal women.

Secondary objective

The secondary objective of this study was to study the effect of soy isoflavone supplementation on:

1. Blood pressure (BP)
2. Body mass index (BMI).

Materials and Methods

Study design

This was a prospective observational study (questionnaire-based).

Study setting

The study was conducted at the Outpatient Department (OPD), Dr. Deshmukh Shree Clinic Nursing Home, Nagpur.

Study population

All perimenopausal and postmenopausal women who gave informed consent to participate in the study and who attended the OPD of Dr. Deshmukh Shree Clinic Nursing Home, Nagpur, were enrolled in the study according to the inclusion and exclusion criteria.

Study duration

The study duration was 4 months (from June 1, 2021, to September 30, 2021).

Sampling technique

Convenience sampling technique was used.
Sample size
One hundred perimenopausal and postmenopausal women were included in the study.

Sample size calculation
Prior data indicated that the difference in the response of matched pairs was normally distributed with a standard deviation of 0.8. If the true difference in the mean response of matched pairs was 2.50 (total MRS score), we required 100 cases to be studied to be able to reject the null hypothesis that this response difference was zero with probability (power) of 1.000. The Type I error probability was kept at 0.05.

Inclusion criteria
Perimenopausal and postmenopausal women with:
1. BMI 20–40 kg/m²
2. Irregular cycles (variable cycle length of >7 days different from normal) in case of perimenopausal women
3. Newly diagnosed patients willing to participate in the study
4. Patients refusing MHT and patients not taking MHT.

Exclusion criteria
1. Perimenopausal and postmenopausal women who had previous treatment with MHT or soy supplements in the past 12 months
2. Women with a history of a cardiovascular event like myocardial infarction within the past 6 months
3. Allergic to soy products
4. Hepatic impairment and renal impairment.

Methodology
Perimenopausal and postmenopausal women attending the OPD were enrolled in the study as per the formulated inclusion and exclusion criteria, after counseling and detailed written informed consent.

Sociodemographic data such as age, marital status, education, and occupation were noted. All the participants were subjected to general physical examination, and BMI was calculated. Detailed menstrual history and obstetric history were elicited. Lifestyle history was elicited. A history of intake of any medication and previous surgery was noted. Detailed history and family history were noted, and baseline investigations were done.

The menstrual status of the patient was evaluated according to the Stages of Reproduction Aging Workshop (STRAW)+10 criteria.10
1. Postmenopausal: No menstrual bleeding for the past 12 months
2. Late perimenopausal: Amenorrhea for ≥60 days
3. Early perimenopausal: Irregular periods without skipping cycles and >7-day difference in length of consecutive cycles.

Menopause Rating Scale questionnaire
It is an internationally accepted tool for the evaluation of menopausal symptoms. It is also validated as a tool to evaluate the response to therapy. The MRS questionnaire consists of 11 common menopausal symptoms which are further grouped into three subscales: somatic, psychological, and urogenital. Each of the symptoms is scored from 0 (none) to 4 (very severe).11

MRS questionnaire was administered to the patients by a face-to-face interview in the local language, before starting soy isoflavone therapy and at the end of the treatment. Baseline investigations were repeated at the end of the treatment. The total score and somatic, psychological, and urogenital subscale scores of both the groups were compared at baseline. Improvement in the mean total score and the mean somatic, psychological, and urogenital subscale scores of both the groups was noted at the end of the treatment, and a percentage reduction was calculated.

The effect of soy isoflavone supplementation on various symptoms was observed and it was ascertained, which subset of symptoms showed maximum improvement. It was also seen whether it was more beneficial in perimenopausal or postmenopausal women.

During the study, the patients were advised to take a balanced diet and maintain a normal level of physical activity. They were given a list of soy-based foods to be avoided during the therapy. They were advised to avoid smoking, alcohol consumption, and refrain from taking vitamin or mineral supplementation. They were prescribed 40 mg soy isoflavone supplements twice daily, to be taken between meals for 12 weeks. They were observed for any untoward side effect or other complaints.

The study visits were scheduled at baseline, 6 weeks, and the end of the treatment, and the participants were contacted telephonically to ensure compliance. Compliance was analyzed by checking empty wrappers. Soy isoflavones were well tolerated and no serious adverse events were noted during the study.

Statistical analysis
The data were compiled using MS Excel and were analyzed using using IBM SPSS software version 20. IBM corp. Armonk New York. Categorical variables were expressed as frequency and proportions, whereas continuous variables were expressed as mean and standard deviation. Chi-square test was used to assess the severity of symptoms in perimenopausal and postmenopausal women, whereas paired t-test was used to assess the improvement in symptoms. \( P < 0.05 \) was considered statistically significant.
Results

According to the STRAW+10 criteria, of the 100 women enrolled, 39 were perimenopausal and 61 were postmenopausal.
1. The mean age of the perimenopausal group was 45.23 years (standard deviation: 3.460 years) and that of the postmenopausal group was 56.25 years (standard deviation [SD]: 8.258 years)
2. The mean age of attaining menopause in the postmenopausal group was 45.72 years (SD: 4.817 years). The average time since menopause was 10.57 years (SD: 8.64 years)
3. The women participating in our study had varied educational qualifications and occupations
4. The mean BMI of perimenopausal women in the study was 25.59 kg/m² and that of postmenopausal women was 25.74 kg/m². The distribution of mean BMI did not differ significantly between the two study groups ($P > 0.05$)
5. The mean systolic BP of perimenopausal women in the study was 120.28 mmHg and that of postmenopausal women was 126.61 mmHg. The distribution of mean systolic BP did not differ significantly between the two study groups ($P > 0.05$)
6. 6 (15.38%) perimenopausal women and 10 (16.39%) postmenopausal women had high caffeine consumption
7. 16 (41.03%) perimenopausal women exercised daily and 11 (28.21%) women practiced yoga. 24 (39.34%) postmenopausal women exercised daily and 17 (27.87%) women practiced yoga
8. 10 (25.64%) perimenopausal women and 21 (34.43%) postmenopausal women took calcium supplements daily
9. 5 (12.82%) perimenopausal women and 14 (22.95%) postmenopausal women took Vitamin D supplements regularly
10. None of the participants had a history of intake of soy supplements
11. 1 (2.56%) perimenopausal women and 3 (4.92%) postmenopausal women reported a history of intake of MHT in the past (>12 months before the start of the study)
12. 12 (19.67%) women had attained surgical menopause. Oophorectomy was done in 4 (6.56%) of them
13. 9 (23.08%) perimenopausal and 23 (37.70%) postmenopausal women were suffering from hypertension
14. 4 (10.26%) perimenopausal and 9 (14.75%) postmenopausal women were suffering from diabetes mellitus
15. 3 (7.69%) perimenopausal and 5 (8.20%) postmenopausal women were suffering from thyroid disorders
16. 2 (5.13%) perimenopausal and 4 (6.56%) postmenopausal women were suffering from rheumatoid arthritis and 6 (9.84%) postmenopausal women were suffering from osteoarthritis
17. 1 (2.56%) perimenopausal and 5 (8.20%) postmenopausal women had suffered a fragility fracture
18. Among perimenopausal women, various problems such as abnormal uterine bleeding (3 patients), fibroid (2), adenomyosis (2), cervicitis (4), vaginitis (4), and urinary tract infections (1) were seen
19. Among postmenopausal women, various problems such as stroke (1 patient), myocardial infarction (2), atrophic vaginitis (1), and cataract (6) were seen.

We documented no statistically significant difference in symptomatology between perimenopausal and postmenopausal women, except for sleep problems and irritability being more prevalent among perimenopausal women [Table 1].

In our study, there was no statistically significant difference in the mean total score, somatic, psychological, and urogenital subscale score between perimenopausal and postmenopausal women. In perimenopausal and postmenopausal women, the highest score was observed in the somatic subscale and the lowest score was observed in the urogenital subscale [Table 2].

The reduction in the mean total score, somatic subscale score, and psychological subscale score in perimenopausal women was statistically significant after 12 weeks of soy isoflavone supplementation [Table 3].

The reduction in the mean total score, somatic subscale score, and psychological subscale score in postmenopausal women was statistically significant after 12 weeks of soy isoflavone supplementation [Table 4].

The reduction in systolic BP, after 12 weeks of soy isoflavone supplementation, in perimenopausal and postmenopausal women was not statistically significant. Of particular note, all the patients reported a reduction in systolic BP [Table 5].

The reduction in BMI, after 12 weeks of soy isoflavone supplementation, in perimenopausal and postmenopausal women was not statistically significant. Of particular note, all the patients reported a reduction in BMI [Table 6].

None of the hypothyroid patients reported worsening of thyroid function necessitating an increase in thyroxine supplementation.

Thus, soy isoflavone supplementation was beneficial in both perimenopausal (38.6% reduction in symptoms)
### Table 1: Analysis of individual symptoms in perimenopausal and postmenopausal women as per Menopause Rating Scale

| Symptoms                        | Group               | None, n (%) | Mild, n (%) | Moderate, n (%) | Severe, n (%) | Very severe, n (%) | Total, n (%) | P     |
|---------------------------------|---------------------|-------------|-------------|-----------------|---------------|-------------------|--------------|-------|
| Hot flashes, sweating           | Perimenopausal      | 12 (30.8)   | 13 (33.3)   | 3 (7.7)         | 9 (23.1)      | 2 (5.1)           | 39 (100.0)  | 0.234NS|
|                                 | Postmenopausal      | 26 (42.6)   | 23 (37.7)   | 4 (6.6)         | 8 (13.1)      | 0                 | 61 (100.0)  |       |
| Heart discomfort                | Perimenopausal      | 25 (64.1)   | 8 (20.5)    | 4 (10.3)        | 2 (5.1)       | 0                 | 39 (100.0)  | 0.792NS|
|                                 | Postmenopausal      | 33 (54.1)   | 17 (27.9)   | 7 (11.5)        | 4 (6.6)       | 0                 | 61 (100.0)  |       |
| Sleep problems                  | Perimenopausal      | 20 (51.3)   | 16 (41.0)   | 2 (5.1)         | 2 (5.6)       | 0                 | 39 (100.0)  | 0.004* |
|                                 | Postmenopausal      | 33 (54.1)   | 13 (21.3)   | 13 (21.3)       | 2 (3.3)       | 0                 | 61 (100.0)  |       |
| Depressive mood                 | Perimenopausal      | 17 (43.6)   | 20 (51.3)   | 2 (5.1)         | 0             | 0                 | 39 (100.0)  | 0.477NS|
|                                 | Postmenopausal      | 26 (42.6)   | 27 (44.3)   | 5 (8.2)         | 3 (4.9)       | 0                 | 61 (100.0)  |       |
| Irritability                    | Perimenopausal      | 18 (46.2)   | 19 (48.7)   | 2 (5.1)         | 0             | 0                 | 39 (100.0)  | 0.050* |
|                                 | Postmenopausal      | 39 (63.9)   | 14 (23.0)   | 7 (11.5)        | 1 (1.6)       | 0                 | 61 (100.0)  |       |
| Anxiety                         | Perimenopausal      | 21 (53.8)   | 16 (41.0)   | 2 (5.1)         | 0             | 0                 | 39 (100.0)  | 0.691NS|
|                                 | Postmenopausal      | 35 (57.4)   | 20 (32.8)   | 5 (8.2)         | 1 (1.6)       | 0                 | 61 (100.0)  |       |
| Physical and mental exhaustion  | Perimenopausal      | 21 (53.8)   | 12 (30.8)   | 4 (10.3)        | 2 (5.1)       | 0                 | 39 (100.0)  | 0.604NS|
|                                 | Postmenopausal      | 25 (41.0)   | 25 (41.0)   | 6 (9.8)         | 5 (8.2)       | 0                 | 61 (100.0)  |       |
| Sexual problems                 | Perimenopausal      | 36 (92.3)   | 2 (5.1)     | 1 (2.6)         | 0             | 0                 | 39 (100.0)  | 0.143NS|
|                                 | Postmenopausal      | 60 (98.4)   | 0           | 0               | 1 (1.6)       | 0                 | 61 (100.0)  |       |
| Bladder problems                | Perimenopausal      | 33 (84.6)   | 4 (10.3)    | 1 (2.6)         | 1 (2.6)       | 0                 | 39 (100.0)  | 0.373NS|
|                                 | Postmenopausal      | 43 (70.5)   | 9 (14.8)    | 6 (9.8)         | 3 (4.9)       | 0                 | 61 (100.0)  |       |
| Dryness of vagina               | Perimenopausal      | 30 (76.9)   | 7 (17.9)    | 2 (5.1)         | 0             | 0                 | 39 (100.0)  | 0.174NS|
|                                 | Postmenopausal      | 52 (85.2)   | 5 (8.2)     | 1 (1.6)         | 3 (4.9)       | 0                 | 61 (100.0)  |       |
| Joint and muscular discomfort   | Perimenopausal      | 16 (41.0)   | 14 (35.9)   | 6 (15.4)        | 2 (5.1)       | 1 (2.6)           | 39 (100.0)  | 0.381NS|
|                                 | Postmenopausal      | 25 (41.0)   | 21 (34.4)   | 6 (9.8)         | 9 (14.8)      | 0                 | 61 (100.0)  |       |

*P<0.05.  P by Chi-square test. P<0.05 is considered to be statistically significant. NS: Statistically nonsignificant

### Table 2: Menopause Rating Scale score at baseline of perimenopausal and postmenopausal women

| MRS domain                     | Perimenopausal | Postmenopausal | P   |
|---------------------------------|----------------|----------------|-----|
| MRS mean total score           | 6.51           | 4.74           | 7.03| 4.86 | 0.586NS|
| Somatic subscale               | 3.49           | 2.95           | 3.44| 2.43 | 0.927NS|
| Psychological subscale         | 2.38           | 2.15           | 2.75| 2.40 | 0.436NS|
| Urogenital subscale            | 0.62           | 1.09           | 0.85| 1.76 | 0.467NS|

MRS: Menopause Rating Scale, NS: Statistically nonsignificant; SD: Standard deviation

### Table 3: Mean Menopause Rating Scale scores in the perimenopausal group at baseline and after 12 weeks of therapy (n=39)

| MRS domain                     | Score before therapy | Score after therapy | Absolute change | Percentage change | Significance (P) |
|---------------------------------|-----------------------|----------------------|-----------------|-------------------|-------------------|
| MRS mean total score           | 6.51                  | 4.01                 | 2.51            | 38.6              | 0.001***          |
| Somatic subscale               | 3.49                  | 2.03                 | 1.48            | 42.5              | 0.001***          |
| Psychological subscale         | 2.38                  | 1.41                 | 1.01            | 42.5              | 0.001***          |
| Urogenital subscale            | 0.62                  | 0.51                 | 0.10            | 16.1              | 0.349NS           |

NS: Statistically nonsignificant, MRS: Menopause Rating Scale, *** highly significant

Among postmenopausal women, the highest score and the least improvement were noted in symptoms of somatic subscale, whereas the lowest score and the least improvement were noted in urogenital subscale. The results of our study are in accordance with the study by Ahsan and Mallick,[13] wherein the greatest improvement was seen in symptoms of somatic subscale (27.7%) and psychological subscale (26.32%) and the least improvement was in urogenital subscale (1.19%) in perimenopausal women.

Among postmenopausal women, the highest score and the least score were noted in symptoms of somatic subscale and urogenital subscale, respectively. However, the greatest improvement was observed in psychological subscale (40.0%) and the least improvement was in the urogenital subscale (14.2%). The results of our study are in accordance with the study by Ahsan and Mallick,[13] wherein the greatest improvement was seen in symptoms of psychological subscale (26.79%) and the least improvement was in urogenital subscale (1.11%) in postmenopausal women. In a study

**DISCUSSION**

In the present study, the highest score and the greatest improvement in perimenopausal women were noted in symptoms of somatic subscale, whereas the lowest score and the lowest improvement were noted in urogenital subscale. The results of our study are in accordance with the study by Ahsan and Mallick,[13] wherein the greatest improvement was seen in symptoms of somatic subscale (27.7%) and psychological subscale (26.32%) and the least improvement was in urogenital subscale (1.19%) in perimenopausal women.

There was no statistically significant effect on systolic BP and BMI in both perimenopausal and postmenopausal women. Psychological subscales. There was no statistically significant effect on systolic BP and BMI in both perimenopausal and postmenopausal women.
conducted by Tranche et al.,[14] the total scores on the MRS questionnaire decreased by 18.1%, after regular consumption of ViveSoy® soy drink for 12 weeks.

In 2002, the Women’s Health Initiative (WHI) study showed that MHT increased the risk of breast cancer, cerebrovascular accidents, and coronary heart disease in healthy postmenopausal women.[15] Of particular note, the results of WHI were prematurely released and were not completely analyzed. The results of the WHI showed that many of the adverse effects of MHT were due to initiating MHT at a late age (mean, 63 years). As MHT is associated with many side effects, even gynecologists are reluctant in prescribing MHT postWHI. These adverse effects diverted the attention to complementary and alternative medicine therapies, the majority of which are based on soy isoflavones (phytoestrogens), presuming them to be safe. Furthermore, soy isoflavones can be used in all the stages of menopause without any serious adverse effect.

Up to 80% of perimenopausal and postmenopausal women experience VMS such as hot flashes and sweating. In our study, 69.23% of perimenopausal women experienced hot flashes, and 57.38% of postmenopausal women experienced hot flashes. We documented a 42.5% reduction in VMS in perimenopausal women and a 33.1% reduction in postmenopausal women. Our results are in synchrony with the study by Ahsan and Mallick,[13] wherein a 40% reduction was seen in VMS. In a study conducted by Tranche et al.,[14] a statistically significant reduction of VMS by 20.4% was observed after regular consumption of ViveSoy® soy drink for 12 weeks.

Lambert et al.,[16] documented a statistically significant decrease in physiological hot flash frequency and hot flash intensity, and self-reported hot flash frequency after 3 months as compared to baseline in red clover extract (phytoestrogens) treatment group but not in placebo group. In this study, the change in total, vasomotor, somatic, and psychological parameters of the Greene Climacteric Scale showed no significant difference between the treatment and placebo groups. Moreover, there was no significant difference in change in systolic and diastolic BP and plasma lipids (low-density lipoprotein [LDL], high-density lipoprotein [HDL], or triglycerides [TC]) between the treatment and placebo groups.

Hot flashes are the most immediate and troublesome consequence of menopause. The median total duration of VMS is 7.4 years. VMS causes physical and mental discomfort, sleep disturbance, and has a negative impact on the quality of life. It is one of the main reasons why menopausal women seek medical help. In our study, 48.72% of perimenopausal women experienced sleep disturbances, and 45.90% of postmenopausal women experienced sleep disturbances. Overall, we documented a 45% reduction in sleep disturbances in perimenopausal women and a 30.1% reduction in postmenopausal women.

VMS is a consequence of natural endogenous estrogen decline and dysregulation during peri- and postmenopause. A relative decrease in circulating estrogen levels alters the norepinephrine and serotonin levels, thus causing dysfunction of the thermoregulatory nucleus.[17] A hot flash is characterized by a small increase in the core body temperature and subsequent sweat response.
The postmenopausal Asian women have a significantly lower incidence (10%–25%) of hot flashes compared to postmenopausal women in Western countries (60%–90%) due to high levels of isoflavones in the diet.\(^{[18]}\)

The frequency and severity of hot fluid are individualized. It is difficult to quantify VMS. Symptoms often subside over time even without any treatment. There is no evidence that lifestyle modifications like lowering the room temperature, exercising, or avoiding triggers such as alcohol and spicy foods can ameliorate VMS.\(^{[19]}\)

Indications of MHT are for the relief of VMS, the prevention of osteoporosis, and vulvovaginal atrophy associated with menopause.

Estrogen remains the most intuitive therapy to combat hot flashes and is currently the gold standard treatment for VMS and is approved by the U. S. Food and Drug Administration. The IMS and Revised Global Consensus Guidelines recommend that the lowest effective dose of MHT should be given for the shortest duration of time, and the duration of treatment should be limited to 5 years. The risk of cancer increases with a longer duration of use and is affected by time from the start of menopause to initiation of MHT treatment. The standard now is to initiate MHT within 1–5 years of onset of menopause. The patients undertaking MHT should have annual monitoring. MHTs are unsuitable for use in the breast cancer-operated patients suffering from VMS.\(^{[20-22]}\)

Although isoflavones cannot entirely replace the role of traditional MHT in relieving menopausal symptoms, they have a good safety profile. The rule of thumb is to use conventional MHT for the relief of acute vasomotor and psychosomatic symptoms for a short time due to greater efficacy, and isoflavones have been recommended for long-term prevention, as these products are usually slow acting and are safe for prolonged use.

Isoflavones significantly lower the frequency and/or severity of hot flashes in menopausal women. Splitting the dose of soy supplement to twice daily decreased the severity of hot flashes more than giving the total amount in one dose, suggesting consistent circulating levels of phytoestrogens to be more effective.\(^{[23]}\) In our study, soy isoflavone supplementation was given twice daily.

In our study, approximately 60% of perimenopausal and postmenopausal women experienced joint and muscular discomfort, and a reduction in the same was noted in 40% of perimenopausal women and 36.1% of postmenopausal women. The postmenopausal decline in estrogen leads to loss of bone mineral density (BMD), causing osteoporosis predisposing to fractures. The annual rates and cumulative amounts of BMD loss are greater 1 year before the onset of menopause and through 2 years after menopause than those occurring between 2 and 5 years after menopause.\(^{[24]}\) Maximal bone loss occurs in the first 2 years after menopause. The rapid bone loss during early postmenopausal years is associated with a marked increase in biochemical markers of bone resorption, and due to the coupling of bone resorption and bone formation, the bone formation also increases over time.\(^{[24]}\) In a study by Sathyapalan et al.,\(^{[25]}\) there was a significant reduction of the mean \(\beta\)CTX (type 1 collagen cross-linked beta C-telopeptide) – a marker of bone resorption and P1NP (type I procollagen-N-propeptide) – a marker of bone formation, with soy protein isoflavone supplementation for 6 months.

The spine is the most sensitive to isoflavones due to the higher content of trabecular bone compared to cortical bone, higher expression of ER\(\beta\), and a larger surface area for receptor binding.\(^{[26]}\) The hip contains a higher percentage of cortical bone and undergoes slower remodeling than the spine.\(^{[27]}\) Isoflavone intake can lead to a significant reduction in joint pain. Soy protein may alleviate osteoarthritis symptoms and biochemical markers of osteoarthritis.\(^{[28]}\) A meta-analysis showed a significant attenuation of spinal bone loss (lumbar spine) after 6 months of 90 mg/day of isoflavone supplement.\(^{[28]}\)

The incidence of cardiovascular events in women increases after menopause due to estrogen deficiency, which leads to a rise in LDL cholesterol, endothelial dysfunction, and reduced carotid arterial pulsatility.\(^{[29]}\) Genistein and daidzein cause arterial relaxation through the release of nitric oxide.\(^{[30]}\) Isoflavones improve systemic arterial compliance, reduce systolic BP, improve endothelial function, and slow the progression of atherosclerosis in the early menopause. Isoflavones cause no change in diastolic BP or lipoprotein levels (total cholesterol, LDL, HDL, and TC).\(^{[31]}\)

In our study, a 0.05% reduction in systolic BP was observed in perimenopausal women and a 1.11% reduction was observed in postmenopausal women. The reduction in systolic BP in both the groups was not statistically significant. This is in contrast to a study conducted by Sathyapalan et al.,\(^{[25]}\) wherein there was a significant reduction in systolic BP with 6 months of soy protein isoflavone supplementation. In the abovementioned study, there were no significant changes observed in lipid parameters and diastolic BP. Similar findings were seen in a study by Tranche et al.,\(^{[14]}\) wherein regular consumption of ViveSoy\textsuperscript{®} soy drink...
for 12 weeks did not cause any statistically significant change in lipid parameters.

The safest and most effective treatment window for cardiovascular disease would be early menopause, before critical atherosclerotic changes set in.

The slowing of metabolism after menopause leads to obesity, which is an important risk factor for cardiovascular diseases. Isoflavones promote weight loss and coupled with exercise lead to a reduction of fat mass. Isoflavones inhibit the mechanisms involved in adipose tissue growth and regulate adipogenesis. In our study, a 3.35% reduction in BMI was observed in perimenopausal women and a 1.43% reduction was observed in postmenopausal women. The reduction in BMI in both the groups was not statistically significant.

Isoflavones improve glycemic control. Genistein, daidzein, and equol, components of isoflavones show higher binding affinity to peroxisome proliferator-activated receptor (PPAR)γ, a drug target for type 2 diabetes. Isoflavones lead to a significant improvement in glucose metabolism through inhibition of glucose uptake at the intestinal brush border through an α-glucosidase inhibitor action, tyrosine kinase inhibitory action, changes in insulin receptor numbers and affinity, intracellular phosphorylation, and alterations in glucose transport. Soy has been shown to inhibit insulin secretion from pancreatic β cells.

Isoflavones, by binding to ERβ, suppress ERα-induced cancer cell proliferation and are, thus, cancer protective. Soy isoflavones do not seem to stimulate endometrial proliferation during short-term treatment.

Urogenital tissues such as bladder, urethra, levator ani, and vaginal mucosa possess Erα and Erβ receptors which have a great affinity for genistein and daidzein. Isoflavone intake does not prevent stress incontinence or urge incontinence. Isoflavones exert a favorable effect on sexual function and quality of life. Sexual problems were noted in 7.69% of perimenopausal women and 1.64% of postmenopausal women, and it was very severe due to severe vaginal dryness. In our study, sexual dysfunction improved by 16.1% in perimenopausal and by 14.2% in postmenopausal women, and the improvement was not statistically significant. This was in contrast to the study by Ahsan and Mallick wherein the complaints of severe sexual dysfunction improved significantly among perimenopausal and postmenopausal women. In a study conducted by Tranche et al., the regular consumption of ViveSoy® soy drink for 12 weeks caused a statistically significant (21.3%) reduction in urogenital symptoms. Whereas, in our study, a 15% reduction in urogenital symptoms was observed, and the improvement was not statistically and clinically significant.

Isoflavone supplementation has a favorable effect on cognitive function, particularly verbal memory, and may induce a feeling of well-being and reduce risks for cognitive impairment. The North American Menopause Society in their study concluded the beneficial effect of soy in women younger than 65, but not older. Isoflavones suppress denervation-induced apoptosis and could prevent denervation-mediated muscle atrophy.

Soy isoflavones also have an antifatigue action. In our study, 46.15% of perimenopausal women and 59.02% of postmenopausal women experienced physical and mental exhaustion. In our study, a 47.5% reduction in symptoms of fatigue was observed in perimenopausal women. Our results are in synchrony with the study by Ahsan and Mallick wherein 29.81% reduction was seen in symptoms of fatigue.

Depression during the perimenopausal period has been influenced by the previous episodes of premenstrual syndrome, hot flashes, postpartum depression, insomnia, nocturnal sweating, socioeconomic strata, and ethnicity, and such depression is more resistant to conventional antidepressants. Soy isoflavones can be used as an add-on therapy to treat depression associated with menopause. In our study, 56.41% of perimenopausal women and 57.38% of postmenopausal women experienced depressive symptoms. We documented a 37.5% reduction in symptoms of depression in perimenopausal and 40% in postmenopausal women.

In 2011, the North American Menopause Society suggested a trial-and-error approach to prescribe isoflavones for menopausal symptoms – initial treatment with high-dose isoflavones (50 mg/day or higher) for 12 weeks when monitoring for possible side effects, but stop if there is no response to treatment after 12 weeks. The total amount of isoflavones required for symptom relief in humans is approximately 40–50 mg/day, and twice-daily doses are more effective.

The potential side effects of isoflavones are nausea, bloating, abdominal discomfort, diarrhea, constipation, malaise, fatigue, headache, dizziness, insomnia, irritability, depressed mood, rash, weight gain, breast cancer, and vaginal bleeding.

**CONCLUSION**

Soy isoflavone supplementation is beneficial in both perimenopausal and postmenopausal women, more so in perimenopausal women. Soy isoflavones are the most effective on the somatic and psychological symptoms,
and therefore, their use is more beneficial during perimenopause. Soy isoflavones are the least effective on the urogenital symptoms. There is no beneficial effect of soy isoflavone supplementation on lowering systolic BP and BMI.

Furthermore, isoflavones:
1. Attenuate lumbar spine BMD loss
2. Improve glycemic control in vitro
3. Lower total blood cholesterol concentrations, LDL, and TC
4. Reduce risk of coronary heart disease, breast cancer, the incidence of breast cancer recurrence, endometrial cancer, ovarian cancer, colorectal cancer, and bladder cancer
5. There are currently no conclusive benefits on urogenital symptoms, stress incontinence, urge incontinence, and cognition
6. Isoflavones have a good safety profile and cause benefits to overall health.

Limitations
Our study was nonrandomized; it was not placebo controlled; and there was no comparison arm. Furthermore, there was no blinding. There would have been a bias, because the MRS questionnaire was administered by a face-to-face interview. Subjective symptom assessment methods were used, which may be plagued with bias. There was a variable interval since the onset of menopause, which was the biggest setback of the study.

Author contributions
All authors have substantially contributed to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work. All authors have contributed to drafting the work and revising it critically for important intellectual content and final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest
There are no conflicts of interest.

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