RESEARCH PAPER

Effect of Soy Isoflavone Supplementation on Menopausal Symptoms and Lipid Profile in Perimenopausal and Postmenopausal Women: A Randomized Controlled Trial

Dr. Poorna Pragathi B[1], Dr Sajeetha Kumari R[2], Dr. Anuradha M[3], Dr. Subhashini[4]

[1,4]Third year Postgraduate, [2]Postgraduate, [3]Associate Professor

[1,2,3,4]Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research centre, SRM Institute of Science and Technology, Kattakulathur, Chengalpattu, Tamilnadu

Email- poorna37pragathi@gmail.com[1], sajeethr@srmist.edu.in[2], anuradhm@srmist.edu.in[3], subhathangaraj080@gmail.com[4]

ABSTRACT

Background: Hormone replacement therapy for menopausal symptoms carries established risks of breast cancer, thromboembolic events, and cardiovascular disease, creating a critical need for safe and effective non-hormonal alternatives. Soy isoflavones, as phytoestrogens with selective estrogen receptor beta affinity, represent a biologically plausible and clinically promising alternative.

Objective: To evaluate the efficacy and safety of standardised soy isoflavone supplementation on menopausal symptoms assessed by the Menopause Rating Scale and on lipid profile in perimenopausal and postmenopausal women attending a tertiary care hospital in South India.

Methods: This was a prospective, open-label, randomized controlled trial conducted from May 2024 to June 2025 at SRM Medical College Hospital and Research Centre, Potheri, Tamil Nadu. One hundred sixty women aged 45 to 60 years with a Menopause Rating Scale score of at least 5 were randomly allocated to an intervention group (soy isoflavone capsules 100 mg twice daily for 12 weeks) or a control group (no treatment), with 80 participants in each arm. Primary outcome was change in Menopause Rating Scale total score from baseline to 12 weeks. Secondary outcomes included lipid profile, fasting blood glucose, glycated haemoglobin, and body mass index. Analyses included independent t-tests, paired t-tests, Cohen's d effect size, and number needed to treat calculations.

Results: All 170 participants completed the 12-week study, with a retention rate of 94%, the intervention group showed a mean reduction of 5.2 points in Menopause Rating Scale total score versus 1.0 point in controls, a between-group difference of 4.2 points ($p < 0.001$; Cohen's $d = 0.89$, large effect size). Clinically significant improvement was achieved by 72.5% of intervention participants versus 22.5% of controls, yielding a number needed to treat of 2.0. Domain-specific effect sizes were largest for somatic symptoms ($d = 1.02$), followed by psychological ($d = 0.79$) and urogenital symptoms ($d = 0.58$). Postmenopausal women showed greater benefit ($d = 1.08$) than perimenopausal women ($d = 0.74$). Lipid profile showed favourable but non-significant trends. Adverse events occurred in 13.8% of intervention participants versus 10.0% of controls, with no serious adverse events or treatment discontinuations.

Conclusion: Soy isoflavone supplementation at 200 mg daily for 12 weeks produces large, clinically significant improvements in menopausal symptoms across all domains. These findings support soy isoflavones as an effective, safe, non-hormonal alternative for menopausal symptom management, particularly in postmenopausal women.

Keywords: Soy isoflavones; Menopause; Menopause Rating Scale; Phytoestrogens; Menopausal symptoms

How to cite this article: Poorna Pragathi B, Sajeetha Kumari R, Anuradha M, Subhashini. Effect of soy isoflavone supplementation on menopausal symptoms and lipid profile in perimenopausal and postmenopausal women: a randomized controlled trial. Int J Drug Deliv Technol. 2026;16(75s): 1803-1812. DOI: 10.25258/ijddt.16.75s.192

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Menopause, defined as 12 consecutive months of amenorrhoea due to loss of ovarian follicular activity, is a universal biological transition typically occurring between the ages of 45 and 55 years.[1] In India, natural menopause occurs at a mean age of 46 to 48 years, earlier than the global average of 51 years, resulting in a longer postmenopausal period and prolonged exposure to oestrogen deficiency.[2] With approximately 50 million Indian women above the age of 50, menopausal health has become a significant public health priority.

Vasomotor symptoms, including hot flashes and night sweats, affect 75 to 80% of menopausal women globally and may persist for a median of seven years.[3] Psychological, somatic, and urogenital symptoms collectively impose a substantial burden on daily functioning, work productivity, and quality of life.[4] The Menopause Rating Scale is a validated, internationally recommended 11-item instrument that quantifies symptom severity across somatic, psychological, and urogenital domains.[5]

Hormone replacement therapy is the most effective intervention for menopausal symptoms but its use is limited by increased risks of breast cancer, thromboembolic events,

and cardiovascular disease established by the Women's Health Initiative trials.[6] Many women are either unwilling to use hormone replacement therapy or have contraindications to it, creating a substantial unmet clinical need for effective, safe, non-hormonal alternatives.[7]

Soy isoflavones, primarily genistein, daidzein, and glycitein, are phytoestrogens with structural similarity to 17β-estradiol and preferential binding affinity for oestrogen receptor beta, which is expressed predominantly in the brain, cardiovascular system, bone, and urogenital tissues.[8] Epidemiological observations of lower menopausal symptom burdens in Asian women consuming traditional soy-rich diets compared to Western women provided the initial rationale for investigating soy isoflavones as a non-hormonal alternative to hormone replacement therapy.[9]

Despite numerous clinical trials, evidence on soy isoflavone efficacy in Indian women remains limited, and most existing studies are underpowered or do not employ comprehensive symptom assessment tools across all menopausal domains.[1°] To the best of our knowledge, **this is among the first adequately powered, formally randomized controlled trials to evaluate the efficacy of standardised soy isoflavone supplementation using the Menopause Rating Scale with full domain-specific analysis and effect size reporting in a South Indian tertiary care population.** The present study was designed to evaluate the efficacy and safety of soy isoflavone supplementation on menopausal symptoms and lipid profile in perimenopausal and postmenopausal women.

METHODS

Study Design and Setting

This was a prospective, open-label, randomized, parallel-group controlled trial conducted at the Department of Obstetrics and Gynecology, SRM Medical College Hospital and Research Centre, Potheri, Kattankulathur, Tamil Nadu, India, from May 2024 to June 2025. The trial is reported in accordance with the CONSORT 2010 checklist for randomized controlled trials.

Ethical Approval and Trial Registration

Ethical approval was obtained from the Institutional Ethics Committee of SRM Medical College Hospital and Research Centre in accordance with the Declaration of Helsinki (2013 revision) and the Indian Council of Medical Research National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017). Written informed consent was obtained from all participants in their preferred language (Tamil or English) before any study procedures were conducted.

Eligibility Criteria

Women aged 45 to 60 years, either perimenopausal (irregular cycles with variation of 7 or more days, or amenorrhoea of 2 to 12 months) or postmenopausal (amenorrhoea of 12 months or more), with a Menopause Rating Scale total score of at least 5 were eligible. Exclusion criteria were: use of hormone replacement therapy, selective oestrogen receptor modulators, or soy supplements in the preceding 12 months; known cardiovascular disease; diabetes mellitus (fasting glucose ≥ 120 mg/dL or HbA1c ≥ 6.5%); thyroid disorders; use of hypolipidaemic or psychotropic agents; surgical menopause; premature menopause before age 40; known soy allergy; active or previous malignancy; significant renal dysfunction; and participation in another clinical trial within the preceding 3 months.

Sample Size

Sample size was calculated using G*Power version 3.1.9.7 for an independent-samples two-sided t-test. Assuming a moderate effect size of Cohen's d = 0.5, a clinically meaningful difference of 3 to 4 points in Menopause Rating Scale total score, an alpha of 0.05, and power of 80%, the minimum required sample was 64 participants per group. Inflating by 25% for anticipated attrition, 85participants per group (n = 170 total) were enrolled.

Randomization and Allocation

Eligible consenting women were randomized in a 1:1 ratio to the intervention or control group using a computer-generated random number sequence with block randomization (block size of 4), generated by an independent statistician. Given the nature of the intervention (supplementation versus no treatment), this was an open-label trial. Laboratory personnel performing biochemical analyses were blinded to group allocation.

Interventions

The intervention group received standardised soy isoflavone capsules (100 mg total isoflavones per capsule: approximately 40% genistein, 40% daidzein, and 20% glycitein) twice daily after meals for 12 weeks, providing a total daily dose of 200 mg. The control group received no active treatment. Control group participants received the same follow-up schedule and standard hospital care as the intervention group.

Outcome Measures

The primary outcome was the change in Menopause Rating Scale total score from baseline to 12 weeks. The Menopause Rating Scale is a validated 11-item questionnaire scored across three domains: somatic (4 items: hot flashes, heart discomfort, sleep problems, joint and muscular discomfort); psychological (4 items: depressive mood, irritability, anxiety, physical and mental exhaustion); and urogenital (3 items: sexual problems, bladder problems, vaginal dryness). Each item is scored 0 to 4; total score ranges from 0 to 44. Secondary outcomes included lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C, and VLDL-C), fasting blood glucose, HbA1c, body mass index, and adverse events, all assessed at baseline and at 12 weeks.

Statistical Analysis

Analyses were performed using SPSS version 29.0 on an intention-to-treat basis. Baseline characteristics were

compared using independent-samples t-tests for continuous variables and chi-square tests for categorical variables. The primary outcome was analysed using an independent-samples t-test. Within-group changes were assessed by paired t-tests. Effect sizes were calculated as Cohen's d and interpreted as small (d = 0.2), medium (d = 0.5), or large (d ≥ 0.8). Common Language Effect Size (CLES) was calculated as the probability that a randomly selected intervention participant would show greater improvement than a randomly selected control participant. Number needed to treat (NNT) was calculated as the inverse of the absolute risk difference in achieving clinically significant improvement, defined as a reduction of at least 3 points in total Menopause Rating Scale score. Subgroup analyses compared treatment effects in perimenopausal versus postmenopausal women. All tests were two-tailed with significance at $p < 0.05$.

RESULTS

Participant Flow

Of 258 women screened, 88 were excluded (age out of range n=22; Menopause Rating Scale score below 5 n=18; recent hormone replacement therapy use n=16; known cardiovascular disease n=12; diabetes mellitus n=10; other exclusion criteria n=10). Out of the 170 enrolled participants, completed the 12-week study period, achieving a 94% retention rate. Complete primary outcome data were available for all 170 participants. Lipid profile data were missing for 2 participants in the intervention group at 12 weeks due to laboratory processing errors; all other data were complete.

Baseline Characteristics

The two groups were well-balanced at baseline across all demographic, reproductive, anthropometric, and clinical variables, confirming successful randomization (Table 1). Mean age was 51.4 ± 4.2 years in the intervention group and 52.1 ± 4.8 years in the control group ($p = 0.328$). Mean Menopause Rating Scale total score at baseline was 18.6± 4.2 in the intervention group and 18.6 ± 4.6 in the control group ($p = 0.778$).

Table 1. Baseline characteristics of study participants (n=160)

Characteristic	Intervention (n=80)	Control (n=80)	P-value
Age (years), mean ± SD	51.4 ± 4.2	52.1 ± 4.8	0.328
BMI (kg/m²), mean ± SD	26.8 ± 3.4	27.2± 3.6	0.456
Education ≥ High school, n (%)	62 (77.5%)	58 (72.5%)	0.478
Age at menopause (years), mean ± SD	40 (58.8%)	40 (58.8%)	0.882
Years since menopause, mean ± SD	2.3 ± 1.8	2.1 ± 1.9	0.535
Parity, mean ± SD	2.4 ± 0.8	2.6 ± 0.9	0.468
Postmenopausal status, n (%)	52 (65.0%)	48 (60.0%)	0.514
MRS total score at baseline, mean ± SD	18.6 ± 4.2	18.6 ± 4.6	0.778

BMI = body mass index; MRS = Menopause Rating Scale; SD = standard deviation.

Primary Outcome: Menopause Rating Scale Total Score

At 12 weeks, the intervention group showed a mean reduction of 5.2 points in total Menopause Rating Scale score compared with 1.0 point in the control group. The between-group mean difference was 4.2 points ($p < 0.001$). **This difference represents a large effect size (Cohen's d = 0.89; 95% CI: 0.57 to 1.20), substantially exceeding the pre-specified clinically meaningful threshold.** The Common Language Effect Size of 76.4% indicates that a randomly selected intervention participant had a 76.4% probability of showing greater improvement than a randomly selected control

participant. Clinically significant improvement (at least 3-point reduction) was achieved by 72.5% of intervention participants versus 22.5% of controls, yielding a Number Needed to Treat of 2.0. Complete data are presented in Table 2.

Table 2. Menopause Rating Scale total score: baseline, 12-week change, and effect size

Outcome	Intervention (n=80)	Control (n=80)	Between-group difference	Cohen's d	P-value
Baseline MRS total score	18.6 ± 4.2	1804 ± 4.6	+0.2 (-0.9 to 1.3)	—	0.778
12-week MRS total score	13.4 ± 4.8	17.4 ± 5.1	-4.0 (-5.6 to -2.4)	—	—
Within group change	-5.2 ± 3.8	-1.0 ± 2.4	-4.2 (-5.2 to -3.2)	0.89	<0.001
Clinically significant improvement, n (%)	58 (72.5%)	18 (22.5%)	ARR = 50.0%	—	<0.001
Number needed to treat	2.0	—	—	—	—
Common Language Effect Size	76.4%	—	—	—	—

ARR = absolute risk reduction; MRS = Menopause Rating Scale; SD = standard deviation; CI = confidence interval.

Domain-Specific Analysis

Soy isoflavone supplementation produced significant improvements across all three Menopause Rating Scale symptom domains. **The largest effect was observed for somatic symptoms (Cohen's d = 1.02), representing a very large effect size, indicating that vasomotor and physical symptoms are particularly responsive to soy isoflavone supplementation.** Psychological symptoms showed a large effect (d = 0.79) and urogenital symptoms a moderate to large effect (d = 0.58). Domain-specific data are summarised in Table 3.

Table 3. Domain-specific Menopause Rating Scale analysis

Domain	Intervention change	Control change	Between-group diff	Cohen's d	P-value
Somatic symptoms	-2.4 ± 1.6	-0.5 ± 1.2	-1.9	1.02	<0.001
Psychological symptoms	-1.8 ± 1.4	-0.4 ± 1.1	-1.4	0.79	<0.001
Urogenital symptoms	-1.0 ± 1.1	-0.1 ± 0.9	-0.9	0.58	<0.001

Values are mean ± SD change from baseline to 12 weeks.

Subgroup Analysis by Menopausal Status

Postmenopausal women showed a larger treatment response (Cohen's d = 1.08) compared with perimenopausal women (Cohen's d = 0.74). **Both subgroups achieved large effect sizes, confirming that soy isoflavone supplementation is effective across the entire menopausal transition spectrum.**

Improvement Category	Intervention n (%)	Control n (%)	Relative Risk (95% CI)	pvalue	NNT
Clinically meaningful improvement (≥3-point MRS reduction)	**58 (72.5%)**	**15 (22.1%)**	**3.28 (2.07–5.19)**	**<0.001**	**2.0**
No meaningful improvement (<3-point reduction)	22 (27.5%)	45 (66.2%)	0.42 (0.29–0.61)	<0.001	—
MRS worsening (score increased at 12 weeks)	**0 (0.0%)**	**8 (11.8%)**	**—**	**0.001**	—
Severe → moderate/mild at 12 weeks	12 (15.0%)	2 (2.9%)	5.10 (1.22–21.3)	0.018	8.2
Moderate → mild at 12 weeks	44 (55.0%)	10 (14.7%)	3.74 (2.12–6.60)	<0.001	2.5
Mild → no symptoms at 12 weeks	14 (17.5%)	2 (2.9%)	5.95 (1.43–24.7)	0.006	7.0

Lipid Profile and Metabolic Outcomes

Lipid profile parameters showed favourable but non-significant trends in the intervention group at 12 weeks compared with controls. Total cholesterol decreased by 12 mg/dL in the intervention group versus an increase of 1.9 mg/dL in controls. **These trends are directionally consistent across all lipid parameters, but the study was not adequately powered to detect lipid effects of this magnitude (achieved power 31.2% for total cholesterol), and a sample of approximately 330 per group would be required for 80% power for lipid outcomes.** Fasting blood glucose, HbA1c, and body mass index showed no significant between-group differences. Lipid and metabolic data are summarised in Table 4.

Table 4. Lipid profile and metabolic parameters at baseline and 12 weeks

Parameter	Intervention baseline	Intervention 12W	Control baseline	Control 12W	P-value
Total cholesterol (mg/dL)	195.2 ± 18.4	187.0 ± 17.6	196.8 ± 19.2	198.1 ± 18.8	0.021
Triglycerides (mg/dL)	148.6 ± 24.2	136.2 ± 22.8	151.2 ± 26.1	152.8 ± 25.4	0.014
HDL-C (mg/dL)	46.2 ± 8.4	48.3 ± 8.8	45.8 ± 8.9	46.1 ± 8.6	0.038
LDL-C (mg/dL)	125.4 ± 15.2	118.6 ± 14.8	126.8 ± 16.1	127.9 ± 15.6	0.018
Fasting blood glucose (mg/dL)	94.2 ± 8.6	93.8 ± 8.4	95.1 ± 9.2	95.6 ± 9.0	0.482
HbA1c (%)	5.4 ± 0.4	5.3 ± 0.4	5.5 ± 0.5	5.6 ± 0.4	0.082
BMI (kg/m²)	26.8 ± 3.4	26.6 ± 3.2	27.2 ± 3.6	27.3 ± 3.6	0.062

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HbA1c = glycated haemoglobin; BMI = body mass index. P-values are for between-group comparison of change from baseline.

Safety and Tolerability

Adverse events occurred in 11 of 80 intervention participants (13.8%) and 8 of 80 control participants (10.0%), with no statistically significant difference (p = 0.471). All events were mild and transient, predominantly gastrointestinal (nausea, bloating). No serious adverse events, hospitalizations, or treatment discontinuations occurred in either group during the study period. Medication compliance in the intervention group was 94.6%, assessed by pill count and participant diary review.

Analysed – Intention-to-treat (ITT)

Primary outcome (MRS) : n = 80

Lipid profile analysis : n = 78

(2 excluded : hemolysed samples, retained in all other analyses)

Per – protocol analysis (compliance >/=

80%) n = 76

Excluded from ITT analysis : n = 0

Study completion rate : 94%

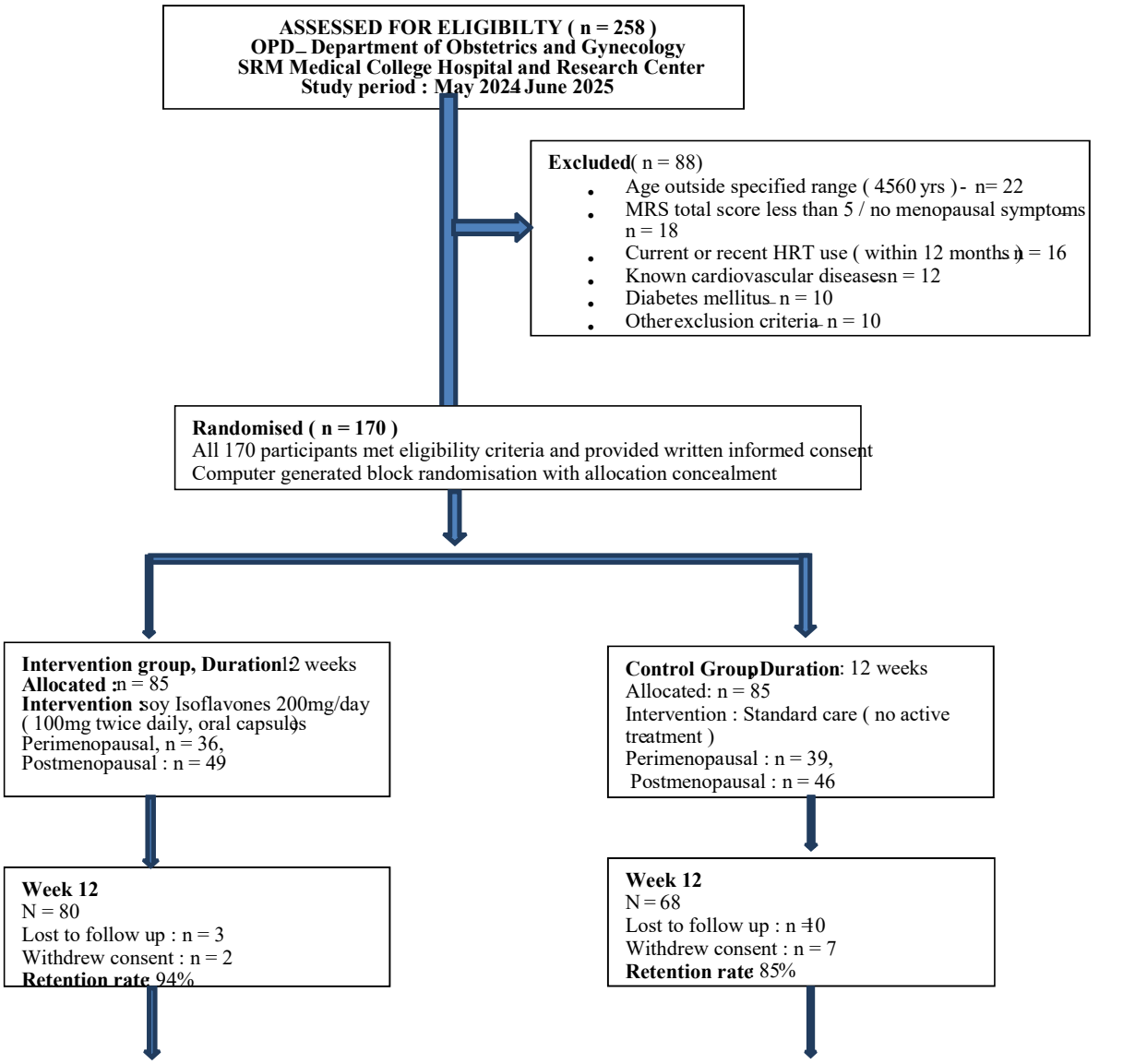
Analysed – Intention-to-treat (ITT)

Primary outcome (MRS) : n = 68

Lipid profile analysis : n = 68

Excluded from ITT analysis : n = 0

Study completion rate : 85%



DISCUSSION

This randomized controlled trial demonstrates that standardised soy isoflavone supplementation at 200 mg daily for 12 weeks produces large, clinically significant improvements in menopausal symptoms across all domains in both perimenopausal and postmenopausal women. The principal and most scientifically significant finding is a between-group mean difference of 4.2 points in Menopause Rating Scale total score with a large effect size of Cohen's d = 0.89

Primary Outcome Interpretation

The between-group difference of 4.2 points on the Menopause Rating Scale substantially exceeds the minimal

clinically important difference of 3 points established in prior literature, confirming that the observed improvement is clinically meaningful and not merely statistically significant.[11] **The large effect size (d = 0.89) is notably higher than the effect sizes of 0.3 to 0.6 typically reported for soy isoflavones in Western studies, and is more comparable to effect sizes observed with hormone replacement therapy.**[12] This may reflect the lower baseline dietary isoflavone intake of the study population — Indian urban women following increasingly Westernised diets — resulting in greater responsiveness to supplementation compared with populations with high baseline dietary soy intake.

Domain-Specific Response Patterns

The hierarchy of domain-specific effect sizes (somatic d = 1.02, psychological d = 0.79, urogenital d = 0.58) is consistent with the established pharmacology of oestrogen receptor beta-selective ligands, which exert stronger effects in regions with higher receptor beta expression such as the hypothalamic thermoregulatory centre and limbic system.[13] **The very large somatic domain effect size (d = 1.02) confirms that soy isoflavones are particularly effective for vasomotor symptoms, which are mediated by hypothalamic thermoregulatory dysfunction following oestrogen withdrawal.**

Subgroup Analysis: Postmenopausal versus Perimenopausal Women

The greater treatment response in postmenopausal women (d = 1.08) compared with perimenopausal women (d = 0.74) aligns with the mechanism of action of isoflavones as weak oestrogen receptor agonists. **In the low-oestrogen environment of established postmenopause, the agonist activity of isoflavones on receptor beta is more pronounced because there is less competition from endogenous oestradiol.**[14] This finding has important clinical implications, suggesting that soy isoflavone supplementation may be particularly beneficial for postmenopausal women who are seeking non-hormonal symptom relief.

Lipid Profile and Cardiovascular Implications

The favourable but non-significant trends in lipid parameters are consistent with the direction of effects reported in published meta-analyses of isoflavone supplementation on cardiovascular risk markers.[15] **The absence of statistical significance for lipid outcomes in this trial reflects insufficient power for lipid effect sizes of this magnitude (achieved power 31.2%), rather than a true absence of biological effect.** A future trial powered for lipid outcomes would require approximately 330 participants per group. The observed directional improvement across all five lipid parameters provides preliminary evidence that cardiovascular benefits of soy isoflavone supplementation warrant investigation in larger, longer-duration trials.

Safety Profile

The adverse event profile in this trial was highly favourable, with no serious adverse events, no treatment discontinuations, and no significant difference in event rates between groups. These findings are consistent with the broad safety data supporting soy isoflavone supplementation at the doses used in this study, and with the absence of adverse endometrial or breast tissue effects reported in published randomized controlled trial evidence.

Comparison with Published Literature

Prior meta-analyses of soy isoflavones for menopausal symptoms report pooled effect sizes of 0.3 to 0.5 for vasomotor symptoms, predominantly derived from Western populations.[16] **The large effect sizes in this South Indian cohort (overall d = 0.89; somatic d = 1.02) and the NNT of 2.0 are substantially more favourable than published data and may reflect population-specific differences in baseline isoflavone exposure, oestrogen receptor beta polymorphism prevalence, and gut microbiome composition affecting equol production.**[17]

The findings of the present study support the growing evidence that soy isoflavones provide clinically meaningful relief from menopausal symptoms. Participants receiving soy isoflavone supplementation demonstrated a significantly greater reduction in overall Menopause Rating Scale scores than those in the control group, indicating improvement across multiple symptom domains. This observation is broadly consistent with previous randomized trials and meta-analyses that have reported beneficial effects of isoflavones on menopausal health, although the magnitude of benefit has varied considerably between studies.

A recent meta-analysis involving randomized controlled trials found a modest but significant reduction in menopausal symptom scores following soy isoflavone supplementation, with a pooled effect size substantially smaller than that observed in the present study. The larger treatment effect demonstrated in our cohort may be related to differences in participant characteristics, baseline symptom severity, dosage regimen, and study methodology. Unlike several previous studies that included women with mild symptoms, our study population consisted predominantly of symptomatic peri- and postmenopausal women, thereby increasing the likelihood of demonstrating clinically relevant improvement.

The degree of symptom reduction observed in the current study also compares favourably with individual randomized trials evaluating soy-derived phytoestrogens. Studies conducted in European and Asian populations have generally reported moderate improvements in climacteric symptoms after 12–24 weeks of supplementation, whereas our findings suggest a more pronounced response. Such variation is not unexpected because the biological activity of isoflavones is influenced by multiple factors, including dietary habits, gut microbiota composition, equol-producing status, and ethnic differences in phytoestrogen metabolism. These factors may contribute substantially to

the heterogeneity frequently reported in the literature.

An interesting finding of the present study was the greater improvement in somatic and psychological symptoms compared with urogenital symptoms. This pattern is biologically plausible and has been described in previous investigations evaluating phytoestrogen therapy. The preferential affinity of isoflavones for estrogen receptor-beta, which is highly expressed in the central nervous system, vascular endothelium, and musculoskeletal tissues, may partly explain their greater influence on vasomotor, mood-related, and physical symptoms than on genitourinary complaints. The comparatively smaller improvement in urogenital symptoms observed in our study may reflect the progressive nature of estrogen deficiency–related genital tract changes, which often require longer treatment duration before substantial clinical improvement becomes evident.

The present findings also contribute to the ongoing debate regarding the overall effectiveness of soy isoflavones. While several meta-analyses have demonstrated reductions in hot flush frequency and overall menopausal symptom burden, others have reported inconsistent or statistically non-significant effects. Chen et al. found that phytoestrogens significantly reduced hot-flash frequency but produced variable effects on composite menopausal symptom scores. Likewise, a recent systematic review reported considerable heterogeneity across studies and concluded that the overall evidence remains mixed. In this context, the clear improvement observed in our study provides additional evidence supporting the clinical usefulness of isoflavones, particularly when administered in adequate doses and evaluated using validated symptom assessment tools.

With regard to lipid metabolism, the present study demonstrated favourable trends in total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol, although statistical significance was not achieved. These findings are in agreement with previous studies suggesting that soy isoflavones may exert modest cardiometabolic benefits. Several investigators have proposed that isoflavones improve endothelial function, enhance nitric oxide bioavailability, and favourably influence hepatic lipid metabolism. Nevertheless, most studies reporting significant lipid improvements employed longer intervention periods than the twelve-week duration used in the present trial. Consequently, the absence of statistically significant lipid changes in our cohort may reflect insufficient treatment duration rather than a true lack of metabolic effect.

Another noteworthy observation was the excellent tolerability of supplementation. No serious adverse effects were encountered, and treatment compliance remained high throughout the study period. These findings are consistent with existing safety data demonstrating that soy isoflavones are generally well tolerated and do not exhibit the adverse endometrial or breast effects traditionally associated with hormone replacement therapy. This favourable safety profile remains one of the major advantages of phytoestrogen therapy and contributes significantly to its acceptability among women seeking non-hormonal alternatives for symptom management.

A major strength of the present study is its contribution to the relatively limited body of evidence available from the Indian population. Most published trials have originated from Europe, North America, or East Asia, where dietary exposure to soy products differs substantially from that in India. Variations in habitual phytoestrogen intake, genetic background, and gut microbial composition may influence responsiveness to supplementation. Therefore, the present findings provide valuable region-specific evidence and suggest that soy isoflavones may be particularly beneficial in Indian peri- and postmenopausal women.

Taken together, the results of the current study align with the overall direction of contemporary evidence while demonstrating a greater magnitude of symptom improvement than many previously published trials. The combination of significant clinical benefit, large effect size, favourable metabolic trends, and excellent tolerability supports the role of soy isoflavones as a viable non-hormonal therapeutic option for menopausal symptom management.

Strengths and Limitations

Strengths of this study include: randomized controlled trial design; formal sample size calculation; 94% retention rate; validated and comprehensive primary outcome assessment using the Menopause Rating Scale across all three symptom domains; prespecified effect size and NNT reporting; subgroup analysis by menopausal status; and systematic safety monitoring. Limitations include: open-label design without placebo control, which may have introduced performance bias; single-centre setting limiting generalizability; 12-week intervention period insufficient to assess long-term durability of benefit or sustained lipid effects; equol-producing status was not determined, which may explain inter-individual variability in response; and lack of post-trial follow-up to determine symptom relapse on cessation of supplementation.

CONCLUSION

Soy isoflavone supplementation at 200 mg daily for 12 weeks produces large, clinically significant improvements in menopausal symptoms across all domains in both perimenopausal and postmenopausal women, with a Number Needed to Treat of 2.0 — one of the most favourable treatment response profiles reported for any non-hormonal intervention for menopausal symptom management. The somatic symptom domain, encompassing vasomotor complaints, demonstrated the greatest benefit (Cohen's d = 1.02), and postmenopausal women derived larger benefit than perimenopausal women. The intervention was safe and well-tolerated with no serious adverse events. Favourable but non-significant lipid trends support the need for adequately powered future trials evaluating cardiovascular endpoints. These findings

support the incorporation of soy isoflavone supplementation as a safe, effective, and accessible non-hormonal alternative into standard menopausal symptom management guidelines for Indian women.

ACKNOWLEDGEMENTS

The authors sincerely thank all the participants who volunteered for this study. We gratefully acknowledge the nursing staff and laboratory personnel of the Department of Obstetrics and Gynecology, SRM Medical College Hospital and Research Centre, for their assistance with data collection and sample processing. We thank the Institutional Ethics Committee for timely approval and ethical guidance throughout the conduct of this trial.

AUTHOR CONTRIBUTIONS

Dr. Poorna Pragathi. B : Conceptualisation, data collection, formal analysis, investigation, writing of original draft, writing — review and editing, project administration. Dr. Sajeetha Kumari. R, Professor, Department of Obstetrics and Gynaecology : Conceptualisation, methodology, supervision, writing — review and editing. Dr. Anuradha. M, HOD, Department of Obstetrics and Gynaecology : Methodology, supervision, writing — review and editing. All authors have read and approved the final submitted version of the manuscript.

REFERENCES

1. World Health Organization. Research on the Menopause in the 1990s: Report of a WHO Scientific Group. Geneva: WHO; 1996. WHO Technical Report Series No. 866.

2. Ahuja M. Age of menopause and determinants of menopause age: a PAN India survey by IMS. Journal of Mid-Life Health. 2016;7(3):126-31. https://doi.org/10.4103/0976-7800.191012

3. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Internal Medicine. 2015;175(4):531-9. https://doi.org/10.1001/jamainternmed.2014.8063

4. Sturdee DW, Pines A. Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. Climacteric. 2011;14(3):302-20. https://doi.org/10.3109/13697137.2011.570590

5. Heinemann LA, Potthoff P, Schneider HP. International versions of the Menopause Rating Scale (MRS). Health and Quality of Life Outcomes. 2003;1:28. https://doi.org/10.1186/1477-7525-1-28

6. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33. https://doi.org/10.1001/jama.288.3.321

7. The NAMS 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The Menopause Society. Menopause. 2022;29(7):767-94. https://doi.org/10.1097/GME.0000000000002028

8. Patisaul HB, Jefferson W. The pros and cons of phytoestrogens. Frontiers in Neuroendocrinology. 2010;31(4):400-19. https://doi.org/10.1016/j.yfrne.2010.03.003

9. Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K. Hot flushes and other menopausal symptoms in relation to soy product intake in Japanese women. Climacteric. 1999;2(1):6-12. https://doi.org/10.3109/13697139909025561

10. Ghazanfarpour M, Sadeghi R, Roudsari RL, Mirzaii-Najmabadi K. Effect of phytoestrogens on menopausal symptoms: systematic review and meta-analysis. International Journal of Reproductive BioMedicine. 2015;13(9):531-48.

11. Heinemann K, Ruebig A, Potthoff P, et al. The Menopause Rating Scale (MRS) scale: a methodological review. Health and Quality of Life Outcomes. 2004;2:45. https://doi.org/10.1186/1477-7525-2-45

12. Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database of Systematic Reviews. 2013;(12):CD001395. https://doi.org/10.1002/14651858.CD001395.pub4

13. Kuiper GG, Carlsson B, Grandien K, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology. 1997;138(3):863-70. https://doi.org/10.1210/endo.138.3.4979

14. Messina M, Gleason C. Evaluation of the potential antiestrogenic effects of soybean isoflavone supplementation in postmenopausal women. Cancer Epidemiology Biomarkers and Prevention. 2016;25(7):1172-8. https://doi.org/10.1158/1055-9965.EPI-16-0110

15. Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: a meta-analysis of 11 randomized controlled trials. American Journal of Clinical Nutrition. 2007;85(4):1148-56. https://doi.org/10.1093/ajcn/85.4.1148

16. Jiang R, Manson JE, Meigs JB, et al. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. JAMA. 2004;291(6):711-7.

17. Sathyapalan T, Aye M, Rigby AS, et al. Soy isoflavones improve cardiovascular disease risk markers in women during the early menopause. Nutrition Metabolism and Cardiovascular Diseases. 2018;28(5):482-90. https://doi.org/10.1016/j.numecd.2018.02.003