Open Access

Journal of Scientific Insights
E-ISSN: 3062-8571
DOI: https://doi.org/10.69930/jsi.v3i4.823
Review Article

ScienceTech Group

Vol. 3 (4), 2026
Page: 379-392

The Effects of Soy Isoflavone on Lipid Profile in Menopausal Women: A Systematic Literature Review of Randomized Controlled Trials

Nur Apriyan [1,*], Asyifa Robiatul Adawiyah [1], Atik Kridawati [1], Lili Indrawati [2], Sugeng Hadisaputra [3]

[1] Departement of Public Health, Faculty of Health Sciences, Universitas Respati Indonesia, Indonesia
[2] Departement of Hospital Administration, Faculty of Health Sciences, Universitas Respati Indonesia, Indonesia
[3] Departement of Nursing Science, Faculty of Health Sciences, Universitas Respati Indonesia, Indonesia
*Email (corresponding author): nur_a@urindo.ac.id

Abstract. *Background: The transition into menopause during the perimenopausal period causes fluctuating ovarian function and adverse lipid shifts, increasing cardiovascular disease (CVD) risks. This systematic literature review evaluates the clinical efficacy of soy isoflavone supplementation on lipid profiles in perimenopausal women, synthesizing evidence from randomized controlled trials (RCTs) only. Methods: A systematic search was conducted in PubMed, Scopus, and ProQuest through May 2026. Of the 355 initially identified records (PubMed: 11, Scopus: 309, ProQuest: 35), four RCTs evaluating perimenopausal cohorts met the strict inclusion criteria for the qualitative synthesis. The reviewed trials investigated interventions ranging from isolated soy protein to specific isoflavone extracts and multi-ingredient nutraceutical combinations. Results: The synthesized data revealed nuanced, baseline-dependent lipidemic outcomes. In healthy, normocholesterolemic perimenopausal women, soy protein or isolated isoflavone intake did not significantly modulate total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or coagulation factors. Conversely, pronounced therapeutic benefits—characterized by significant reductions in TC, LDL-C, and triglycerides, along with improved metabolic biomarkers—were observed exclusively in perimenopausal cohorts with baseline metabolic syndrome or severe vasomotor symptoms, or when co-administered with metabolic-synergistic factors such as myo-inositol. Conclusion: Soy isoflavones do not uniformly alter lipid profiles in perimenopausal women. Their cardioprotective efficacy is heavily contingent upon baseline metabolic status, offering substantial lipid-modulating benefits for metabolically vulnerable cohorts while showing negligible effects in healthy individuals during the menopausal transition.*

Keywords: *Soy Isoflavones; Lipid Profile; Perimenopause; Menopausal Transition; Cardiovascular Risk*

1. Introduction

The perimenopausal transition represents a critical biological phase in a woman's life, characterized by progressive ovarian senescence and fluctuating estrogen production. Beyond the structural and symptomatic manifestations, such as vasomotor instability, sleep disturbances, and psychological distress, this endocrinological shift profoundly alters systemic metabolism (Gatenby & Simpson, 2024; Jeong & Park, 2022; Peacock et al., 2023). Specifically, the decline in circulating 17ß-estradiol fundamentally impairs lipid metabolism, often precipitating an atherogenic lipid profile marked by elevated total cholesterol (TC),

Received: 24 June 2026 / Accepted: 20 July 2026 / Available online: 24 July 2026

increased low-density lipoprotein cholesterol (LDL-C), accelerated accumulation of triglycerides (TG), and a concomitant reduction or dysfunction of high-density lipoprotein cholesterol (HDL-C) (Mauvais-Jarvis et al., 2013; Torosyan et al., 2022; Zimodro et al., 2024). Consequently, the perimenopausal period serves as a crucial window wherein cardiovascular disease (CVD) risks escalate substantially, shifting from a historically cardioprotected status during the reproductive years to an accelerated vascular aging trajectory (Meyer & Barton, 2016; Torosyan et al., 2022; Zimodro et al., 2024).

To mitigate these transitional metabolic complications, conventional Hormone Replacement Therapy (HRT) has long been utilized as a primary medical intervention. However, long-term adherence to conventional HRT is significantly constrained by clinical apprehensions regarding adverse sequelae, including increased risks of breast cancer, thromboembolic events, and stroke (Bennett & Mathur, 2024). These safety limitations have fueled a global paradigm shift toward evidence-based complementary therapies, with soy-derived phytoestrogens—predominantly soy isoflavones such as genistein, daidzein, and glycitein —emerging as leading candidates (Anderson et al., 1999; Jassi et al., 2010; Silva et al., 2021; Vitale et al., 2013). Mechanistically, soy isoflavones exhibit structural similarities to endogenous 17β-estradiol, allowing them to bind to estrogen receptors (ERα) and to ERβ, which is highly expressed in vascular endothelial cells and the myocardium (Chen et al., 2022; Meyer & Barton, 2016; Vitale et al., 2013). Through these receptor-mediated pathways and distinct non-genomic antioxidant mechanisms, soy isoflavones are hypothesized to modulate hepatic lipid synthesis, enhance LDL receptor expression, and suppress lipid peroxidation, thereby offering a natural, safer cardioprotective alternative (Anderson et al., 1999; Shukla et al., 2007; Vitale et al., 2013).

Despite compelling preclinical data and biological plausibility (Shukla et al., 2007), evidence from human clinical trials on the lipid-modulating efficacy of soy isoflavones in perimenopausal women remains paradoxically fragmented and highly inconsistent. While some randomized controlled trials (RCTs) document robust therapeutic reductions in circulating atherogenic lipoproteins, other high-quality trials yield null results, showing no substantial differences compared to placebo or whey protein controls (Dent et al., 2001; Greany et al., 2008; Jassi et al., 2010; Tokede et al., 2015). These disparities are further compounded by structural heterogeneity across clinical designs, including variations in the baseline metabolic health of the cohorts, the severity of menopausal transition symptoms, the mode of administration (e.g., isolated extracts vs. whole soy protein), and the concomitant use of synergistic metabolic cofactors such as myo-inositol (D'Anna et al., 2014; Setchell et al., 2001; Silva et al., 2021; Trimarco et al., 2016).

While several broad systematic reviews have previously evaluated the impact of phytoestrogens on menopausal health, they frequently pool perimenopausal, early postmenopausal, and late postmenopausal cohorts together, which introduces significant physiological confounding given the highly distinct hormonal dynamics of these sub-stages (Geraci et al., 2021; Silva et al., 2021; Tokede et al., 2015). To date, there is a distinct lack of a refined, targeted systematic synthesis focused exclusively on the perimenopausal transition—a phase in which metabolic plasticity is highest and therapeutic interventions may yield the most profound preventive outcomes. Therefore, this systematic literature review aims to rigorously evaluate and synthesize clinical evidence from randomized controlled trials (RCTs) on the effects of soy isoflavone supplementation on lipid profiles in perimenopausal women. By dissecting the modulating influences of baseline metabolic status, dosage formulations,

and trial methodologies, this study seeks to resolve existing ambiguities and provide a definitive, evidence-based consensus to guide clinical practice and dietary recommendations for cardiovascular risk mitigation during the menopausal transition.

The novelty of this systematic literature review lies in its hyper-targeted clinical focus on the perimenopausal transition window, a distinct metabolic phase that is consistently conflated with established postmenopause in existing clinical syntheses. While prior broader systematic reviews have pooled highly heterogeneous cohorts across various menopausal stages, this study isolates and scrutinizes the lipidemic response to soy isoflavones exclusively within perimenopausal physiology. Furthermore, this review transcends simplistic generalizations about efficacy by introducing a critical, multidimensional stratification. It systematically evaluates how baseline metabolic syndrome status, the severity of transitional symptoms, and the presence of synergistic nutraceutical cofactors (such as myo-inositol or specific compound matrices) modulate treatment outcomes (D'Anna et al., 2014; Silva et al., 2021; Tokede et al., 2015; Torosyan et al., 2022; Trimarco et al., 2016). By mapping these specific clinical and formulation-dependent boundaries, this review provides a pioneering, precise, evidence-based framework that resolves the historical fragmentation of soy isoflavone clinical data, offering targeted therapeutic clarity for cardiovascular risk mitigation during the menopausal transition. This study is relevant to SDG 3 (Good Health and Well-Being) and SDG 5 (Gender Equality).

2. Methods

2.1. Study Design

This study employed a systematic literature review (SLR) approach following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines (Page et al., 2021).

2.2. Theoretical Framework

This systematic literature review is theoretically anchored in the paradigm of receptor-mediated cardiovascular endocrinology, specifically drawing on the Estrogen Receptor (ER) Signaling Pathway and the Phytoestrogen Cardioprotection Hypothesis (Kuiper et al., 1996; Messina, 2010). The conceptual framework mapping the interaction between perimenopausal physiological transition, soy isoflavone consumption, and systemic lipid modification is operationalized through three distinct biochemical vectors:

2.2.1. Selective Estrogen Receptor Modulator (SERM) Mechanism

During the perimenopausal transition, progressive ovarian follicular depletion induces a precipitous decline in circulating 17ß-estradiol. Structurally homologous to endogenous estrogen, soy isoflavones (principally genistein and daidzein) function as natural SERMs. This framework relies on the differential binding affinities of estrogen receptor subtypes: isoflavones exhibit a strong preference for ERß, which is highly expressed in vascular endothelial cells and adipose tissue, over ERα, which predominates in reproductive tissues (Chen et al., 2022; Vitale et al., 2013). Isoflavones compensate for the transitional estrogen deficit, activating downstream cardioprotective transcription without triggering adverse oncological proliferation (Anderson et al., 1999; Meyer & Barton, 2016; Vitale et al., 2013).

2.2.2. Receptor-Mediated Hepatic Lipid Clearance

The genomic framework dictates that binding of soy isoflavones to hepatic estrogen receptors triggers transcriptional up-regulation of hepatic low-density lipoprotein (LDL) receptors. Enhanced LDL receptor density on hepatocytes accelerates the clearance rate of circulating apolipoprotein B-containing lipoproteins. Concurrently, isoflavones modulate the transcription of Sterol Regulatory Element-Binding Proteins (SREBPs), key molecular switches regulating de novo lipogenesis. This dual pathway theoretically accounts for the reduction of systemic Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C), and Triglycerides (TG) (Shukla et al., 2007).

2.2.3. The Basal Metabolic and Nutraceutical Matrix Dependency

A novel extension of this framework posits that the lipid-modulating efficacy of phytoestrogens is not absolute but highly contingent on the subject's baseline metabolic environment. In normocholesterolemic systems, the lipid regulatory pathways operate at homeostatic equilibrium, rendering exogenous isoflavone modulation negligible. Conversely, in metabolic dysfunction or a severe vasomotor crisis, the homeostatic threshold is disrupted, rendering hepatic receptors hypersensitive to isoflavone stimulation (Dent et al., 2001; Greany et al., 2008; Jassi et al., 2010; Tokede et al., 2015). Furthermore, when isoflavones are complexed with synergistic metabolic cofactors (such as myo-inositol), a multi-targeted pathway is activated, improving insulin sensitivity and amplifying the downstream lipolytic cascade (D'Anna et al., 2014; Trimarco et al., 2016).

2.3. PICOS Framework

The review applied the Population-Intervention-Comparison-Outcome-Study (PICOS) framework.

Component	Description
Population	Perimenopausal women undergoing the menopausal transition, including normocholesterolemic individuals, those experiencing severe vasomotor symptoms, or individuals with comorbid baseline metabolic syndrome
Intervention	Supplementation with soy isoflavones, including isolated isoflavone extracts (e.g., genistein, daidzein), whole soy protein formulations, or multi-ingredient nutraceutical complexes containing soy isoflavones.
Comparison	Placebo controls, non-isoflavone protein controls (e.g., whey protein), active standard care, or baseline values within crossover trial designs.
Outcomes	**Primary Outcomes:** Systemic lipid profile biomarkers including Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), and Triglycerides (TG).
Study Design	Randomized Controlled Trials (RCTs), including parallel-group and crossover double-blind clinical trial designs.

2.4. Search Strategy

The literature search was conducted between March and April 2026 using:

1. Scopus
2. PubMed
3. ProQuest

Example Boolean search string:
(isoflavones[MeSH Terms]) OR (soy isoflavones)) OR (genistein)) OR (daidzein)) OR (glycitein)) AND (postmenopause[MeSH Terms])) OR (postmenopausal women)) AND (triglycerides[MeSH Terms])) OR (triglycerides)) OR (lipid profile)) AND (blood glucose[MeSH Terms])) OR (fasting glucose)) OR (glycemic control)) AND (randomized controlled trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])

2.5. Inclusion Criteria

1. Population: Perimenopausal women undergoing the menopausal transition (defined by irregular menstrual cycles or fluctuating ovarian function), including healthy individuals, those presenting with metabolic vulnerabilities, or cohorts with baseline metabolic syndrome.
2. Intervention: Randomized trials utilizing explicit oral soy isoflavone interventions, including isolated components (e.g., genistein, daidzein), full soy protein matrices, or structured multi-ingredient nutraceutical complexes where soy isoflavones serve as a primary active ingredient.
3. Comparison: Controlled designs featuring an inactive placebo, non-isoflavone dietary protein controls (e.g., whey protein isolates), standard active care, or baseline parameters in a crossover trial layout.
4. Outcomes: Studies reporting quantitative data on at least one primary lipid biomarker, including Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), or Triglycerides (TG).
5. Study Design: Peer-reviewed Randomized Controlled Trials (RCTs) with parallel-group or crossover configurations, published with full-text availability.

2.6. Exclusion Criteria

1. **Population:** Studies focusing exclusively on established late postmenopausal cohorts (e.g., several years post-menopause without perimenopausal tracking) or women undergoing surgically induced menopause (oophorectomy).
2. **Intervention:** Interventions involving non-soy derived phytoestrogens (e.g., red clover, flaxseed, lignans) or trials assessing dietary soy intake via general food frequency questionnaires without standardized dosages.
3. **Outcomes:** Studies that failed to isolate or measure circulating lipid and lipoprotein fractions as defined outcomes.
4. **Study Design:** Non-randomized clinical trials, observational cohorts, case-control designs, cross-sectional studies, animal models, *in vitro* laboratory experiments, abstracts without full text, and systematic reviews or meta-analyses.

2.7. Screening and Eligibility Process

Duplicate records were removed using EndNote and Mendeley software. Two reviewers independently screened titles and abstracts before conducting a full-text eligibility assessment.

2.8. Quality Appraisal

Methodological quality was assessed using the adapted Critical Appraisal Skills Program (CASP) and Joanna Briggs Institute (JBI) criteria.

The appraisal evaluated:

1. research clarity,
2. methodological appropriateness,
3. sampling adequacy,
4. data collection quality,
5. analytical rigor,
6. ethical considerations,
7. Relevance to the review topic.

Most studies demonstrated moderate-to-high methodological quality.

2.9. Data Analysis

A systematic narrative synthesis approach was utilized to analyze the extracted clinical data. Due to the marked clinical and methodological heterogeneity across the trials, specifically regarding participant baseline characteristics, soy formulations, and co-administered nutraceutical components, a formal quantitative meta-analysis was deemed inappropriate.

The analytical process was operationalized through the following steps:

1. **Data Tabulation:** Study characteristics, including sample sizes, subject demographics, intervention types, dosages, and durations, were systematically tabulated.
2. **Biomarker Stratification:** Changes in primary lipid fractions—specifically Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), and Triglycerides (TG)—were evaluated from baseline to post-intervention.
3. **Heterogeneity Scrutiny:** Findings were stratified and critically analyzed based on predefined clinical boundaries:
   a. *Baseline Metabolic Profile:* Distinguishing outcomes between healthy normocholesterolemic cohorts and those presenting with metabolic syndrome or vulnerabilities.
   b. *Formulation Matrix:* Dissecting the differential effects of isolated soy isoflavones versus whole soy protein or combination formulas containing synergistic co-factors (e.g., myo-inositol).

2.10. PRISMA 2020 Flow Diagram

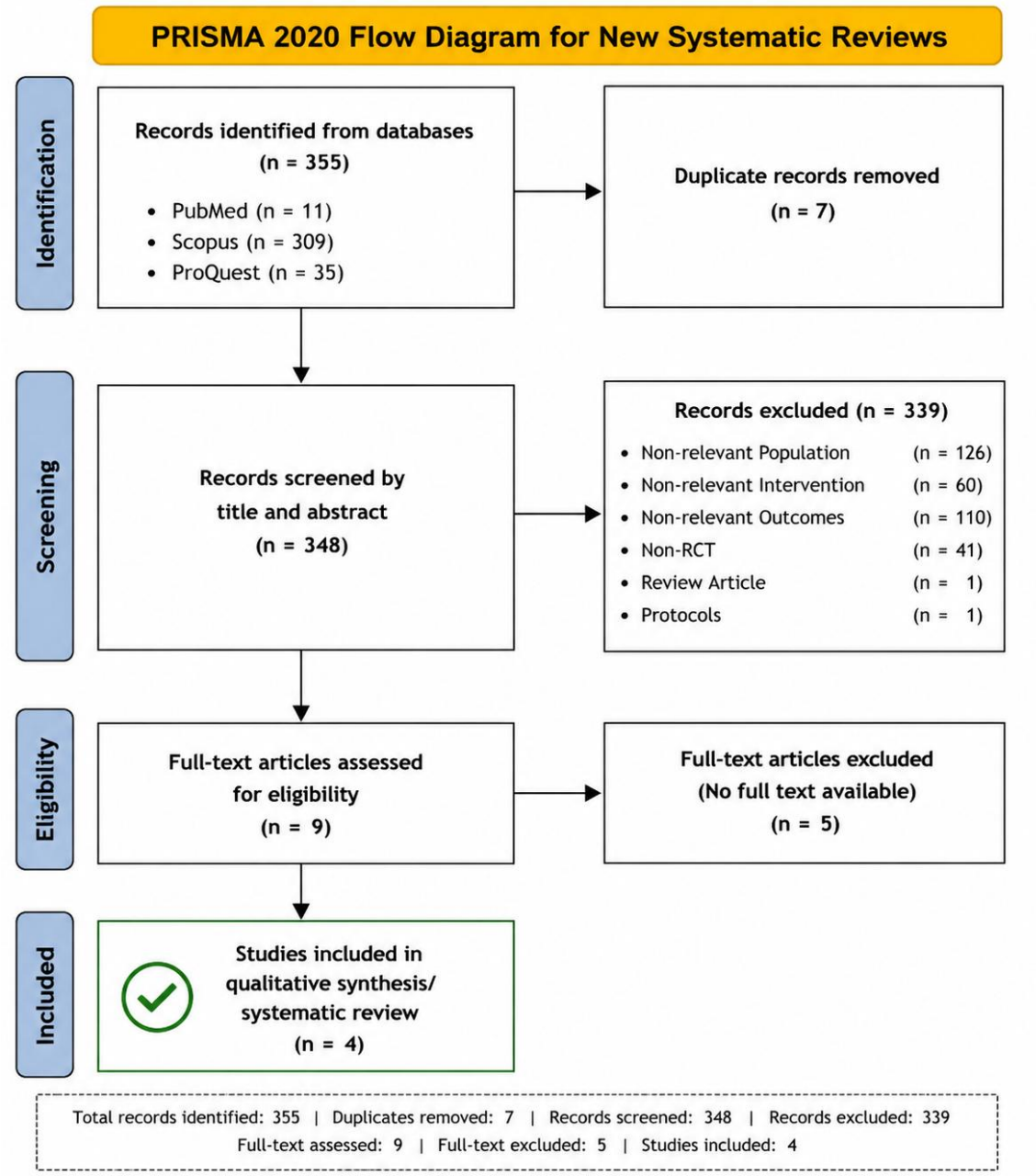

Figure 1. PRISMA 2020 Flow Diagram

The PRISMA framework improved methodological transparency and reproducibility in the review process.

3. Results and Discussion

3.1. Result

The primary baseline methodologies and clinical parameters of the four randomized controlled trials (RCTs) included in this systematic synthesis are comprehensively tabulated in Table 1.

Table 1. Baseline Characteristics and Methodological Features of the Included RCTs

Author & Year	Country	Study Design	Sample Size (N)	Participant Characteristics	Intervention Matrix & Daily Dosage	Duration
Dent et al. (2001)	USA	Paralle, randomized, double-blind	69	Healthy, normo-cholesterolemic perimenopausal women	Whole soy protein 40gr/dL containing either: • Isoflavone-rich 80.4mg/dL • Isoflavone-poor 4.4mg/dL • Whey protein (Control)	24 weeks
Turhan et al. (2009)	Turkey	Parallel, randomized, double-blind	34	Healthy perimenopausal women	• Isolated soy isoflavone extract (80mg/dL) • Placebo control	3 months
D'Anna et al. (2014)	Italy	Parallel, randomized, double-blind	71	Perimenopausal women with established Metabolic Syndrome	• Multi-ingredient combination: Specific flavonoid extract synergized with Myo-inositol • Placebo control	6 months
Trimarco et al. (2018)	Italy	Crossover, randomized, double-blind	72	Perimenopausal women presenting with severe vasomotor symptoms and cardiovascular risk	• Multi-ingredient nutraceutical matrix containing Soy Isoflavones 60mg/dL • Placebo control	8 weeks

The comprehensive systematic search and eligibility screening yielded 4 randomized controlled trials (RCTs) evaluating the lipid-modulating effects of soy isoflavones in perimenopausal women. As detailed in Table 1, the included trials were published over a 15-year period (2001–2016), reflecting sustained clinical interest in this therapeutic domain. Geographically, the evidence base exhibits a prominent European clustering, with two trials conducted in Italy (D'Anna et al., 2014; Trimarco et al., 2016) and one in Turkey (Turhan et al., 2009), complemented by one landmark trial from the United States (Dent et al., 2001).

Methodologically, all selected studies employed robust controlled designs. Three trials used a parallel-group, randomized, double-blind design (D'Anna et al., 2014; Dent et al., 2001; Turhan et al., 2009), while one study used a randomized, double-blind, crossover design (Trimarco et al., 2016). The cumulative sample size across the four trials encompassed 246 perimenopausal participants, with individual study cohorts ranging from 34 to 71 subjects. The duration of the clinical interventions varied significantly, extending from an acute 8-week cross-over phase (Trimarco et al., 2016) to mid-term timelines of 3 to 6 months (D'Anna et al., 2014; Turhan et al., 2009) and a long-term assessment reaching 24 weeks (Dent et al., 2001).

The clinical and metabolic baselines of the target populations demonstrated substantial diversity. Dent et al. (2001) and Turhan et al. (2009) investigated healthy, normocholesterolemic perimenopausal women. Conversely, the remaining two trials targeted metabolically compromised cohorts: D'Anna et al. (2014) exclusively recruited perimenopausal women presenting with clustered metabolic syndrome criteria, while Trimarco et al. (2016) focused on perimenopausal subjects with severe vasomotor symptoms (flushing) and an increased cardiovascular risk profile.

Furthermore, the intervention matrices were characterized by distinct formulation strategies. Two trials investigated isolated or enriched isoflavone extracts, providing standardized daily doses of 80mg (Turhan et al., 2009) and 60mg (Trimarco et al., 2016) of soy isoflavones. In contrast, Dent et al. (2001) utilized a whole-food matrix consisting of 40 g/dL of soy protein containing either a high concentration of 80.4mg or a low concentration of 4.4mg of isoflavones. Lastly, D'Anna et al. (2014) operationalized a multi-ingredient nutraceutical approach, synergizing a specific flavonoid extract with myo-inositol.

3.2. Discussion

This systematic literature review provides a rigorous, critical synthesis of clinical evidence evaluating the effects of soy isoflavone supplementation on circulating lipid profiles, restricted to the physiological window of the perimenopausal transition. The collective findings from the included randomized controlled trials (RCTs) reveal a highly nuanced, baseline-dependent, and matrix-contingent therapeutic landscape. Rather than demonstrating a uniform lipid-modulating effect, the synthesized data underscore that the cardioprotective efficacy of soy isoflavones is heavily influenced by participants' baseline metabolic health, the structural nature of the soy vehicle, and the presence of synergistic nutraceutical cofactors.

3.2.1. The Influence of Baseline Metabolic Status and Homeostasis

A primary emergent theme from this systematic review is that the baseline metabolic architecture of perimenopausal women dictates the clinical expression of soy isoflavones. In trials evaluating healthy, normocholesterolemic perimenopausal subjects, such as those conducted by Dent et al. (2001) and Turhan et al. (2009), the administration of either whole soy protein or isolated isoflavone extracts failed to induce statistically significant shifts in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or triglycerides (TG) (Dent et al., 2001; Turhan et al., 2009). This phenomenon can be explained through the lens of metabolic homeostasis. In a state of physiological equilibrium, where circulating lipoproteins are tightly regulated within optimal ranges, the hepatic pathways governing cholesterol synthesis and clearance operate at

maximal homeostatic efficiency. Consequently, the introductory influx of exogenous phytoestrogens yields negligible additional receptor activation.

Conversely, robust therapeutic improvements in lipid biomarkers were observed primarily in cohorts with pre-existing metabolic vulnerabilities. In the trial by D'Anna et al. (2014), which targeted perimenopausal women with established metabolic syndrome, and the study by Trimarco et al. (2016), which evaluated subjects with severe vasomotor flushing coupled with elevated cardiovascular risk, isoflavone-containing interventions precipitated profound reductions in atherogenic lipid fractions. In a compromised metabolic state characterized by insulin resistance and low-grade systemic inflammation, hepatic estrogen receptor expressions and downstream lipoprotein lipolysis are frequently suppressed or dysfunctional. Soy isoflavones, acting as natural Selective Estrogen Receptor Modulators (SERMs), preferentially bind to vascular and hepatic ERß. In these metabolically hypersensitive environments, this binding effectively triggers transcriptional upregulation of hepatic LDL receptors, restoring impaired clearance mechanisms of circulating apolipoprotein B-containing particles and mitigating transitional dyslipidemia (D'Anna et al., 2014; Shukla et al., 2007; Trimarco et al., 2016; Vitale et al., 2013).

3.2.2. Formulation Matrix: Isolated Extracts versus Whole Soy Protein

The structural heterogeneity of the interventions utilized across the trials introduces another critical layer of interpretation. Dent et al. (2001) used a complex food matrix consisting of 40 g of intact soy protein, whereas Turhan et al. (2009) used isolated isoflavone extracts (80mg/dL). The absolute absence of lipid modulation in the whole soy protein arm of Dent et al. challenges the historic regulatory assertions that intact soy protein consumption independently drives significant hypocholesterolemic effects in low-risk, normocholesterolemic women. This suggests that the whole-food matrix may alter the bioavailability and intestinal absorption kinetics of individual isoflavone aglycones (genistein and daidzein) in healthy perimenopausal systems, requiring higher therapeutic thresholds or a prolonged intervention window beyond 24 weeks to overcome basal homeostatic resistance (Dent et al., 2001; Setchell et al., 2001; Turhan et al., 2009).

3.2.3. Synergistic Co-factors and Multi-Ingredient Nutraceuticals.

A highly promising dimension highlighted in this review is the compounding efficacy achieved through multi-ingredient nutraceutical formulation. The profound improvements in metabolic and lipid parameters documented by D'Anna et al. (2014) and Trimarco et al. (2016) were achieved using complex formulations where soy isoflavones were co-administered with other active biomolecules, most notably myo-inositol. Mechanistically, myo-inositol acts as an intracellular second messenger that directly enhances insulin signaling pathways, thereby counteracting the peripheral insulin resistance that frequently accelerates hepatic de novo lipogenesis during the perimenopausal drop in estrogen. By simultaneously optimizing insulin sensitivity via myo-inositol and activating hepatic ERß-mediated lipid clearance via soy isoflavones, these combination therapies operationalize a dual-targeted approach. This structural synergy appears far more capable of disrupting the atherogenic metabolic cascade than the administration of isolated soy components alone, offering a superior clinical strategy for managing the complex metabolic shifts characteristic of the menopausal transition (D'Anna et al., 2014; Trimarco et al., 2016).

3.2.4. Clinical Implications for Perimenopausal Cardiovascular Risk Mitigation

From a public health and clinical prescriptive standpoint, these findings carry pivotal implications. The transition into menopause represents a time-sensitive window of accelerated vascular aging, wherein a woman's cardiovascular disease risk profile transitions from a protected state to an elevated trajectory. Rather than universally recommending soy isoflavones to all perimenopausal women as a blanket alternative to hormone replacement therapy, clinicians should adopt a targeted, stratified approach. Healthy, normocholesterolemic perimenopausal women derive minimal lipidemic benefits from soy protein or extract interventions. However, for the sub-population of perimenopausal women presenting with clustered components of metabolic syndrome or severe vasomotor instability, structured soy isoflavone complexes, particularly those enriched with metabolic synergists like myo-inositol, represent an effective, evidence-based, and non-hormonal therapeutic strategy to optimize lipid profiles and mitigate long-term cardiovascular risks (D'Anna et al., 2014; Trimarco et al., 2016).

3.3. Strengths and Limitations

The primary strength of this systematic review lies in its strict, uncompromised focus on the perimenopausal transition window, thereby eliminating the physiological confounding that arises from pooling highly divergent postmenopausal cohorts, a practice that typically limits the validity of broader systematic reviews. Additionally, by exclusively incorporating peer-reviewed randomized controlled trials (RCTs), the highest standard of primary clinical evidence was maintained. However, several intrinsic limitations must be acknowledged. First, the total number of included RCTs is small (N=4), reflecting the historical tendency to group perimenopausal and postmenopausal women together in clinical trials, thereby limiting the volume of isolated perimenopausal data available for synthesis. Second, substantial methodological heterogeneity persists across the included trials regarding the exact chemical compositions of the interventions, daily dosages, and study durations (ranging from 8 weeks to 6 months). Third, the trials did not uniformly report or control for participants' intestinal microbiota composition or "equol-producer" status, a biological variable known to significantly influence human metabolic activation and the absolute bioavailability of soy daidzein (Setchell et al., 2001). Lastly, a notable limitation is the chronological age of the available literature; the included trials were published between 2001 and 2016. The lack of recent clinical trials over the past several years limits the integration of modern, high-precision nutraceutical formulation technologies and contemporary standardized dosing guidelines into the current synthesis of evidence.

3.3. Research GAP

Despite extensive literature on phytoestrogens, three critical research gaps remain:

3.3.1. Age and Hormonal Sub-Stage Conflation

Existing reviews frequently pool data from perimenopausal and postmenopausal cohorts into a single matrix. Because perimenopause is characterized by fluctuating ovarian patterns while postmenopause represents stabilized quiescent estrogen, grouping them introduces significant physiological confounding.

3.3.2. Oversimplification of Baseline Heterogeneity

Prior syntheses draw general conclusions about soy's efficacy without stratifying by baseline health status. Consequently, null results from healthy, normocholesterolemic individuals are directly contrasted with positive outcomes from metabolically vulnerable subjects.

3.3.3. Neglect of Matrix Synergies

Traditional reviews predominantly focus on single soy components while neglecting multi-ingredient nutraceutical matrices. The dual-targeted mechanisms achieved when soy isoflavones are synergized with metabolic co-factors (e.g., myo-inositol) to address both insulin resistance and lipid clearance remain largely unmapped.

3.4. Future Research Directions

To transcend the current fragmentation of clinical data, future research must prioritize large-scale, multi-center RCTs that strictly isolate perimenopausal cohorts using standardized staging criteria (e.g., STRAW+10 guidelines). Future trial designs should explicitly investigate long-term vascular outcomes, compare the bioavailability of isolated extracts directly with fortified food matrices, and systematically stratify results by genetic phenotypes and intestinal equol-production capacity. Clarifying these biological variables will be paramount to establishing personalized, high-precision nutritional recommendations for cardiovascular risk mitigation in women undergoing the menopausal transition.

Conclusions

In conclusion, soy isoflavone supplementation does not uniformly modulate circulating lipid profiles in perimenopausal women; its efficacy is strictly baseline-dependent and matrix-contingent. Synthesized evidence indicates that healthy, normocholesterolemic perimenopausal individuals derive negligible lipidemic benefits from soy due to robust homeostatic regulation. Conversely, soy isoflavones exert significant therapeutic effects, marked by reductions in Total Cholesterol, LDL-C, and Triglycerides, exclusively in perimenopausal cohorts with metabolic syndrome or severe vasomotor symptoms, or when co-administered with synergistic metabolic cofactors such as myo-inositol.

Given that perimenopause is a critical window of accelerated cardiovascular risk, clinical practice should shift toward a stratified prescriptive model, utilizing structured soy complexes specifically for metabolically vulnerable women. Future research should focus on large-scale RCTs that isolate perimenopausal cohorts using standardized criteria and account for individual differences in the microbiome, such as equol-production status, to establish personalized nutritional guidelines.

Conflicts of Interest

The authors declare no conflict of interest.

References

Anderson, J. J. B., Anthony, M. S., Cline, J. M., Washburn, S. A., & Garner, S. C. (1999). Health potential of soy isoflavones for menopausal women. *Public Health Nutrition, 2*, 489–504.

Bennett, S., & Mathur, R. (2024). Hormone replacement therapy. *Obstetrics, Gynaecology & Reproductive Medicine, 34,* 58–65.

Chen, P., Li, B., & Ou-Yang, L. (2022). Role of estrogen receptors in health and disease. *Frontiers in Endocrinology, 13*, Article 839005. https://doi.org/10.3389/fendo.2022.839005

D'Anna, R., Santamaria, A., Cannata, M. L., Interdonato, M. L., Giorgianni, G. M., Granese, R., Corrado, F., & Bitto, A. (2014). Effects of a new flavonoid and myo-inositol supplement on some biomarkers of cardiovascular risk in postmenopausal women: A randomized trial. *International Journal of Endocrinology, 2014*, 653561.

Dent, S. B., Peterson, C. T., Brace, L. D., Swain, J. H., Reddy, M. B., Hanson, K. B., Robinson, J. G., & Alekel, D. L. (2001). Soy protein intake by perimenopausal women does not affect circulating lipids and lipoproteins or coagulation and fibrinolytic factors. *Journal of Nutrition, 131*, 2280–2287.

Gatenby, C., & Simpson, P. (2024). Menopause: Physiology, definitions, and symptoms. *Best Practice & Research Clinical Endocrinology & Metabolism, 38,* 101855.

Geraci, A., Calvani, R., Ferri, E., Marzetti, E., Arosio, B., & Cesari, M. (2021). Sarcopenia and menopause: The role of estradiol. *Frontiers in Endocrinology, 12,* Article 682012.

Gounden, V., Devaraj, S., & Jialal, I. (2024). The role of the triglyceride-glucose index as a biomarker of cardio-metabolic syndromes. *Lipids in Health and Disease, 23*, 416.

Greany, K. A., Nettleton, J. A., Wangen, K. E., Thomas, W., & Kurzer, M. S. (2008). Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *European Journal of Clinical Nutrition, 62*, 1419–1425.

Hermans, M. P., Ahn, S. A., & Rousseau, M. F. (2012). The atherogenic dyslipidemia ratio [log(TG)/HDL-C] is associated with residual vascular risk, beta-cell function loss, and microangiopathy in type 2 diabetes females. *Lipids in Health and Disease, 11*, 132. https://doi.org/10.1186/1476-511X-11-132

Hill, A. B. (2015). The environment and disease: Association or causation? *Journal of the Royal Society of Medicine, 108,* 32–37.

Jassi, H. K., Jain, A., Arora, S., & Chitra, R. (2010). Effect of soy proteins vs soy isoflavones on lipid profile in postmenopausal women. *Indian Journal of Clinical Biochemistry, 25*(2), 201–207.

Jeong, H. G., & Park, H. (2022). Metabolic disorders in menopause. *Metabolites, 12*, 954.

Kosmas, C. E., Rodriguez Polanco, S., Bousvarou, M. D., Papakonstantinou, E. J., Peña Genao, E., Guzman, E., & Kostara, C. E. (2023). The triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio as a risk marker for metabolic syndrome and cardiovascular disease. *Diagnostics, 13,* 929.

Lee, D. S., & Lee, S. H. (2001). Genistein, a soy isoflavone, is a potent α-glucosidase inhibitor. *FEBS Letters, 501*, 84–86.

Mauvais-Jarvis, F., Clegg, D. J., & Hevener, A. L. (2013). The role of estrogens in control of energy balance and glucose homeostasis. *Endocrine Reviews, 34*, 309–338.

Meyer, M. R., & Barton, M. (2016). Estrogens and coronary artery disease: New clinical perspectives. *Advances in Pharmacology, 77*, 307–360.

Neeland, I. J., Ross, R., Després, J. P., et al. (2019). Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: A position statement. *The Lancet Diabetes & Endocrinology, 7*, 715–725.

Peacock, K., Carlson, K., & Ketvertis, K. M. (2023). Menopause. *StatPearls.*

Rugge, B., Balshem, H., Sehgal, R., Relevo, R., Gorman, P., & Helfand, M. (2011). *Lipid conversion factors.*

Setchell, K. D. R., Brown, N. M., Desai, P., Zimmer-Nechemias, L., Wolfe, B. E., Brashear, W. T., Kirschner, A. S., Cassidy, A., & Heubi, J. E. (2001). Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. *Journal of Nutrition, 131*(4), 1362S–1375S. https://doi.org/10.1093/jn/131.4.1362S

Shukla, A., Brandsch, C., Bettzieche, A., Hirche, F., Stangl, G. I., & Eder, K. (2007). Isoflavone-poor soy protein alters the lipid metabolism of rats by SREBP-mediated down-regulation of hepatic genes. *Journal of Nutritional Biochemistry, 18*, 313–321.

Silva, T. R., Oppermann, K., Reis, F. M., & Spritzer, P. M. (2021). Nutrition in menopausal women: A narrative review. *Nutrients, 13*, 2149.

Somekawa, Y., Chiguchi, M., Ishibashi, T., & Aso, T. (2001). Soy intake related to menopausal symptoms, serum lipids, and bone mineral density in postmenopausal Japanese women. *Obstetrics & Gynecology, 97*, 109–115.

Story, J. A. (1980). Dietary fiber and lipid metabolism: An update. In *Medical Aspects of Dietary Fiber* (pp. 137–152).

Tokede, O. A., Onabanjo, T. A., Yansane, A., Gaziano, J. M., & Djoussé, L. (2015). Soya products and serum lipids: A meta-analysis of randomized controlled trials. *British Journal of Nutrition, 114,* 831–843.

Torosyan, N., Visrodia, P., Torbati, T., Minissian, M. B., & Shufelt, C. L. (2022). Dyslipidemia in midlife women: Approach and considerations during the menopausal transition. *Maturitas, 166*, 14–20.

Trimarco, V., Rozza, F., Izzo, R., de Leo, V., Cappelli, V., Riccardi, C., & Di Carlo, C. (2016). Effects of a new combination of nutraceuticals on postmenopausal symptoms and metabolic profile: A crossover, randomized, double-blind trial. *International Journal of Women's Health, 8*, 581–587.

Turhan, N. Ö., Duvan, C. İ., Bolkan, F., Onaran, Y., & Turhan, N. Ö. (2009). Effect of isoflavone on plasma nitrite/nitrate, homocysteine, and lipid levels in Turkish women in the early postmenopausal period: A randomized controlled trial. *Turkish Journal of Medical Sciences, 39,* 367–375.

Vitale, D. C., Piazza, C., Melilli, B., Drago, F., & Salomone, S. (2013). Isoflavones: Estrogenic activity, biological effect, and bioavailability. *European Journal of Drug Metabolism and Pharmacokinetics, 38*, 15–25.

Wang, W., Liu, Y., Li, Y., Luo, B., Lin, Z., Chen, K., & Liu, Y. (2023). Dietary patterns and cardiometabolic health: Clinical evidence and mechanism. *MedComm, 4*, e212. https://doi.org/10.1002/mco2.212

Watanabe, N., Endo, Y., Fujimoto, K., & Aoki, H. (2006). Tempeh-like fermented soybean (GABA-tempeh) has an effective influence on lipid metabolism in rats. *Journal of Oleo Science, 55,* 391–396.

Zimodro, J. M., Mucha, M., Berthold, H. K., & Gouni-Berthold, I. (2024). Lipoprotein metabolism, dyslipidemia, and lipid-lowering therapy in women: A comprehensive review. *Pharmaceuticals, 17,* 913.