

Use of Plant-Based Therapies and Menopausal Symptoms

A Systematic Review and Meta-analysis

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JAMA; The Journal of the American Me...	1%	General Medicine	JAMA, ProQuest	157.375	Q1	38.80	Q1	709	ISI, Scopus, PubMed, Embase

Introduction

- Menopause is considered the end of a woman's reproductive life, generally indicated by the time when menstrual periods stop permanently.
- The menopausal transition and its associated changes vary widely. Symptoms associated with menopause include **hot flashes, night sweats, and vaginal dryness** , with **50.3% to 82.1% of menopausal women** reporting hot flashes or night sweats.
- Medical treatments for these symptoms are available, including hormone replacement therapy.
- However, given the potentially negative health consequences of hormone replacement therapy on cardiovascular health and breast cancer, 40% to 50% of women in Western countries choose to use complementary therapies, including plant-based therapies.
- × **Common symptoms of menopause, their impact on the quality of life of women**
- × **The only treatment is not medical therapy**

- These therapies include the oral use of phytoestrogens such as dietary soy isoflavones and soy extracts; herbal remedies such as red clover and black cohosh; and Chinese and other medicinal herbs. (× How they affect menopause symptoms)
- Most of these studies were limited by inadequate power (limited sample size), a short follow-up period, suboptimal quality (high dropout rates), and inconsistent findings.

We conducted a **systematic review and meta-analysis** of intervention studies evaluating the **association of plant-based therapies with menopausal symptoms.**

Method: Data Sources and Search Strategy

- This review was conducted using a predefined protocol and in accordance with PRISMA and MOOSE guidelines. (× **Registration: PROSPERO, and ID**)
- Three electronic databases (Ovid MEDLINE, EMBASE, and Cochrane Central) were searched until March 27, 2016, without language restriction. (×**Few databases searched**)
- The computer-based searches combined terms related to (1) the exposures (or interventions, where appropriate) such as herbal, phytoestrogens, soy, isoflavone, ginseng, black cohosh, *Cimicifuga*, ERr 731 rhubarb raponticin, St John's wort, complementary medicine, traditional medicine, and Chinese medicine; (2) menopausal symptoms (eg, hot flashes, night sweats, vasomotor symptoms, vaginal dryness); (3) study design (eg, clinical trials, randomized clinical trials); and (4) relevant population (eg, humans). (× **Mesh, AND-OR, Reference list= cross referencing, gray literature, reference manager= Endnote**)
- Two independent reviewers screened the titles and abstracts of all studies initially identified, according to the selection criteria. Any disagreement was resolved through consensus or consultation with a third independent reviewer. (×**Full text**)

Study Selection and Eligibility Criteria

- Intervention studies were eligible if they were randomized clinical trials (RCTs); assessed effects of any plant-based therapy listed above in perimenopausal, menopausal, or postmenopausal women, compared with a placebo; and collected end points for menopausal symptoms, including hot flashes, night sweats, and vaginal dryness.

Data Extraction

- Two authors (S. K., C. O.-W.) independently extracted data and a consensus was reached in case of any inconsistency with involvement of a third author (T. M.). A predesigned electronic data abstraction form was used to extract relevant information. In instances of multiple publications, the most up-to-date information was extracted.
- ×What information was extracted?

×Quality assessment

Assessing the Risk of Bias

- Two reviewers (S. K., T. M.) independently rated the quality of studies.
- The Cochrane Collaboration's tool was used to assess the risk of bias.

(× Selection bias, performance bias, detection bias, attrition bias, and reporting bias)

(× Entering risk of bias into the software and getting their shape)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Abbaspoor et al. 2011	+	+	-	-	-	?
Ghanbari et al. 2017	?	?	?	?	?	?
Ghazanfarpour et al. 2013	?	+	+	+	-	?
Golian Tehrani et al. 2014	+	+	+	+	-	-
Motaghi Dastenaie et al. 2019	?	+	+	+	?	?
Naseri et al. 2018	?	+	+	+	+	+
Sadeghi et al. 2019	+	?	?	?	?	-

Statistical Analysis

- Mean differences.
- To enable a consistent approach to the meta-analysis and enhance interpretation of the findings, units of measurement were converted where appropriate.
- The inverse variance weighted method was used to combine summary measures using random-effects models to minimize effects of between-study heterogeneity.
- We also conducted sensitivity analyses.
- Heterogeneity was assessed using the Cochrane χ^2 statistic and the I2 statistic and was distinguished as low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $< 75\%$), or high ($I^2 \geq 75\%$). We evaluated publication bias using funnel plots and Egger regression symmetry tests.
- All tests were 2-tailed; $P \leq .05$ was considered statistically significant. Stata 13 was used for all analyses.

Results: Study Identification and Selection

- We identified 5218 relevant citations. After screening titles and abstracts, 192 articles were selected for detailed evaluation of their full texts.
- Of those, 62 articles, based on 62 unique RCTs, met our inclusion criteria and were included in the review.
- 52 unique studies about **biologically** based therapies (36 on phytoestrogens and 16 on black cohosh and other biologically based therapies) and 10 unique studies on **medicinal herbs**.

Characteristics of Included Studies

- The 62 RCTs reported results for 6653 unique women. Twenty-one RCTs were based in Europe; 17 in Asia-Pacific; 10 in North America; 7 in South America; and 7 in the Middle East.
- The baseline age of participants ranged from 55 to 75 years. The duration of the interventions ranged from 4 weeks to 2 years, but the majority (28 studies) had a 12-week intervention period.

5218 Potentially relevant citations identified

5191 From electronic databases

27 From manual screening of reference lists

5026 Excluded on the basis of title and/or abstract

192 Full-text articles retrieved for more detailed evaluation

130 Excluded

71 Relevant outcomes not reported

23 Study design not relevant

21 Estimates not extractable (in figures only)

7 Review articles

4 Population not relevant

4 Duplicates

62 Articles eligible for analysis

52 Articles (52 unique studies) on biologically based therapies
36 On phytoestrogens
16 On other biologically based therapies

10 Articles (10 unique studies) on Chinese medicinal herbs and other herbs

×Number of articles obtained from each database

Table 1. Characteristics of the 62 Randomized Clinical Trials Included in the Systematic Review and Meta-analysis				
		Biologically Based Therapies ^a		
		Phytoestrogens (Soy Isoflavones, Red Clover Isoflavones, and Other Phytoestrogens)	Black Cohosh and Other Biologically Based Therapies	Medicinal Herbs: Chinese and Other Medicinal Herbs ^b
Eligible studies				
No. of unique studies		36 ²⁴⁻⁵⁹	16 ^{19,60-74}	10 ^{3,75-83}
Duration of follow-up, median (IQR), wk		12 (12-16)	12 (8-21)	12.0 (12-16)
Participants				
Total		3762	1654	1237
Median (IQR), No.		80 (51-157)	87 (52-123)	92 (64-110)
Age, median (IQR), y		53.5 (53.0-54.0)	52.0 (51.6-55.0)	52 (50-53)
Location				
Europe		15	2	4
North America		7	3	0
Asia-Pacific		7	4	6
South America		5	2	0
Middle East		2	5	0

Results

- **Biologically Based Therapies and Menopausal Outcomes**
- **Medicinal Herbs and Menopausal Outcomes**

Biologically Based Therapies and Menopausal Outcomes

- **Biologically Based Therapies: 1. Phytosterogen (Soy and Red clover) (36), 2. Blackcohash (16)**
- **phytoestrogen** : Use with a decrease in the number of **daily hot flashes and in vaginal dryness scores** And was not associated with significant changes in 24-hour **night sweat**.
- **Soya: daily hot flashes and in vaginal dryness**

Medicinal Herbs and Menopausal Outcomes

- Because of the **limited number of studies**, it was not possible to perform meta-analysis on the associations of Chinese medicinal herbs and non-Chinese medicinal herbs with menopausal symptoms.

Sensitivity Analyses and Assessments of Bias, Study Quality, and Heterogeneity

- Sensitivity Analysis
- Pooled mean difference
- Risk of bias
- Heterogeneity

Quality assessment, Table of risk of bias, Search result of data base, Table of characteristic

Table 2. Pooled Mean Difference in the Number of Hot Flashes in 24 Hours by Subgroups of Randomized Clinical Trials Defined by Characteristic of Study Participants and Study Design

Subgroups by Study Characteristics	No. Studies	Intervention Group	Control Group	Difference, Mean (95% CI) ^a	P Value for Heterogeneity ^b
Association Between Use of Phytoestrogens and Number of Hot Flashes in 24 h, by Study-Level Characteristics ^c					
Location					
Europe	9	599	615	−2.16 (−3.25 to 1.07)	.09
North America	3	195	197	0.05 (−0.69 to 0.79)	
South America	3	89	89	−1.50 (−3.75 to 0.75)	
Asia-Pacific	3	115	121	−0.25 (−1.38 to 0.89)	
Duration of treatment, wk					
≤12	8	489	486	−1.26 (−2.39 to −0.13)	.87
>12	10	509	536	−1.38 (−2.35 to −0.40)	
No. of participants					
≥100	8	725	748	−1.67 (−2.81 to −0.52)	.38
<100	10	273	274	−0.94 (−1.78 to −0.11)	
Risk of bias ^d					
High	3	155	176	−3.09 (−7.29 to 1.11)	.03
Low	15	843	846	−0.92 (−1.53 to −0.32)	
Association Between Use of Any Soy Isoflavones (Dietary, Supplementary, and Extracts) and Number of Hot Flashes in 24 h, by Study-Level Characteristics ^e					
Location					
Europe	5	431	439	−1.53 (−2.18 to −0.89)	.06
North America	2	111	112	0.41 (−0.26 to 1.07)	
South America	2	59	59	−0.83 (−3.64 to 1.98)	
Asia-Pacific	1	77	83	−0.90 (−1.49 to −0.31)	
Duration of treatment, wk					
≤12	5	357	353	−1.26 (−2.63 to 0.10)	.63
>12	5	321	340	−0.90 (−1.46 to −0.33)	
No. of participants					
≥100	4	489	501	−1.21 (−1.98 to −0.43)	.44
<100	6	189	192	−0.77 (−1.64 to 0.10)	
Risk of bias					
High	2	105	117	−0.87 (−1.40 to −0.33)	.80
Low	8	573	576	−1.03 (−1.75 to −0.31)	
Association Between Use of Red Clover and Number of Hot Flashes in 24 h, by Study-Level Characteristics ^f					
Location					
Europe	3	168	176	−3.31 (−9.35 to −2.74)	.87
North America	1	84	85	0.60 (−1.38 to 0.18)	
South America	1	30	30	−2.80 (−3.65 to 1.95)	
Asia-Pacific	2	38	38	0.45 (−0.49 to 1.39)	
Duration of treatment, wk					
≤12	2	132	133	−1.28 (4.22 to 1.66)	.76
>12	5	188	196	−2.09 (−5.40 to 1.23)	
No. of participants					
≥100	3	236	247	−2.66 (−6.55 to −1.22)	.54
<100	4	84	82	−1.15 (−3.35 to −1.03)	

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Figure 2. Meta-analysis of Randomized Clinical Trials on the Associations Between Use of Phytoestrogen Supplementation and Menopausal Symptoms

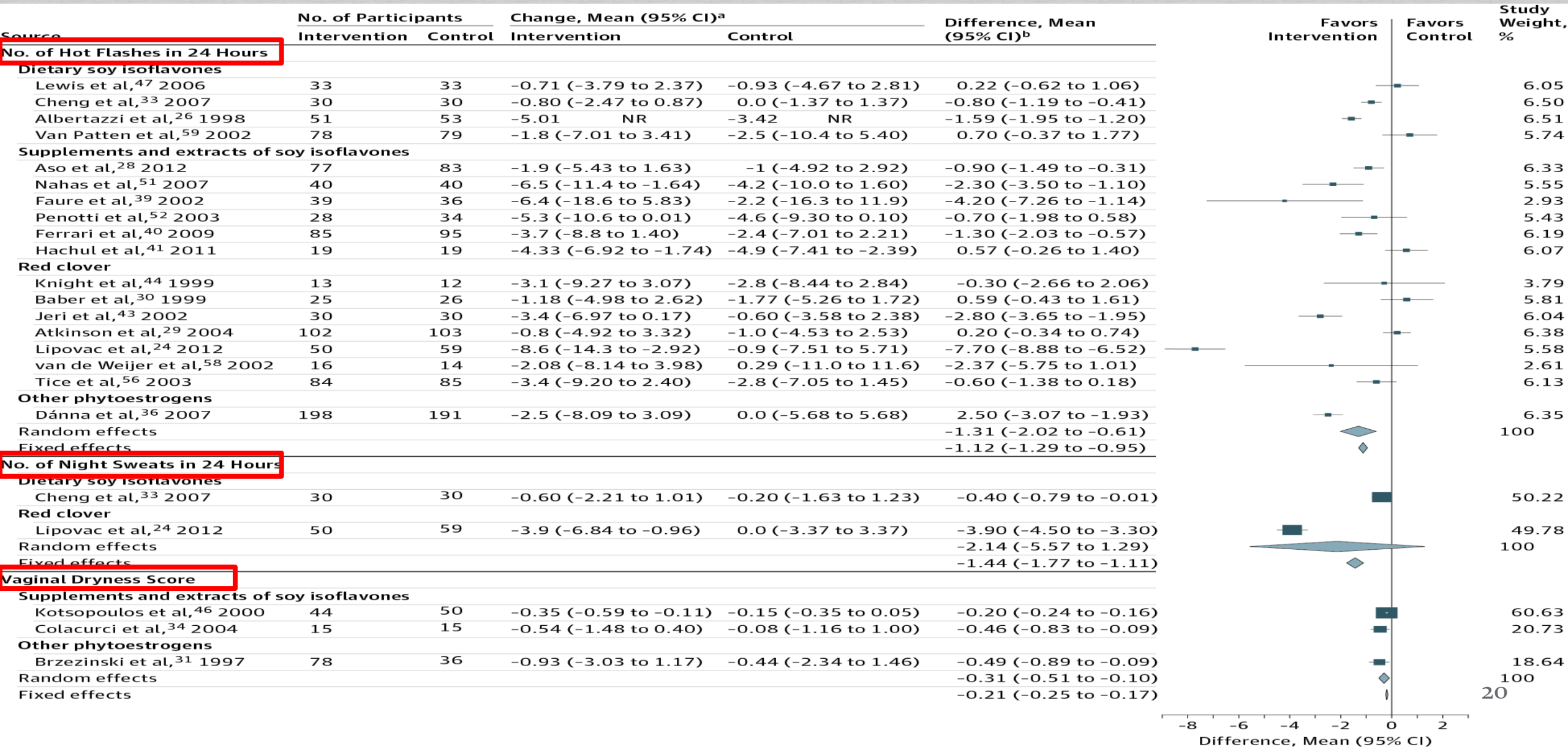
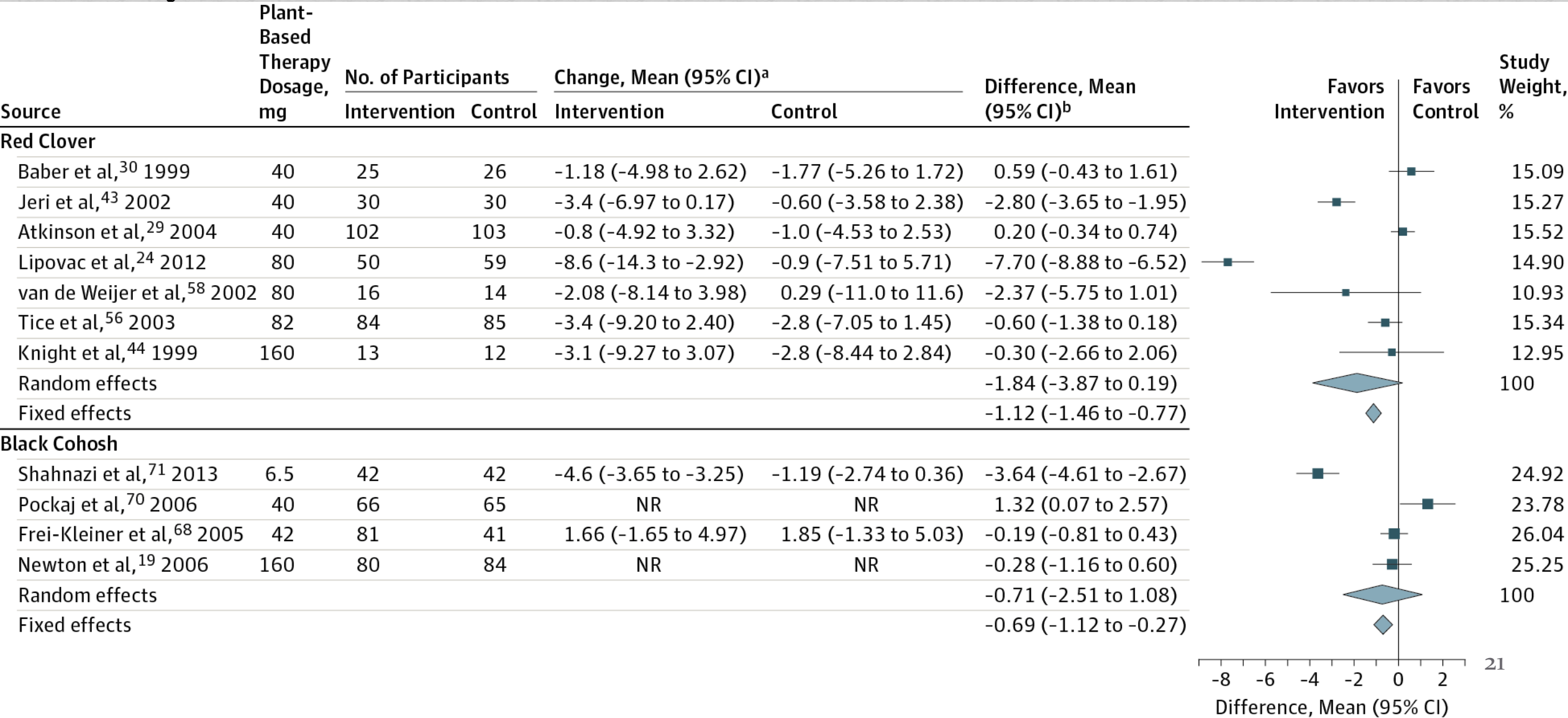


Figure 3. Meta-analysis of Randomized Clinical Trials Assessing the Associations Between Use of Red Clover and Black Cohosh and Number of Daily Hot Flashes



Discussion

- Composite phytoestrogen supplementation and individual phytoestrogen interventions, such as dietary and supplemental soy isoflavones, were associated with improvement in some menopausal symptoms, including modest reductions in hot flashes and vaginal dryness but no significant reduction in night sweats.
- Kupperman Index
- Our sensitivity analyses differentiating the association between overall phytoestrogen use and menopausal symptoms by type of phytoestrogen intervention yielded broadly similar results.
- Red clover AND Black cohosh

- The major subtypes of **phytoestrogen**, isoflavones, have a chemical structure similar to that of estradiol (ie, a form of estrogen) and therefore also appear to have estrogen-like properties. However, this mechanism of action also could be associated with adverse effects such as endometrial hyperplasia.

Limitation:

- **First**, it is possible that both measured and unmeasured **publication bias** can limit our overall findings.
- **Second**, the **quality** of included studies was limited. **Variation in study quality** contributed to the heterogeneity of findings noted in several of the **meta-analyses** presented in our study.
- Other sources of heterogeneity are likely to include **population differences**, including **ethnicity** differing **age ranges**.
- Furthermore, the **supplements** used in the trials may vary in quality and composition which might have contributed to the heterogeneity in effects observed in our analyses.
- **Third**, the **number of available studies in some analyses was small**, precluding our ability to quantitatively investigate the sources of the observed heterogeneity.
- **Fourth**, **self-reported measures** of vasomotor symptoms may be subject to memory and reporting bias.
- Interpret results with caution.
- Clinical control of flushing and skin inflammation.

- × **Absence of goal and research question**
- × **Comparison of results with literature review**
- × **Possible reasons for differences and similarities with previous studies**

Conclusion

- This meta-analysis of clinical trials suggests that composite and specific **phytoestrogen** supplementations were associated with modest reductions in the frequency of hot flashes and vaginal dryness but no significant reduction in night sweats.
- However, because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health.

- × **Conflict of interest**
- × **Acknowledgment**

thanks

FOR ATTENTION