Use of Plant-Based Therapies and Menopausal Symptoms
A Systematic Review and Meta-analysis

Presented by:

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JAMA; The Journal of the American Me... 1% ISSN/ISBN: 0098-7484, 1538-3598	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?**

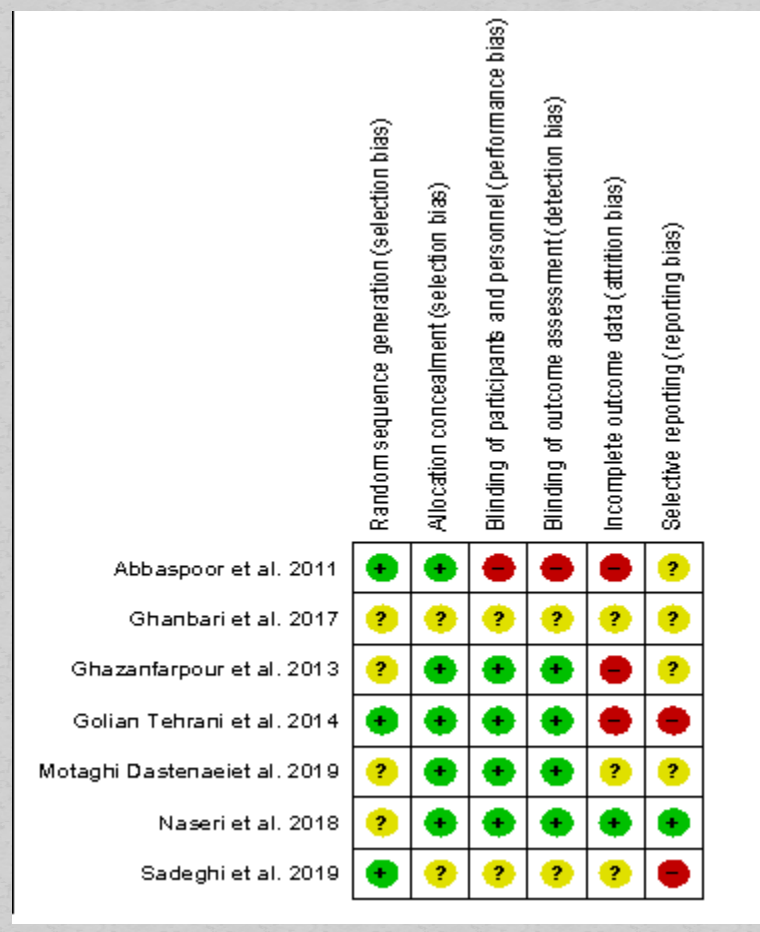
×Quality assessment

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)



Statistical Analysis

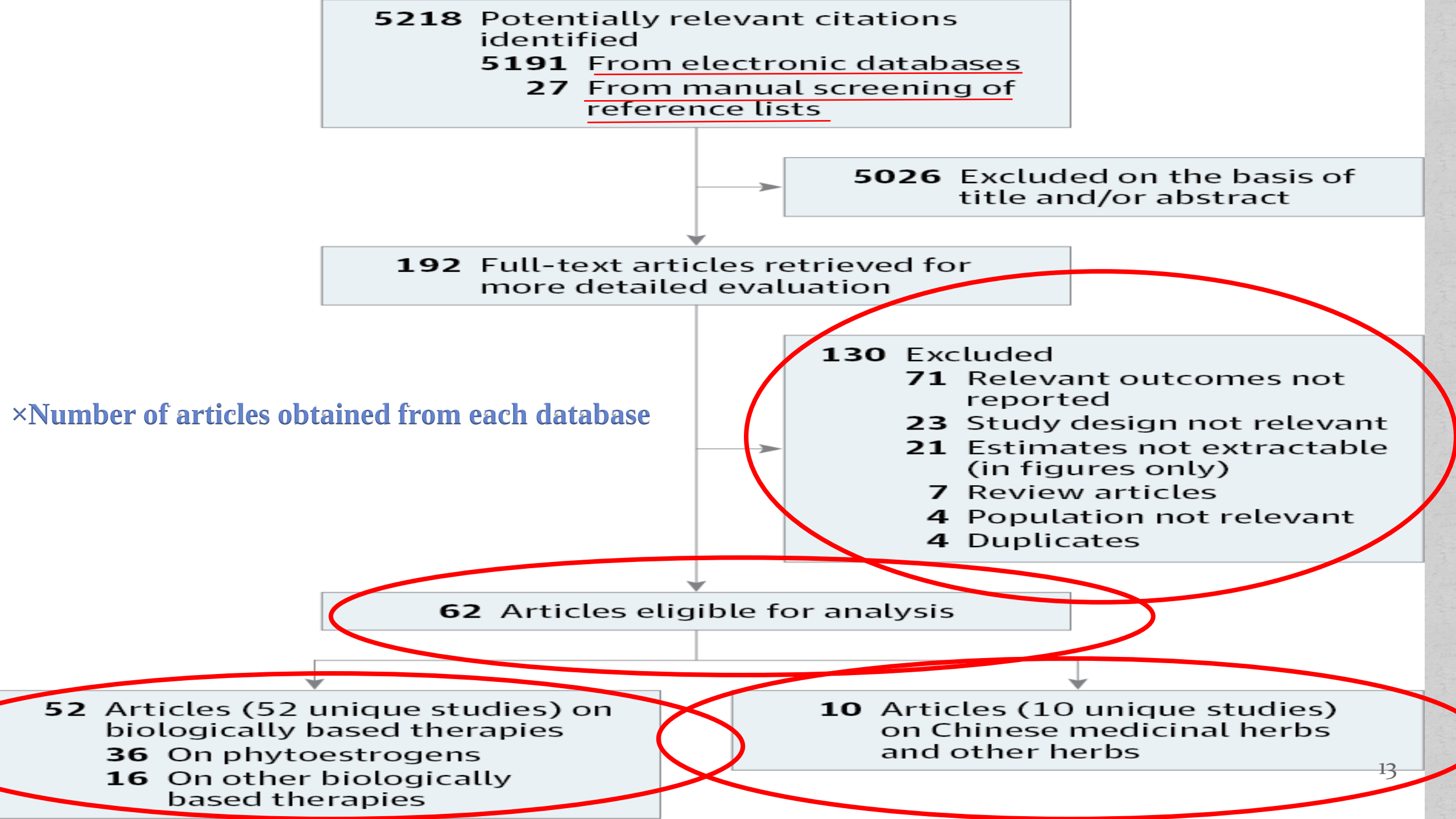
- **Mean differences**.
- To enable a consistent approach to the meta-analysis and enhance interpretation of the findings, **units of measurement were converted** where appropriate.
- The inverse variance weighted method was used to combine summary measures using **random-effects** models to minimize effects of between-study **heterogeneity.**
- We also conducted **sensitivity analyses.**
- **Heterogeneity** was assessed using the **Cochrane χ2 statistic and the I2 statistic** and was distinguished as low (I^2 ≤25%), moderate (I^2 >25% and <75%), or high (I^2 ≥75%). We evaluated **publication bias** using **funnel plots** and **Egger regression** symmetry tests.
- All tests were 2-tailed; P ≤.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 62RCTs 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.



×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. Blackcohosh (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[c]					
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					
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)	

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

Source	No. of Participants		Change, Mean (95% CI)[a]		Difference, Mean (95% CI)[b]	Study Weight, %
	Intervention	Control	Intervention	Control		
No. of Hot Flashes in 24 Hours						
Dietary soy isoflavones						
Lewis et al,[47] 2006	33	33	−0.71 (−3.79 to 2.37)	−0.93 (−4.67 to 2.81)	0.22 (−0.62 to 1.06)	6.05
Cheng et al,[33] 2007	30	30	−0.80 (−2.47 to 0.87)	0.0 (−1.37 to 1.37)	−0.80 (−1.19 to −0.41)	6.50
Albertazzi et al,[26] 1998	51	53	−5.01 NR	−3.42 NR	−1.59 (−1.95 to −1.20)	6.51
Van Patten et al,[59] 2002	78	79	−1.8 (−7.01 to 3.41)	−2.5 (−10.4 to 5.40)	0.70 (−0.37 to 1.77)	5.74
Supplements and extracts of soy isoflavones						
Aso et al,[28] 2012	77	83	−1.9 (−5.43 to 1.63)	−1 (−4.92 to 2.92)	−0.90 (−1.49 to −0.31)	6.33
Nahas et al,[51] 2007	40	40	−6.5 (−11.4 to −1.64)	−4.2 (−10.0 to 1.60)	−2.30 (−3.50 to −1.10)	5.55
Faure et al,[39] 2002	39	36	−6.4 (−18.6 to 5.83)	−2.2 (−16.3 to 11.9)	−4.20 (−7.26 to −1.14)	2.93
Penotti et al,[52] 2003	28	34	−5.3 (−10.6 to 0.01)	−4.6 (−9.30 to 0.10)	−0.70 (−1.98 to 0.58)	5.43
Ferrari et al,[40] 2009	85	95	−3.7 (−8.8 to 1.40)	−2.4 (−7.01 to 2.21)	−1.30 (−2.03 to −0.57)	6.19
Hachul et al,[41] 2011	19	19	−4.33 (−6.92 to −1.74)	−4.9 (−7.41 to −2.39)	0.57 (−0.26 to 1.40)	6.07
Red clover						
Knight et al,[44] 1999	13	12	−3.1 (−9.27 to 3.07)	−2.8 (−8.44 to 2.84)	−0.30 (−2.66 to 2.06)	3.79
Baber et al,[30] 1999	25	26	−1.18 (−4.98 to 2.62)	−1.77 (−5.26 to 1.72)	0.59 (−0.43 to 1.61)	5.81
Jeri et al,[43] 2002	30	30	−3.4 (−6.97 to 0.17)	−0.60 (−3.58 to 2.38)	−2.80 (−3.65 to −1.95)	6.04
Atkinson et al,[29] 2004	102	103	−0.8 (−4.92 to 3.32)	−1.0 (−4.53 to 2.53)	0.20 (−0.34 to 0.74)	6.38
Lipovac et al,[24] 2012	50	59	−8.6 (−14.3 to −2.92)	−0.9 (−7.51 to 5.71)	−7.70 (−8.88 to −6.52)	5.58
van de Weijer et al,[58] 2002	16	14	−2.08 (−8.14 to 3.98)	0.29 (−11.0 to 11.6)	−2.37 (−5.75 to 1.01)	2.61
Tice et al,[56] 2003	84	85	−3.4 (−9.20 to 2.40)	−2.8 (−7.05 to 1.45)	−0.60 (−1.38 to 0.18)	6.13
Other phytoestrogens						
Dánna et al,[36] 2007	198	191	−2.5 (−8.09 to 3.09)	0.0 (−5.68 to 5.68)	2.50 (−3.07 to −1.93)	6.35
Random effects					−1.31 (−2.02 to −0.61)	100
Fixed effects					−1.12 (−1.29 to −0.95)	
No. of Night Sweats in 24 Hours						
Dietary soy isoflavones						
Cheng et al,[33] 2007	30	30	−0.60 (−2.21 to 1.01)	−0.20 (−1.63 to 1.23)	−0.40 (−0.79 to −0.01)	50.22
Red clover						
Lipovac et al,[24] 2012	50	59	−3.9 (−6.84 to −0.96)	0.0 (−3.37 to 3.37)	−3.90 (−4.50 to −3.30)	49.78
Random effects					−2.14 (−5.57 to 1.29)	100
Fixed effects					−1.44 (−1.77 to −1.11)	
Vaginal Dryness Score						
Supplements and extracts of soy isoflavones						
Kotsopoulos et al,[46] 2000	44	50	−0.35 (−0.59 to −0.11)	−0.15 (−0.35 to 0.05)	−0.20 (−0.24 to −0.16)	60.63
Colacurci et al,[34] 2004	15	15	−0.54 (−1.48 to 0.40)	−0.08 (−1.16 to 1.00)	−0.46 (−0.83 to −0.09)	20.73
Other phytoestrogens						
Brzezinski et al,[31] 1997	78	36	−0.93 (−3.03 to 1.17)	−0.44 (−2.34 to 1.46)	−0.49 (−0.89 to −0.09)	18.64
Random effects					−0.31 (−0.51 to −0.10)	100
Fixed effects					−0.21 (−0.25 to −0.17)	

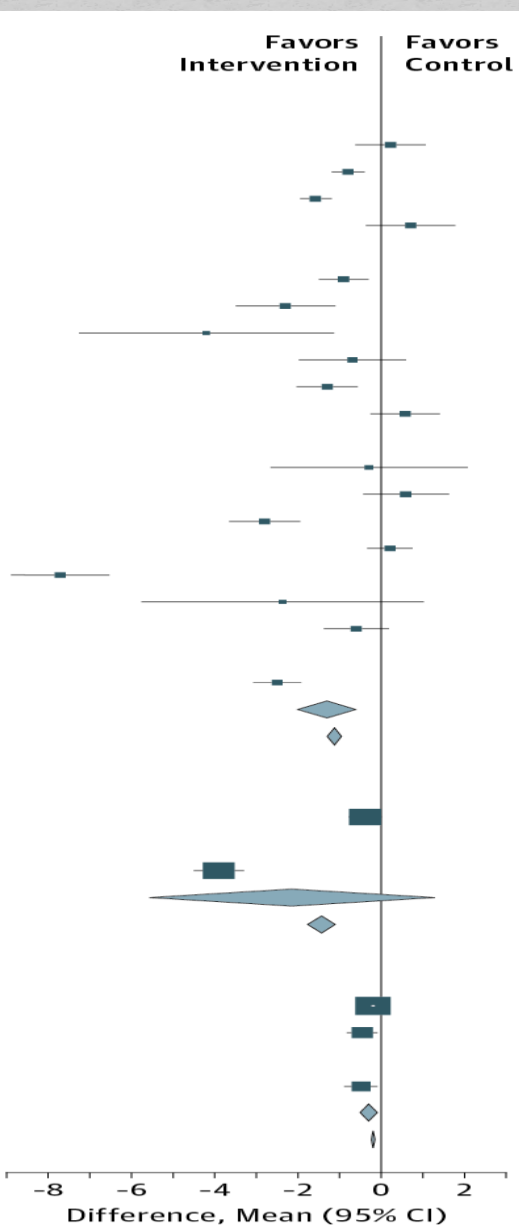
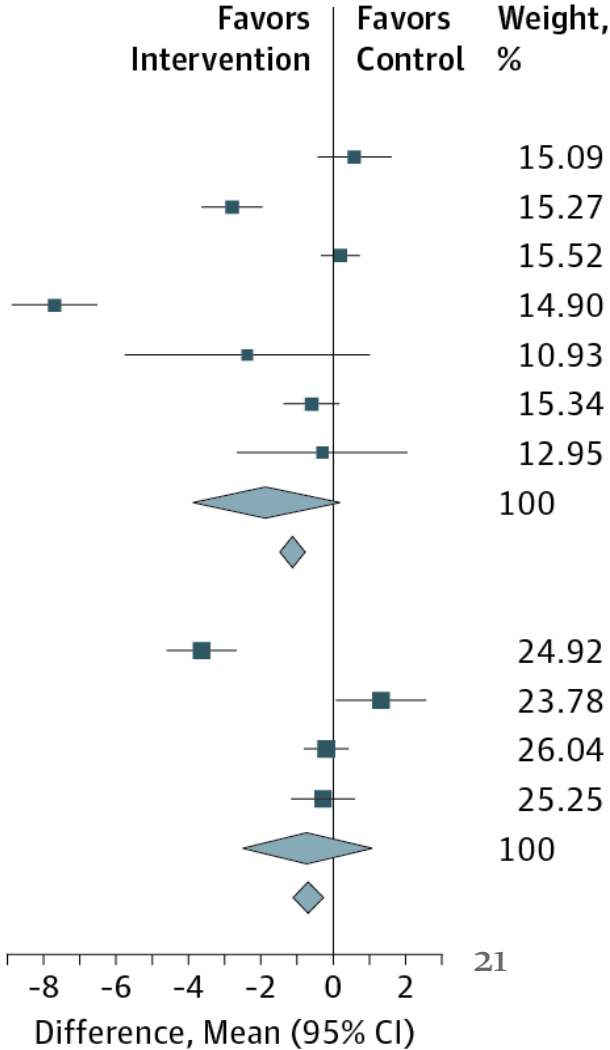


Figure 3. Meta-analysis of Randomized Clinical Trials Assessing the Associations Between Use of Red Clover and Black Cohosh and Number of Daily Hot Flashes

Source	Plant-Based Therapy Dosage, mg	No. of Participants		Change, Mean (95% CI)[a]		Difference, Mean (95% CI)[b]	Study Weight, %
		Intervention	Control	Intervention	Control		
Red Clover							
Baber et al,[30] 1999	40	25	26	-1.18 (-4.98 to 2.62)	-1.77 (-5.26 to 1.72)	0.59 (-0.43 to 1.61)	15.09
Jeri et al,[43] 2002	40	30	30	-3.4 (-6.97 to 0.17)	-0.60 (-3.58 to 2.38)	-2.80 (-3.65 to -1.95)	15.27
Atkinson et al,[29] 2004	40	102	103	-0.8 (-4.92 to 3.32)	-1.0 (-4.53 to 2.53)	0.20 (-0.34 to 0.74)	15.52
Lipovac et al,[24] 2012	80	50	59	-8.6 (-14.3 to -2.92)	-0.9 (-7.51 to 5.71)	-7.70 (-8.88 to -6.52)	14.90
van de Weijer et al,[58] 2002	80	16	14	-2.08 (-8.14 to 3.98)	0.29 (-11.0 to 11.6)	-2.37 (-5.75 to 1.01)	10.93
Tice et al,[56] 2003	82	84	85	-3.4 (-9.20 to 2.40)	-2.8 (-7.05 to 1.45)	-0.60 (-1.38 to 0.18)	15.34
Knight et al,[44] 1999	160	13	12	-3.1 (-9.27 to 3.07)	-2.8 (-8.44 to 2.84)	-0.30 (-2.66 to 2.06)	12.95
Random effects						-1.84 (-3.87 to 0.19)	100
Fixed effects						-1.12 (-1.46 to -0.77)	
Black Cohosh							
Shahnazi et al,[71] 2013	6.5	42	42	-4.6 (-3.65 to -3.25)	-1.19 (-2.74 to 0.36)	-3.64 (-4.61 to -2.67)	24.92
Pockaj et al,[70] 2006	40	66	65	NR	NR	1.32 (0.07 to 2.57)	23.78
Frei-Kleiner et al,[68] 2005	42	81	41	1.66 (-1.65 to 4.97)	1.85 (-1.33 to 5.03)	-0.19 (-0.81 to 0.43)	26.04
Newton et al,[19] 2006	160	80	84	NR	NR	-0.28 (-1.16 to 0.60)	25.25
Random effects						-0.71 (-2.51 to 1.08)	100
Fixed effects						-0.69 (-1.12 to -0.27)	



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
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