Phytoestrogens for treatment of menopausal symptoms: a systematic review
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CRD summary
This review assessed the efficacy and tolerability of phytoestrogens for treating menopausal symptoms. The authors concluded that the available evidence suggests that phytoestrogens do not improve hot flushes or other menopausal symptoms, although they are well tolerated. This was generally a well-conducted and clearly presented review, and the authors' conclusions regarding efficacy are likely to be robust.

Authors' objectives
To assess the efficacy and tolerability of phytoestrogens for treating menopausal symptoms.

Searching
MEDLINE and the Cochrane Library were searched from 1966 to March 2004; the keywords were reported. The reference lists in identified reports and reviews were checked. The journals Menopause, and Obstetrics and Gynecology were searched from 1998 to 2003 for relevant abstracts of annual meetings of the North American Menopause Society and the American College of Obstetricians and Gynecologists. Studies were only included if they were reported in English.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a duration of at least 4 weeks were eligible for inclusion. The mean study duration was 17 weeks (range: 4 to 104).

Specific interventions included in the review
Studies that compared phytoestrogen-containing supplements or foods with placebo or non-phytoestrogen control were eligible for inclusion. The review defined phytoestrogens as including isoflavones, lignans and coumestans. The review classified phytoestrogens as: soy foods, beverages and powders; soy extracts; and red clover extracts. The included studies were conducted in ten different countries.

Participants included in the review
Studies of perimenopausal and postmenopausal women with hot flushes or other menopausal symptoms were eligible for inclusion. In the included studies, where reported, the mean age of the participants was 53 years, the mean duration of menopause was 4.3 years and the mean number of hot flushes per day was 7. The studies differed in the percentage of women with surgical menopause (mean 17.7%, range: 0 to 32, where reported). None of the studies included women taking hormone replacement therapy. Three studies only included women who had been treated for breast cancer.

Outcomes assessed in the review
Studies that reported the frequency of hot flushes or menopausal symptom scores were eligible for inclusion. The review also assessed adverse effects. The Greene Climacteric Scale and the Kupperman Index were the most commonly used instruments used to assess symptoms; other studies used study-specific scales or questionnaires.

How were decisions on the relevance of primary studies made?
At least one reviewer selected studies. Where there was doubt about eligibility it was discussed with at least one other reviewer.

Assessment of study quality
The studies were assessed on the basis of: allocation concealment; blinding of the participants, providers and outcome assessors; use of intention-to-treat analysis; the number of participants who withdrew or were lost to follow-up; and the
validity of measures used for the outcomes. The authors did not state who performed the validity assessment.

**Data extraction**

Two reviewers independently extracted the data using a standardised form. The authors of the primary studies were contacted about missing data. Where possible, effect sizes representing treatment differences in hot flush frequency were calculated for the individual studies. Effect sizes were classified according to Cohen as showing small (0.2), moderate (0.5) or large (0.8) effects of treatment.

**Methods of synthesis**

How were the studies combined?
The studies were grouped by type of phytoestrogen and outcome, and then combined in a narrative. Studies of red clover were also pooled, using a random-effects meta-analysis, to calculate weighted mean differences (WMDs) and 95% confidence intervals (CIs).

How were differences between studies investigated?
Differences between the studies were discussed in the text of the review. Statistical heterogeneity was assessed using the chi-squared statistic. A subgroup analysis was used to examine the effects of dose of red clover (40 or 80 mg), inclusion of data from a 160-mg treatment arm, and adequate allocation concealment. Studies in women who had been treated for breast cancer were considered separately.

**Results of the review**

Twenty-five RCTs (n=2,348) were included, of which five were crossover RCTs.

All but 3 RCTs reported double-blinding. Seven RCTs described adequate allocation concealment. Eleven RCTs reported the use of intention-to-treat analysis, but only one clearly included all randomised patients in the analysis of the results. The mean drop-out rate was 15.5%. Only 6 studies assessed the outcomes using a validated symptom score.

Soy foods, beverages and powders (11 RCTs, n=1,094).

The total daily dose in 8 RCTs ranged from 34 to 134 mg. Of 8 RCTs evaluating hot flushes, seven showed no statistically significant difference between soy products and placebo and one favoured soy products. None of the 8 RCTs assessing symptom scores found a difference between treatments in overall symptom scores.

Soy extract (9 RCTs, n=854).

The studies used different products with daily isoflavone doses ranging from 50 to 150 mg. Of 5 RCTs (including the two largest RCTs with 177 patients each) assessing hot flushes, three found no significant difference between treatments and two favoured soy extract over placebo. Of 5 RCTs assessing symptom scores, one found soy extract significantly improved total symptom scores (assessed using the Kupperman Index) compared with placebo, while another found no significant difference between treatments in total Kupperman Index score or a visual analogue scale. The other RCTs reported effects for specific items in scales or only reported changes from baseline.

Red clover extracts (5 RCTs, n=400).

All studies used the same proprietary formula, Promensil. One study also included a treatment arm with Rimostil. Only the two smallest RCTs (30 patients each) found significant improvements in hot flush frequency with red clover. There was no statistically significant difference between red clover extract and placebo in pooled hot flush frequency (WMD -0.60, 95% CI: -1.71, +0.51). Statistically significant heterogeneity was found (P=0.04). The results were similar after including a higher dose treatment arm, grouping studies by drug dose and analysing only studies with adequate allocation concealment. None of the 4 RCTs using the Greene Climacteric Scale to assess symptoms found any difference between treatments.

Women treated for breast cancer (3 RCTs, n=396).
There was no significant difference between phytoestrogens and control in terms of either hot flushes (2 RCTs) or symptom scores (1 RCT).

Adverse effects (12 RCTs). Two of the 12 RCTs reported increased adverse effects with phytoestrogens compared with control; one found increased gastrointestinal effects (47% versus 22% with placebo), while the other found increased rates of gastrointestinal effects or supplement unpalatability (75% versus 17% with control; plus 25% dropped out due to dislike of taste of soy). The other studies reported similar rates of adverse effects between treatments.

**Authors' conclusions**
The evidence available suggests that phytoestrogens do not improve hot flushes or other menopausal symptoms, but are well tolerated.

**CRD commentary**
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and attempts were made to locate unpublished studies, thus limiting the possibility of publication bias. No attempts were made to minimise language bias; the restriction to English language studies might have resulted in the loss of some relevant data. The process of selecting studies was not done entirely in duplicate, which might have led to errors and bias. The authors employed methods to minimise bias during the extraction of data, but it was unclear if the validity assessment was also conducted in duplicate. Validity was assessed using specified established criteria.

The narrative synthesis was appropriate in view of the differences among the studies. Pooling data for red clover studies was questionable given the finding of statistically significant heterogeneity. However, the studies were also discussed in a narrative synthesis and differences between the studies were examined. The results were discussed with reference to study quality. This was generally a well-conducted and clearly presented review, and the authors' conclusions about the efficacy of phytoestrogens are likely to be robust. The high rates of gastrointestinal symptoms and complaints of unpalatability of some soy beverages suggest these may not be well tolerated.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that population-based observational studies are required to improve understanding of women's use of alternative medicines. In addition, future adequately powered RCTs should examine the most popular treatments and compare them with both placebo and short-term hormone replacement therapy, using outcomes of hot flush frequency and severity and standardised validated menopausal symptom scales.

**Bibliographic details**

PubMedID
15458907

DOI
10.1097/01.AOG.0000140688.71638.d3

**Other publications of related interest**
This additional published commentary may also be of interest. Kessenich CR. Review: plant based oestrogens do not relieve hot flushes or other menopausal symptoms. Evid Based Nurs 2005;8:83.
Subject indexing assigned by NLM

MeSH
Female; Hot Flashes /drug therapy; Humans; Isoflavones /administration & dosage /therapeutic use; Menopause; Middle Aged; Phytoestrogens; Phytotherapy; Plant Preparations /administration & dosage /therapeutic use; Plants, Medicinal; Prospective Studies; Randomized Controlled Trials as Topic

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.