Trifolium pratense isoflavones in the treatment of menopausal hot flushes: a systematic review and meta-analysis

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CRD summary
The authors concluded that Trifolium pratense isoflavones appear effective in treating hot flushes, but the clinical relevance of the effect is unclear, adverse events related to short-term use were not apparent and long-term use requires further research. The conclusions were drawn from a few studies involving few participants and showing conflicting evidence, and may not be reliable.

Authors' objectives
To evaluate the effects of Trifolium pratense isoflavone supplements on the frequency of hot flushes in menopausal women.

Searching
MEDLINE (from 1951), EMBASE (from 1974), CINAHL (from 1982), AMED (from 1985) and the Cochrane Library (Issue 2) were searched to April 2006; the search terms were reported. Additional relevant studies were identified by checking the bibliographies of retrieved articles and departmental files, and by contacting experts in the field and manufacturers and distributors. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised clinical trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies evaluating oral monopreparations of Trifolium pratense (red clover) isoflavones for treating hot flushes were eligible for inclusion. All included studies used a standard preparation of isoflavones (Promensil, Novogen Ltd, Australia) in doses of 40 to 80 mg/day. Two studies also evaluated the other standard doses, Rimostil (Novogen Ltd) at 57 mg/day and Promensil at 160 mg/day. Treatment duration was 12 or 16 weeks. All of the included studies used placebo as the control treatment. All patients received dietary advice.

Participants included in the review
Studies including healthy menopausal women were eligible for inclusion. Women in the included studies were peri- or postmenopausal, amenorrhagic for more than 6 months and experienced at least three hot flushes per day.

Outcomes assessed in the review
The primary outcome was the change from baseline in the frequency of hot flushes per day. All of the included studies assessed hot flush frequency using patient diaries. Adverse effects were also reported.

How were decisions on the relevance of primary studies made?
Two reviewers selected the studies, with any disagreements resolved by discussion.

Assessment of study quality
The quality of the studies was assessed using the Jadad scale, rating the description of randomisation, blinding and withdrawals. Each study was allocated a score from 0 (lowest) to 5 (highest). One reviewer assessed study quality and a second reviewer checked the assessment; any disagreements were resolved through discussion.
Data extraction
One reviewer extracted the data and a second reviewer checked the extraction; any disagreements were resolved by discussion. Data to assess the change between baseline and end point for each treatment arm were extracted; the variance of the change was estimated.

Methods of synthesis
How were the studies combined?
A random-effects model was used to calculate summary weighted mean differences (WMDs) and 95% confidence intervals (CIs) for the main outcome. Data on safety were presented narratively.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test and the I-squared statistic. The effects of different treatment doses and different meta-analysis methods on the pooled estimates were evaluated by sensitivity analysis.

Results of the review
Five RCTs (400 patients) were included in the review.

Three studies were assigned a score of 5 on the Jadad scale; the other two studies were given 4 and 2 points, respectively.

The use of Trifolium pratense isoflavone supplements was associated with a non statistically significant lower rate of hot flushes per day compared with placebo (WMD -1.45, 95% CI: -2.94, 0.03, p=0.05; statistical heterogeneity: I-squared 49.5%, p=0.09).

Compared with placebo, including the higher dose of isoflavones in the analysis resulted in a larger difference (WMD -1.63, 95% CI: -2.97, -0.28, p<0.02).

One study reported no adverse effects during treatment with isoflavones; the other included studies provided no information on toxicity.

Authors' conclusions
There was evidence of a marginally significant effect of Trifolium pratense isoflavones in the treatment of hot flushes in menopausal women, but the clinical relevance of this effect was unclear. Adverse events during short-term use were not apparent but data on long-term administration were missing.

CRD commentary
This review addressed a well-defined question in terms of the participants, intervention and study design. Five relevant databases were searched and some attempts were made to identify unpublished articles, thereby reducing the risk of publication bias. No language restrictions were applied, which limits the risk of language bias. The authors stated that an evaluation of publication bias was planned, but it was not assessed because of the size of the included studies. The authors attempted to minimise bias and errors during the review process by carrying out critical review stages in duplicate. Individual study results varied with two of the five studies favouring placebo; variation between the studies was not further explored.

The authors' conclusions about effectiveness were drawn from a few studies involving only a small number of patients and the conclusion about adverse events was based on a single study only, thus compromising the validity of the results. The pooled results were not statistically significant by usual scientific convention (p=0.05), so the conclusion regarding a marginally significant effect does not appear to be justified. One of the review authors was funded by a manufacturer of the supplement.
Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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