Phytoestrogens for menopausal vasomotor symptoms (Review)

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[Intervention Review]

Phytoestrogens for menopausal vasomotor symptoms

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ABSTRACT

Background

Vasomotor symptoms, such as hot flushes and night sweats, are very common during the menopausal transition. Hormone therapy has traditionally been used as a highly effective treatment, but concerns about increased risk of some chronic diseases have markedly increased the interest of women in alternative treatments. Some of the most popular of these treatments are foods or supplements enriched with phytoestrogens-plant-derived chemicals that have estrogenic action.

Objectives

To assess the efficacy, safety and acceptability of food products, extracts and dietary supplements containing high levels of phytoestrogens when compared with no treatment, placebo or hormone therapy for the amelioration of vasomotor menopausal symptoms (such as hot flushes and night sweats) in perimenopausal and postmenopausal women.

Search methods

Searches targeted the following electronic databases: the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of randomised trials (29 July 2013), the Cochrane Register of Controlled Trials (CENTRAL; 29 July 2013), MEDLINE (inception to 29 July 2013), EMBASE (inception to 29 July 2013), AMED (1985 to 29 July 2013), PsycINFO (inception to 29 July 2013) and CINAHL (inception to 29 July 2013). Attempts were made to access grey literature by sending letters to pharmaceutical companies and performing searches of ongoing trial registers. Reference lists of included trials were also searched.

Selection criteria

Studies were included if they were randomised, included perimenopausal or postmenopausal participants with vasomotor symptoms (hot flushes or night sweats), lasted at least 12 weeks and provided interventions such as foods or supplements with high levels of phytoestrogens (not combined with other herbal treatments). Trials that included women who had breast cancer or a history of breast cancer were excluded.

Data collection and analysis

Selection of trials, extraction of data and assessment of quality were undertaken by at least two review authors. Most trials were too dissimilar for their results to be combined in a meta-analysis, so these findings are provided in narrative 'Summary of results' tables. Studies were grouped into broad categories: dietary soy, soy extracts, red clover extracts, genistein extracts and other types of phytoestrogens. Five trials used Promensil, a red clover extract; results of these trials were combined in a meta-analysis, and summary effect measures were calculated.

Main results

A total of 43 randomised controlled trials (4,364 participants) were included in this review. Very few trials provided data suitable for inclusion in a meta-analysis. Among the five trials that yielded data assessing the daily frequency of hot flushes suitable for pooling, no significant difference overall was noted in the incidence of hot flushes between participants taking Promensil (a red clover extract) and those given placebo (mean difference (MD) -0.93, 95% confidence interval (CI) -1.95 to 0.10, I^2 = 31%). No evidence indicated a difference in percentage reduction in hot flushes in two trials between Promensil and placebo (MD 20.15, 95% CI -12.08 to 52.38, I^2 = 82%). Four trials that were not combined in meta-analyses suggested that extracts with high (> 30 mg/d) levels of genistein consistently reduced the frequency of hot flushes. Individual results from the remaining trials were compared in broad subgroups such as dietary soy, soy extracts and other types of phytoestrogens that could not be combined. Some of these trials found that phytoestrogen treatments alleviated the frequency and severity of hot flushes and night sweats when compared with placebo, but many trials were small and were determined to be at high risk of bias. A strong placebo effect was noted in most trials, with a reduction in frequency ranging from 1% to 59% with placebo. No indication suggested that discrepant results were due to the amount of isoflavone in the active treatment arm, the severity of vasomotor symptoms or trial quality factors. Also, no evidence indicated that these treatments caused oestrogenic stimulation of the endometrium or the vagina or other adverse effects when used for up to two years.

Authors' conclusions

No conclusive evidence shows that phytoestrogen supplements effectively reduce the frequency or severity of hot flushes and night sweats in perimenopausal or postmenopausal women, although benefits derived from concentrates of genistein should be further investigated.

PLAIN LANGUAGE SUMMARY

Phytoestrogens for vasomotor menopausal symptoms

Review question: This Cochrane review has evaluated whether phytoestrogen treatments reduce the number and severity of hot flushes and whether they are safe and acceptable.

Background: Hormone therapy is an effective treatment for controlling the most common menopausal symptoms-hot flushes and night sweats. However, it is now recommended only in low doses given for the shortest possible time because of concerns about increased risk of some chronic diseases. Many women have started to use therapies that they perceive as 'natural' and safe, but they often do not have good information about the potential benefits and risks. Some of these therapies contain phytoestrogens-a group of plant-derived chemicals that are thought to prevent or treat disease. Phytoestrogens are found in a wide variety of plants, some of which are foods, particularly soy, alfalfa and red clover.

Study characteristics: This review found 43 RCTs conducted up to July 2013 that included 4,084 participants with hot flushes who were close to the menopause or were menopausal. Evidence obtained is current to July 2013.

Key results: Some trials reported a slight reduction in hot flushes and night sweats with phytoestrogen-based treatment. Extracts containing high levels of genistein (a substance derived from soy) appeared to reduce the number of daily hot flushes and need to be investigated further. Overall no indication suggested that other types of phytoestrogens work any better than no treatment. No evidence was found of harmful effects on the lining of the womb, stimulation of the vagina or other adverse effects with short-term use.

Quality of the evidence: Many of the trials in this review were small, of short duration and of poor quality, and the types of phytoestrogens used varied substantially.

BACKGROUND

Description of the condition

Menopause is a significant event in the lives of most women, as it marks the end of a woman's natural reproductive life. The perimenopausal and early postmenopausal years are typically characterised by falling levels of endogenous oestrogen, which can give rise to vasomotor symptoms that are severe and disruptive, particularly in the early and late menopausal transition and in early postmenopause, as categorised by the STRAW (STages of Reproductive Aging Workshop) criteria (Harlow 2012). These vasomotor symptoms include hot flushes (also known as 'hot flashes'), sweating and sleep disturbances.

Hot flushes are described as sudden feelings of heat in the face, neck and chest (WHO 1996). Hot flushes are frequently accompanied by skin flushing and perspiration, followed by a chill as core body temperature drops (Freedman 2001; Kronenberg 1990). Flushes vary in frequency, duration and severity and may be spontaneous and unpredictable (Freedman 1995). Hot flushes that occur during the night are typically referred to as night sweats. Flushes and night sweats are events of concern in themselves because they can disrupt sleep patterns and alter daily activities, which can lead to fatigue and decreased quality of life (Ayers 2013; NAMS 2004). Hot flushes are thought to result from both the brain's response to diminished hormones and hormonal fluctuations that occur during the menopausal transition, which leads to instability of thermoregulatory mechanisms (that regulate temperature) in the hypothalamus (Deecher 2007; Freedman 2001; Kronenberg 1987).

The prevalence of vasomotor symptoms varies with ethnicity. Flushes are less common among East Asian women (median 16%) than among American and European women (median 55%) (Freeman 2007). Up to 40% of Western women are affected severely enough to seek medical help (Freeman 2007; Gold 2006). An Australian prospective study with 13-year follow-up reported that the mean duration of troublesome vasomotor symptoms was 5.5 years (Col 2009). A study of more than 10,000 British women 54 to 65 years of age found that more than half (54%) were currently experiencing vasomotor symptoms (averaging 34 hot flushes or night sweats per week), which were problematic in 40% of cases and were fairly stable across the age range (Hunter 2012). Although hot flushes are reported as more prevalent and intense in the perimenopausal and early postmenopausal years, they continue to be important in up to 14.6% of women in their sixties and in 8.6% of women in their seventies (Roussouw 2007).

Description of the intervention

Most therapies designed to combat menopausal vasomotor symptoms aim to supplement levels of circulating oestrogen (Sikon 2004). The treatment of choice has traditionally been hormone therapy (HT), but, despite its effectiveness for symptom reduction, a marked and global decline has occurred in the prescription and use of HT because of concerns about long-term use, particularly worry about increased risk of chronic diseases (Bestul 2004; Haas 2004; Travers 2006). Although the combination of HT and unopposed oestrogen therapy was previously prescribed to prevent the onset of cardiovascular events as women grew older, a report of the Women's Health Initiative (WHI) trial, in 2002, indicated that the risks of this treatment outweighed the benefits (Roussouw 2002). Combined therapy was linked with increased risk of breast cancer, stroke, thromboembolism (blood clots), gallbladder disease and dementia. Unopposed oestrogen therapy increased the risk of stroke, thromboembolism and gallbladder disease, and other studies reported an increase in the incidence of breast cancer (Beral 2003). Data now available from 11 years of follow-up provided by WHI show that risks are influenced by the age of the woman, the time since menopause and whether the HT was combined or consisted of oestrogen only (NAMS 2012). Contraindications to HT include a family history or increased risk of cardiovascular disease, blood clotting disorders, venous thromboembolism or certain hormone-sensitive cancers (Anderson 2003; Grady 2000). Some women report adverse effects when taking HT (Bakken 2004; Bjorn 1999); potential side effects include breast tenderness, bloating and genital bleeding. Regulatory bodies around the world are now advocating that HT should be prescribed only in the smallest dose and for the shortest possible time (Europ Med Ag 2006; UK MHRA 2007).

Potential health risks associated with HT and further uncertainty surrounding actual benefits to be gained from it have caused many women to seek non-medical alternatives (Bair 2005; Newton 2002). 'Natural' therapies appear to be very popular among women; a survey of 866 women 45 to 65 years of age reported that 61% agreed or strongly agreed with the statement that natural approaches are better than hormone pills for menopausal symptoms (Newton 2002). In a national survey on women's use of complementary alternative medicine (CAM), more than 50% of CAM users indicated that such use was consistent with their beliefs, and 55% said that they wanted a natural approach to treatment (Chao 2006).

However, sufficient research on the risks and benefits of these approaches is lacking. A survey of women seen at a university clinic reported that 70% of women taking dietary supplements did not inform their doctors about their use, and only 4% had received information about such supplements from a healthcare provider (Mahady 2003). In a national survey, when women using CAM for menopausal symptoms consulted a doctor, their disclosure rate (of CAM) was much higher, with only 36% of women reporting

that they did not disclose their self treatment with CAM to their doctors (Wade 2008).

Therapies based on phytoestrogens are among the most common alternatives to HT. Phytoestrogens are nonsteroidal plant compounds of diverse structure that are found in many fruits, vegetables and grains (Knight 1996; Thompson 1991). The most common types of phytoestrogens are coumestans, lignans and isoflavones. These compounds structurally resemble oestradiol (E2) and are shown to have weak oestrogenic activity (Makela 1994; Setchell 1998). When ingested in relatively large quantities, dietary phytoestrogens have been shown to have significant biological effects in several animal species (Adlercreutz 1995) and in humans (Wilcox 1990). In humans, they appear to have both oestrogenic and anti-oestrogenic effects, depending on the concentrations of circulating endogenous oestrogens and oestrogen receptors (Bolego 2003).

Isoflavones are among the most oestrogenically potent phytoestrogens; the major dietary isoflavones, genistein and daidzein, are found almost exclusively in legumes such as soy, chick peas, lentils and beans (Cassidy 1993). Urinary excretion of equol, a weak oestrogen, in humans eating soy-supplemented diets can greatly exceed the concentration of urinary endogenous oestrogens; this enhances the plausibility of human physiological health effects (Setchell 1984). Other classes of phytoestrogens-lignans and prenylated flavonoids-also have potent oestrogenic activity but are not as well studied (Adlercreutz 1987; Milligan 1999). Soy, a particularly abundant source of isoflavones, is a staple ingredient in the traditional Asian diet. It is postulated that high intake of soy among Asian women may account for lower rates of some menopausal symptoms in this group. Asian populations, such as those in Japan, Taiwan and Korea, are estimated to consume 20 to 150 mg per day of isoflavones, with a mean of about 40 mg from tofu (soy bean curd) and miso (soy bean paste). Soy includes such products as tofu, miso, aburage (fried thin tofu) and fermented or boiled soy beans. Further evidence that soy might be beneficial is suggested by a cohort study of Japanese women (Nagata 2001), which found a significant inverse association between frequency of flushes and higher levels of soy consumption. However, the findings of this study are contradicted by data from a cross-sectional study, which found that women who frequently consumed soy products were not less likely to report hot flushes or night sweats than women who never consumed soy products (Sievert 2007). Thus it is not clear whether frequent soy consumption explains the lower rate of hot flushes among different ethnic groups. Red clover (*Trifolium pratense*), another source of isoflavones, contains compounds that are metabolised to genistein and daidzein after consumption. The most studied red clover product is Promensil.

Potential adverse effects of phytoestrogens have included deficits in sexual behaviour in rats and impaired fertility in livestock (Bennetts 1946). No specific examples of toxicity among humans have been noted in countries in which soy is consumed regularly (Setchell 1997). It is generally considered difficult for humans to consume the quantity of isoflavones from natural soy foods needed to reach toxicological levels that induce pathological effects, as recorded in animals.

How the intervention might work

No clear explanation is known for how phytoestrogens might work in reducing hot flushes among perimenopausal and postmenopausal women.

It has been suggested that phytoestrogens act as selective oestrogen receptor modulators (SERMs), exerting anti-oestrogenic effects in the high-oestrogen environment of premenopause and oestrogenic effects in the low-oestrogen environment of postmenopause, where they act as weak agonists by stimulating oestrogen receptors (Seibel 2003). Phytoestrogens appear to show greater affinity for the oestrogen receptor beta (ERβ) than for the classical oestrogen receptor alpha (ERα). As a result, they preferentially express oestrogenic effects in the central nervous system, blood vessels, bone and skin without causing stimulation of the breast or uterus (Kuiper 1997). Thus, phytoestrogens may reduce vasomotor symptoms through their action on the vascular system without causing unwanted oestrogenic effects on other body systems.

Why it is important to do this review

Current use of phytoestrogen products among perimenopausal and postmenopausal women with vasomotor symptoms is high; an American cross-sectional analysis of more than 2,000 women (Study of Women's Health Across the Nation (SWAN)) reported that 11% of women with vasomotor symptoms used flaxseed products and 19% used soy products (Gold 2007). Several reviews have examined the efficacy of phytoestogen products in alleviating menopausal symptoms, but most have found no benefit or a very slight reduction in the frequency of daily hot flushes compared with placebo. Government agencies and healthcare organisations have also scrutinised the effects of phytoestrogens, particularly isoflavones (AFSSA 2005; Com Tox 2003). The North American Menopause Society (NAMS) position statement on the treatment of menopause-associated vasomotor symptoms suggests that women should consider isoflavone supplementation if their menopausal flushing does not respond to other interventions (NAMS 2004; NAMS 2011). However, NAMS acknowledges that the evidence base for this recommendation is poor.

Thus, the aim of this review is to synthesise all available evidence on the efficacy, safety and acceptability of products containing phytoestrogens to assist women with vasomotor menopausal symptoms to reduce their symptoms by making good evidence-based treatment decisions.

OBJECTIVES

To determine the efficacy, safety and acceptability of food products, extracts and dietary supplements containing high levels of phytoestrogens when compared with no treatment, placebo or hormone therapy for the amelioration of vasomotor menopausal symptoms (such as hot flushes and night sweats) in perimenopausal and postmenopausal women.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled comparisons of food products, extracts or dietary supplements containing high levels of phytoestrogens (e.g. at least 30 mg/d of isoflavones) versus placebo, HT, no treatment or products containing low levels of phytoestrogens for the alleviation of vasomotor menopausal symptoms.

Types of participants

Inclusion criteria

- Perimenopausal women, defined as women in the 45- to 55-year age range, who have menstruated within the past 12 months and are seeking treatment for menopausal vasomotor symptoms
- Postmenopausal women, defined as women who are older than 45 years of age, who have not menstruated for longer than 12 months and are seeking treatment for menopausal symptoms

Women experiencing spontaneous or surgical menopause (bilateral oophorectomy (removal of both ovaries)) were eligible. Trials were eligible only when most women had vasomotor symptoms.

Source of recruitment

Any healthcare setting or the community

Exclusion criteria

- Intercurrent major disease
- Previous HT (hormone therapy) within one month of commencement of the study or an oestrogen implant within the past year
- Women with breast cancer or a history of breast cancer
- Women with no or inconsequential vasomotor symptoms at baseline

Types of interventions

All food products or dietary supplements containing high levels of phytoestrogens (> 30 mg/d of isoflavones, > 100 µg 8-prenylnaringenin or > 10,000 µg total lignans) versus placebo, hormone therapy, no treatment or food products with low levels of phytoestrogens given as perimenopausal or postmenopausal therapy for the alleviation of vasomotor menopausal symptoms for a period of at least 12 weeks. Studies in which phytoestrogens were combined with other therapies were excluded.

Types of outcome measures

Primary outcomes

- Efficacy
  - Change in vasomotor menopausal symptom scores (without distinction between types of vasomotor symptoms)
  - Change in frequency of individual vasomotor symptoms or severity of individual vasomotor symptom scores (e.g. hot flushes and night sweats)
  - Incidence of vasomotor symptoms (hot flushes and night sweats) after treatment

Studies were included if they measured vasomotor symptoms on a subscale of a compendium score, for example, Greene Score, Kupperman Index, Nordin Score, MacLennan Score or any other general menopausal symptom score that derives numerical results from a combination of vasomotor menopausal symptoms.
In addition, studies were included that measured individual vasomotor symptoms, for example, severity or frequency, or both, of hot flushes and night sweats (evaluated subjectively by participants, usually in daily diaries).

Secondary outcomes

- Safety
  - Stimulation of the endometrium (endometrial thickness, rates of atrophic endometrium)
  - Vaginal stimulation (pH, maturation value)
  - Adverse events
- Acceptability
  - Acceptability of therapy (withdrawal due to adverse events or satisfaction rates)

Studies were included if they measured specific safety outcomes, such as measures of physiological oestrogenicity of the endometrium and vagina. Other possible safety outcomes could be measured that are related to the effects of oestrogen action on other tissue and organs, but these will be assessed in future reviews if evidence of a beneficial effect on symptoms is noted.

Search methods for identification of studies

The Trials Search Co-ordinator designed the search strategy for use with the electronic databases. The complete search strategies are listed in the Appendices of this review.

Electronic searches

The Trials Search Co-ordinator of the Menstrual Disorders and Subfertility Group (MDSG) searched for all published and unpublished randomised controlled trials (RCTs) of phytoestrogens for vasomotor symptoms, with no language restriction, using the following electronic databases.

- MEDLINE (see Appendix 1).
- EMBASE (see Appendix 2).
- PsycInfo (see Appendix 3).
- AMED (see Appendix 4).
- Cochrane Central Register of Controlled Trials (see Appendix 5).
- MDSG Specialised Register of Controlled Trials (see Appendix 6).

The principal author of the review (AL) searched the following trial registers and websites.

- Trial registers for ongoing and registered trials: http://www.controlled-trials.com
- Citation indexes: http://scientific.thomson.com/products/sci
- Conference abstracts in the Web of Knowledge: http://www.wokinfo.com/
- LILACS database, for trials from the Portuguese- and Spanish-speaking world: http://bases.bireme.br/cgibin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F
- Results from clinical trials of marketed pharmaceuticals: http://www.clinicalstudyresults.org
- PubMed: http://www.ncbi.nlm.nih.gov/pubmed/
- OpenSIGLE database: http://opensigle.inist.fr/
- Google

Searching other resources

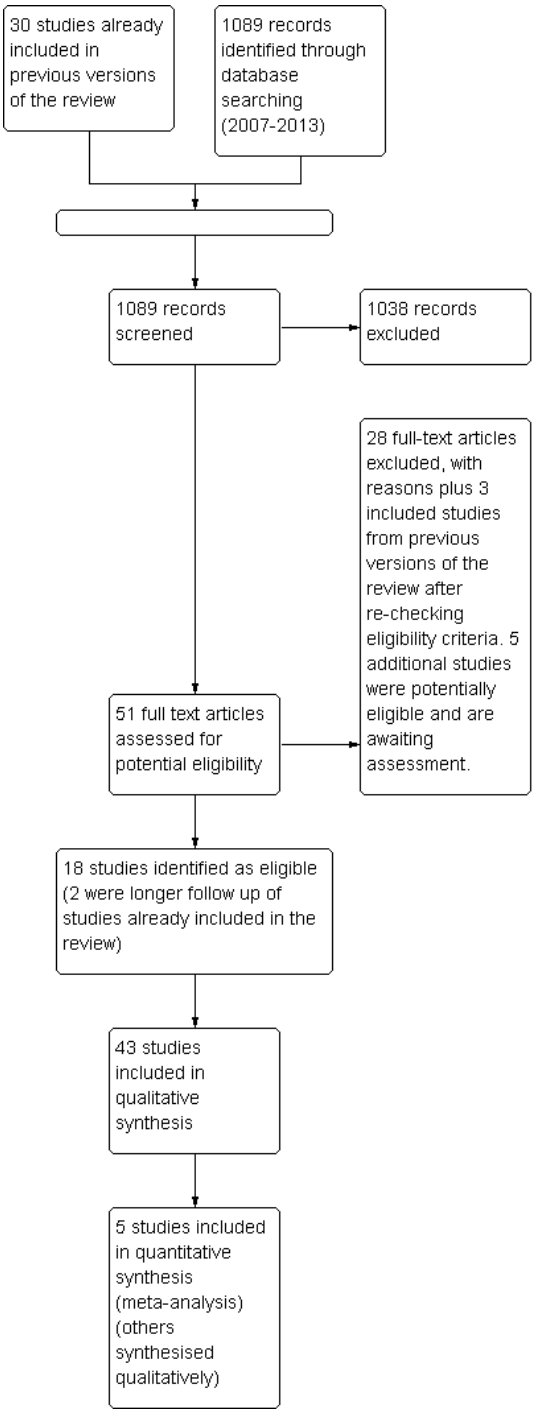
The reference lists of retrieved potentially eligible studies and relevant reviews were also searched. Novogen, manufacturer of a standardised extract of phytoestrogens (Promensil), was contacted for details of unpublished trials.

Data collection and analysis

Selection of studies

Trials for inclusion in the review were selected at different times by two review authors (AL and FK, JM or JB) after the search strategy described previously was employed. First, titles and abstracts were scanned, and full-text copies of those that appeared relevant were retrieved to determine whether they met the inclusion criteria for the review. If necessary, authors of potential trials for inclusion were contacted to clarify study eligibility. Disagreements over selection were resolved by consensus. The selection process for the 2013 update has been documented on a flow chart (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Data were extracted independently by at least two review authors (AL and FK, JM or JB), who used a specially designed data extraction form. Any discrepancies in data extraction were resolved by consensus. When necessary, additional information on trial methodology or original trial data were sought from the principal or corresponding author of any trials that met the eligibility criteria (see Acknowledgements for details of the authors who provided additional clarification of data beyond that reported in the publications).

Data extracted included details on study characteristics (participants, interventions and comparison groups) and outcome data. When necessary, missing data were imputed from data in other, similar trials or were calculated by using formulas suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of risk of bias in included studies

All assessments of risk of bias were performed independently by at least two review authors (AL and FK, JM or JB), who used the Cochrane 'Risk of bias assessment tool' (Higgins 2011); results were compared. Any discrepancies were resolved by consensus. Criteria assessed included randomisation method, allocation concealment, blinding of participants and investigators, blinding of assessors, incomplete outcome data and selective outcome reporting. Summary assessments of risk of bias are presented in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

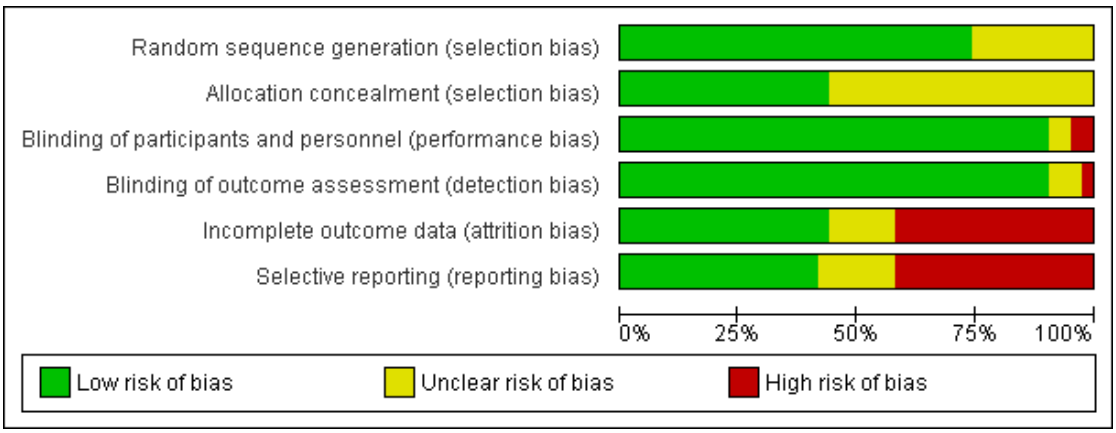
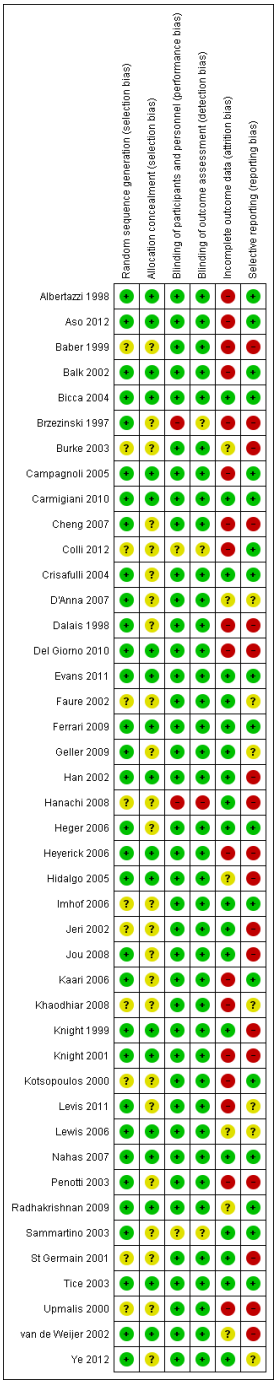


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Risk of bias assessments have been incorporated into sensitivity analyses (see below).

Measures of treatment effect

When trials were combined in a meta-analysis, summary effect measures were calculated. For dichotomous data, the numbers of events in the intervention and control groups were used to calculate risk ratios (RRs), together with their 95% confidence intervals (CIs). For continuous data, the weighted mean difference (MD) between groups, together with 95% CIs, was calculated. For all other studies, findings in the individual study publications were reported in narrative format and compared.

Unit of analysis issues

The primary unit of analysis was per woman randomised. Only first-phase data from cross-over trials were analysed.

Dealing with missing data

When data were missing, attempts were made to obtain these data from the authors of relevant included studies. Clarifications of data and details from the publications were received from a number of study authors (see Acknowledgements).

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of included studies were sufficiently similar to warrant meta-analysis. When meta-analyses were performed, statistical heterogeneity was assessed by the Chi^2 test (with $P < 0.10$ considered evidence of statistical heterogeneity) and the I^2 metric. An I^2 value > 50% was considered to represent substantial heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the review authors have attempted to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. No funnel plot was generated, as most of the studies were synthesised narratively because of substantial heterogeneity.

Data synthesis

A priori, it was decided that results from the included studies would be combined in meta-analysis only if similarities were noted in the baseline experience of hot flushes among participants: the composition, type and dosage of the phytoestrogen interventions; the duration of the studies; and the outcomes measured. Significant heterogeneity was seen in the isoflavone concentration of foods and extracts used in the trials that were considered to contain high levels of phytoestrogens. Because of this variation in isoflavone concentration and the variation in the general mix of constituents of each phytoestrogen intervention, pooling of different food products, tablets and extracts was not considered appropriate, and results were reported separately for each trial in table format (see Table 1 Table 2 and Table 3).

Data from five trials were combined in meta-analyses because the intervention was a standardised dose of Promensil (Baber 1999; Jeri 2002; Knight 1999; Tice 2003; van de Weijer 2002). It was planned that a fixed-effect model would be used to combine studies in the meta-analyses, although both fixed-effect and random-effects estimates were calculated initially and results compared.

In the forest plots, an increase in the risk of a particular binary outcome that may be beneficial (e.g. improvement in hot flush severity) or detrimental (e.g. proportion with adverse events) is displayed graphically in the meta-analyses to the right of the centre line, and a decrease in the risk of an outcome to the left of the centre line. Similarly, for continuous data, for some outcomes a higher value for an outcome may be considered beneficial (e.g. greater change in vasomotor symptom score) or detrimental (e.g. number of hot flushes per day), and interpretation will be guided by considering the graph labels that are reversed for benefit as opposed to detriment.

Subgroup analysis and investigation of heterogeneity

For most trials, when results were reported in tabular form, subgroup analysis was undertaken because of variation in the phytoestrogen interventions. Trials were grouped a priori according to the type of phytoestrogen given in the experimental arms. Subgroups included the following.

- Trials in which the phytoestrogen given was in the form of dietary soy, such as flour, beverage or powder containing isoflavones.
- Trials in which the phytoestrogen given was in the form of a soy isoflavone extract.
- Trials in which the phytoestrogen given was in the form of a red clover extract.
- Trials in which the phytoestrogen given was in the form of a predominantly genistein extract.
- All other trials.

Statistical heterogeneity between the results of studies pooled in meta-analyses was examined by inspecting the scatter in the data points and the overlap in their confidence intervals and, more formally, by checking results of the Chi^2 test and the I^2 quantity. A priori, it was planned to look at the possible contribution of

differences in trial design to any heterogeneity identified in this manner. When substantial heterogeneity was indicated that could not be explained, a random-effects model was reported as a more appropriate method for estimating an average treatment effect.

Sensitivity analysis

Sensitivity analysis was conducted to compare differences among participants, interventions, outcomes and methodological quality of included studies.

- Comparison of trial results of all included studies with those studies at low risk of bias (with at least double blinding, adequate concealment, intention-to-treat analyses).
- Comparison of trial results of all included studies with those studies in which a power calculation was performed for sample size.
- Comparison of trial results of all included studies with those studies in which women were required to have at least five moderate to severe hot flushes per day before they were eligible to participate.
- Comparison of trial results of all included studies with those studies using more than 50 mg/d of isoflavones in the treatment group.

Overall summaries: 'Summary of results' tables

As few of the studies could be combined in meta-analyses, separate 'Summary of results' tables were generated to display efficacy, safety and acceptability outcomes for each trial (Table 1, Table 2 and Table 3). Study results in these tables should be considered by referring to the quality of the individual study (Figure 3) to aid in interpretation of overall results.

RESULTS

Description of studies

Results of the search

For earlier versions of this review, 30 studies (2,730 participants) were included, 31 were excluded and 11 were awaiting classification (further details on the total number of potentially eligible trials are not available).

For the 2013 update of the review, the search retrieved 51 potentially eligible additional studies through inspection of titles and abstracts (Figure 1).

Included studies

Of 51 potentially eligible studies in the 2013 update, a further 16 new studies met the inclusion, criteria together with two additional studies, which were later publications of studies already included in the review, with longer follow-up or additional results. A total of 43 RCTs (with 4,364 participants) is included in the review (Figure 1). Full details of the included studies are displayed in an additional table (Characteristics of included studies).

Study design and setting

A total of 38 studies used a parallel-group design, and the remaining five used a cross-over design. One cross-over trial had no washout period, and in the remaining four trials, the washout period ranged from seven days to one month. One cross-over trial was combined with parallel-group trials in forest plots; only data from the first phase of the trial before cross-over were used in these analyses.

Participants

Most participants were recruited solely from menopause clinics or through a mixture of advertisements and flyers placed in medical practices or in the community; the source of recruitment was not specified in 14 trials. Participants in these trials were experiencing vasomotor symptoms (hot flushes or night sweats) ranging from at least one flush per day to up to 15 flushes per day. Fifteen other trials were included in which vasomotor symptoms or scores on menopausal symptom indices were measured at baseline, although specification of the level of these symptoms was not a requirement for inclusion in the trial. Two of the trials measured the effects of treatment in subgroups (only those women with symptoms at baseline) of randomly assigned participants. One trial excluded women with severe menopausal symptoms who required medical treatment. Menopausal status was most often confirmed by follicle-stimulating hormone (FSH), luteinising hormone (LH) and plasma oestradiol measurements and/or by amenorrhoea ranging from two months to up to 10 years. Elderly women were not included; participants usually ranged in age from 40 to 65 years, although one trial included women up to 75 years of age. Because the minimum threshold of the last menstrual period ranged from two to 12 months or longer, many trials included a mix of perimenopausal and postmenopausal women. Three trials explicitly recruited perimenopausal women; women were required to have no more than one menstrual period during the three months before recruitment (ages ranged from 45 to 55 years) in one trial; in another, women were required to have had at least one period over the past 12 months (average time since last menstrual period was 16 weeks), and in another, women were 45 to 55 years of age and showed cycle irregularity over the previous 12 months or last menstruation at least three but no longer than 12 months previously. In most of the trials, women using HT, currently or

recently, were excluded. Other exclusion criteria included women on a vegetarian diet or on a soy-rich diet, malignancy, comorbidities and taking medication that might interfere with assessment of vasomotor symptoms. It was not clear in most trials whether participants had a natural or surgical menopause, but nine trials specifically excluded women with a surgical menopause. Women in five trials were from Australia, seven trials were performed in Italy, eight in the USA, seven in Brazil and the remainder in Israel, Japan, Canada, Sweden, France, Ukraine, Belgium, Ecuador, Peru, Austria, Taiwan, the Netherlands, India, China and Iran.

Interventions

Interventions used in the trials varied substantially.

Type and method of delivery of phytoestrogen

Trials were grouped into broad categories according to method of delivery and type of phytoestrogen.

- Thirteen trials assessed the effects of dietary substances in the form of flour, powder or beverages derived from soy isoflavones with varying amounts of phytoestrogen enrichment.
- Twelve trials assessed the effects of varying types of soy isoflavone extracts, usually in tablet form.
- Nine trials assessed the effects of red clover extracts (five of the nine used a standardised extract manufactured by Novogen under the brand name Promensil).
- Five trials assessed the effects of mainly genistein extracts on hot flushes.
- The remaining trials (n = 6) assessed other types of phytoestrogen supplements: Three trials investigated the effects of flaxseed dietary supplements (two of which had soy dietary supplement arms and were included in the first category and the other trial also assessed the effects of a flaxseed extract in addition to the flaxseed dietary supplement); one looked at two doses of a hop extract (*Humulus luputus* L.), one investigated the effects of a standardised natural S-(-)equol containing supplement (SE5-OH) (a metabolite of isoflavones) and another investigated the effects of an extract taken from the roots of *Rheum rhaponticum* (ERr 731) (which is considered a phytoestrogen supplement). The authors of this trial noted that ERr 731 has been used by perimeopausal and postmenopausal women in Germany since 1993.

Duration

Duration of the interventions provided was three months in most of the trials (or three months for the first phase of cross-over trials). Five trials had a duration of 16 weeks, nine trials had a duration of 24 weeks, one trial had a duration of 10 months, four trials had a duration of one year and three trials had a duration of two years.

Comparison groups

The phytoestrogen interventions were mostly placebo controlled, although three open studies compared phytoestrogens with other types of control, either different diet with no phytoestrogens or calcium tablets. One other study included a blinded arm that compared flaxseed extract capsules with placebo capsules and another unblinded arm in which flaxseed dietary powder was used. Six placebo-controlled studies compared different doses of the phytoestrogen intervention, and two other placebo-controlled studies compared different types of phytoestrogens (e.g. comparison of a soy diet with a linseed diet or flaxseed muffins with soy muffins). Three studies compared phytoestrogens with HT and placebo, and another compared phytoestrogens solely with HT without a control group.

Outcomes

Most of the trials were pilot studies that did not use power calculations. The effect of the interventions provided in the included studies on total menopausal scores derived from general menopausal symptom questionnaires (such as that of Kupperman and Greene) was not an outcome of this review, although studies were included if they measured vasomotor symptoms on a subscale of a compendium score. Most included studies assessed the effectiveness of the intervention as the primary outcome, although effectiveness was measured in different ways (number of hot flushes per day after treatment, percentage decrease in frequency of hot flushes, severity score after treatment, proportion that reported any reduction in frequency). A few studies separately reported on the frequency and severity of night sweats. Frequency of hot flushes or night sweats was generally reported by participants themselves in a daily diary. Severity was recorded usually in the scales or subscales of general menopause symptom rating scales in different categories, but a few studies required that women record severity in prespecified categories in their daily diaries. Menopause symptom scales included Menopause Symptoms Questionnaire, Menopause Rating Scale, Kupperman Index, Greene Climacteric Scale, Menopause-Specific Quality of Life Questionnaire, Women's Health Questionnaire and the modified Climacteric Symptom Evaluation Checklist. These instruments commonly used a 4-point scale from 0 (no symptoms) to 3 (severe symptoms) to categorise severity, but a few scales used a larger number of categories.

Two studies specifically assessed the safety of the intervention (as measured by effects on endometrial stimulation) as the primary outcome, and 14 others assessed these measures as secondary outcomes. A few studies also assessed the effects of the intervention on the vaginal epithelium or on pH-each of which is a surrogate outcome that is a biological indicator of oestrogenic activity. Adverse events were reported in a few trials but generally were collected as spontaneous reports. Most trials provided details of withdrawals before the study was completed, and a few indicated whether these occurred because of adverse effects or because of problems with acceptability of the intervention.

Excluded studies

Of 51 potentially eligible studies for the 2013 update, 28 were excluded because women were not symptomatic at baseline, the studies were not randomised, the duration of the study was less than 12 weeks, the interventions assessed were not included in the review, women had breast cancer, the intervention was a combination treatment, the study was a dose-finding study that did not include a control group or the interventions were not considered phytoestrogens. A further three studies, originally included in the review, were also excluded because the participants had minimal vasomotor symptoms at baseline (Dodin 2005; Duffy 2003; Woo 2003). A total of 60 studies have been excluded from the review (Characteristics of excluded studies). Five studies were considered potentially eligible in the 2013 update and are awaiting classification; a total of eight studies are now awaiting classification.

Risk of bias in included studies

Risk of bias in the included studies is summarised in chart format (Figure 2 and Figure 3). However, given that the results are mostly presented in narrative format in subgroups to reduce the variability of the intervention, the overall risk of bias of each study is also included in the 'Additional tables' summarising the results, so that the reader can judge the quality of the trial evidence for each subgroup separately.

Allocation

In all, 32 of the studies gave full descriptions of an adequate randomisation procedure and were considered at low risk of bias. The remaining 11 trials claimed that randomisation was the method of allocation, but the method was not described; these trials were considered at unclear risk of bias. Less than half of the studies (n = 19) reported methods to conceal allocation and were considered at low risk of bias; the remaining trials reported no details and were considered at unclear risk of bias.

Blinding

Nearly all of the trials reported that treatments were blind to participants, investigators and outcome assessors, but the procedures used to ensure that this occurred were not always described. In many studies, the outcome assessors were the participants, as they evaluated their own experience of hot flushes through questionnaires. In four studies, blinding was not possible because the interventions were different types of diets or because phytoestrogens were compared with calcium (although for this latter study, lack of blinding was not likely to affect measurement of the primary outcome-endometrial stimulation).

Incomplete outcome data

For 20 studies, no dropouts or withdrawals were discussed, numbers were balanced between groups or missing data were imputed; these studies were considered at low risk of bias for incomplete outcome data. Eighteen studies were considered at high risk of bias; in these studies, dropouts and withdrawals ranged from 16% to 31%. Five studies were considered at unclear risk of bias, as the percentage of dropouts ranged from 10% to 15% and/or dropouts were unbalanced between randomly assigned groups.

Selective reporting

Eighteen studies had low risk of bias, as all prespecified and potential outcomes were reported; seven had unclear risk of bias and 18 had high risk of bias because adverse events were not reported or because outcomes that had been prespecified were not reported.

Effects of interventions

Five of the included studies assessed the effects of Promensil, which is a standardised product, and their data were combined in a meta-analysis. Because of the heterogeneity of the phytoestrogen interventions provided in the other included studies (dose, composition, type), these data could not be pooled but were synthesised in narrative format and displayed in separate tables for efficacy, safety and acceptability outcomes (*see* Table 1, Table 2 and Table 3).

Dietary soy

Primary outcome: efficacy

Of the 13 included studies that used some type of substance containing dietary soy and that had efficacy analyses of any kind, seven studies indicated that no significant differences in primary efficacy outcomes were noted between the soy intervention and control groups.

Of the remaining six studies, one study assessed vasomotor symptoms specified as "somatic" symptoms on the Menopause Rating Scale. The Carmigiani study reported that both women on hormone therapy and women taking dietary soy supplementation (90 mg isoflavone) had significantly improved somatic symptoms (hot flushes and muscle/joint problems) (46% and 50%, respectively) when compared with placebo (29%) (Carmigiani 2010). This study found a significant difference in the frequency of hot flushes. The Albertazzi study of 104 women compared soy powder containing 76 mg/d of isoflavones with casein powder over 12 weeks (Albertazzi 1998). Investigators reported a mean reduction of 1.6 flushes per day (95% CI -1.95 to -1.2) for participants consuming soy powder compared with placebo. This was also expressed as a 45% reduction in the number of hot flushes with soy

powder compared with a 30% reduction with placebo powder. Two studies found that severity or intensity of hot flushes was significantly reduced by the intervention. Brezinski compared a phytoestrogen-enriched diet that was individualised for each participant by a dietician (exceeding the cutoff point of > 30 mg/d of isoflavones) versus a regular diet that avoided phytoestrogen-containing foods consumed by a control group (Brzezinski 1997). Hot flushes (rated in a menopause symptoms questionnaire) were reduced in severity in both arms of the study but to a significantly greater extent in the phytoestrogen diet group. This study was one of the few that was not blinded, and knowledge of treatment could have affected participants' assessments. In the Radhakrishnan study, a significantly higher proportion of women (84%) reported improvement in hot flush symptoms (severity) with soy protein when compared with placebo (60%), but no evidence was found of a significant difference in the hot flush score (mean hot flushes per day) after six months (Radhakrishnan 2009). Two studies reported other significant differences, but it is unclear whether the scores represented frequency or severity or a combination of the two. The Cheng study reported that women taking 60 mg isoflavones daily had a significantly lower hot flush score (57%) than those taking placebo, but details on what the score represented are not clear (both number of daily hot flushes and intensity were recorded) (Cheng 2007). The Hanachi study reported that soy milk significantly reduced hot flushes by 72% compared with control after three months, but no details were given of the actual values for each group (Hanachi 2008).

Secondary outcomes: safety

Of the six studies that assessed adverse events, five were negative (no significant differences between randomised groups) and one was positive. The positive study (Knight 2001) found that 75% of participants in the soy group had adverse events compared with 17% of the placebo group. Side effects included bloating, nausea, weight gain and concerns about bowel function.

In all three studies that assessed the effects of phytoestrogens on the endometrium, no evidence of a significant difference between groups was found.

Of four studies that assessed the effects of a soy diet on the vaginal maturation index, three found no evidence of a significant difference between phytoestogen and control groups, but one study reported that this index increased by 103% from baseline with a soy diet compared with a 6% increase with linseed and an 11% increase with placebo (Dalais 1998).

Secondary outcomes: acceptability

Of the four studies that assessed the acceptability of the phytoestrogen intervention compared with control, one study reported a difference in the rate of withdrawal due to adverse events (Knight 2001) (P value not reported). This small study reported that 25% of participants who consumed a beverage containing soy powder withdrew from the study because of dislike of the taste compared with 8% in the placebo group.

Sensitivity analyses

Dietary food supplements varied enormously in the type of product used in the trials, the formulation and the isoflavone content (42 mg/d to 134 mg/d). Sensitivity analysis was undertaken to attempt to explain differences in efficacy outcomes between the six positive studies and the seven negative studies. In particular, the difference between positive and negative trials was not explained by the level of isoflavones in the food product. Variability in trial results could have been caused by other factors for which no controls could be applied. Intestinal florae convert soy isoflavone to equol-a more potent oestrogenic isoflavone that is absorbed along with unconverted genistein and daidzein; this conversion is variable (Adlercreutz 1990) and may have influenced the heterogeneity of the results. The severity of hot flushes at baseline could also explain the differences. In the six positive studies, severity of hot flushes among participants was variable; two trials required that women have at least five or eight moderate to severe flushes per day, but in the other trials, hot flushes were mild or were unspecified.

Quality of the trials in this subgroup was variable; only one positive trial had low risk of bias. Of the six trials with positive findings, two trials had very high dropout rates (24% and 21%) and two trials were unblinded and were thus considered at high risk of bias.

Soy extracts

Primary outcome: efficacy

Of the 12 studies that compared various types of soy extract in capsule or tablet form (11 vs placebo and one vs HT), nine studies (all vs placebo) reported significant differences in efficacy outcomes (frequency or severity). Five trials (Bicca 2004; Faure 2002; Khaodhiar 2008; Nahas 2007; Ye 2012) reported a reduction in the frequency of flushes (one also found a reduction in the frequency of night sweats); four trials found a reduction in severity of flushes as measured by the Kupperman vasomotor symptom score (Han 2002; Jou 2008; Nahas 2007) or by a subjective rating by participants on a scale of 1 to 3 (Upmalis 2000). This latter trial reported that severity of night sweats did not differ at the end of the study according to group. Not all of the positive studies described benefit from soy extracts; one trial found that women were significantly MORE likely to have hot flushes after isoflavone treatment (48.4%) than after placebo (31.7%), although this was a secondary outcome in the trial (Levis 2011). The trial that compared soy extract with oestrogen therapy (ET; Kaari 2006) reported no differences between them in the percentage of participants reporting

any reduction in hot flushes (at six months, P = 0.74; Student's *t* test).

Secondary outcomes: safety

Of the eight studies that assessed safety outcomes, one assessed effects on endometrial stimulation, four on vaginal pH, five on endometrial thickness, six on vaginal maturation index and six on adverse events. The trial that compared soy extract with ET (unopposed oestrogen therapy) (Kaari 2006) reported significant improvement in vaginal pH and maturation index in the ET group. The soy extract group had a significantly thinner endometrium, less endometrial stimulation and fewer adverse events (all of which were genital bleeding in the ET group). One of the three other trials that compared soy extract with placebo found significantly greater improvement in vaginal pH in the soy group (Bicca 2004). One of the six studies that assessed adverse events reported that women taking soy extracts had a significant increase in rate of constipation and in fractures compared with women taking placebo (although this latter outcome was not considered to be related to treatment) (Levis 2011). For all other studies, no evidence was found of differences in endometrial thickness, vaginal maturation index or incidence of adverse events.

Secondary outcomes: acceptability

Two studies assessed the acceptability of the interventions as measured by withdrawal due to adverse events; no evidence of a difference between groups was found.

Sensitivity analyses

Sensitivity analyses exploring the effects of quality issues, levels of isoflavones in the active arm (ranging from 33 mg/d to 200 mg/d) or severity of flushes at baseline did not explain the differences in results. The five placebo-controlled trials that found a difference in flush frequency (Bicca 2004; Faure 2002; Khaodhiar 2008; Nahas 2007; Ye 2012) out of the nine that measured this outcome reported reduction ranging from 50% to 74% with soy extract compared with reduction ranging from 21% to 43% with placebo. In contradiction to these findings, one trial actually reported a greater proportion of hot flushes after treatment with soy extracts versus placebo. Six trials had a longer duration than the more usual 12 weeks, ranging from 16 weeks to two years. The trial that compared soy extract versus ET (Kaari 2006) found no difference in the percentage of participants reporting a reduction in hot flush frequency, but participants had only mild symptoms at baseline (55% and 72% had hot flushes at baseline in the soy and ET groups, respectively). Although no placebo group was included in the study, the authors concluded that their results suggest that the soy isoflavone extract at 120 mg/d was effective in relieving the frequency of hot flushes; however, the trial was considered at high risk of bias.

Severity scores were significantly different in four of the seven trials that measured this outcome; three trials used the Kupperman vasomotor scale (rating severity from 0 to 3; Han 2002; Jou 2005; Nahas 2004), and the other used a simple severity scale (with scores of 1 to 3 representing mild, moderate and severe symptoms) scored daily by participants (Upmalis 2000). Variability in the results of included trials was not explained by sensitivity analyses of quality and other aspects of the studies.

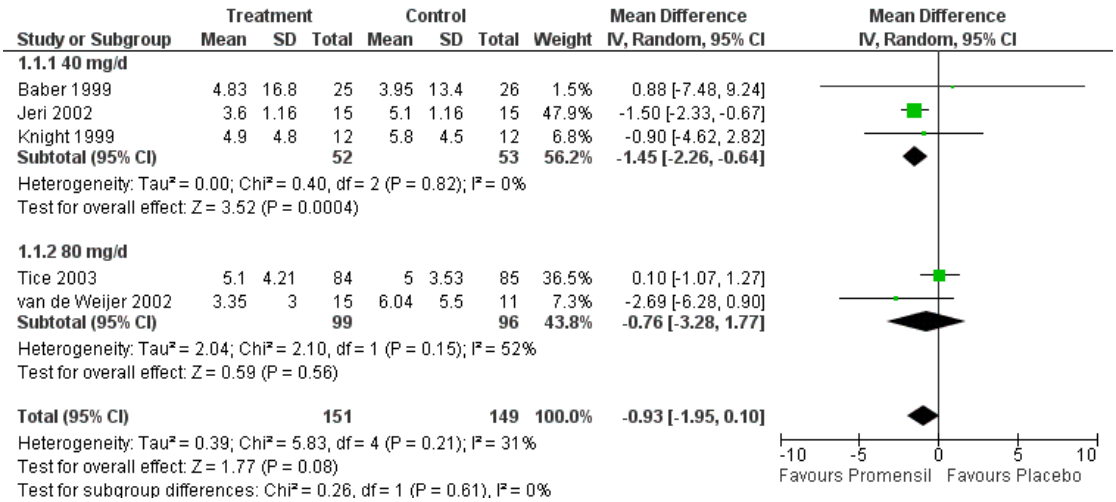
Red clover extracts

Nine trials assessed the effects of red clover extracts on outcomes. Five of these used Promensil, and data from these trials were included in meta-analyses. The other trials used MF11RCE (80-mg isoflavones), a red clover supplement with 40 mg isoflavones or a red clover extract with 120 mg isoflavones. We used data from the first phase of the Baber and Imhof cross-over trials.

Primary outcome: efficacy

Promensil: Five studies reported on the incidence of daily hot flushes after treatment with two different doses of Promensil (40 mg/d and 80 mg/d) (Baber 1999; Jeri 2002; Knight 1999; Tice 2003; van de Weijer 2002). No significant differences were reported between groups in the overall incidence of hot flushes (MD -0.93, 95% CI -1.95 to 0.10, I^2 = 31%; Figure 4). Although subgroup analysis suggested benefit for a dose of 40 mg daily of Promensil, this finding should be viewed with caution, as two of the three trials had substantial risk of bias. One moderately sized trial of good quality and one small trial at high risk of bias assessed the percentage reduction in the number of hot flushes from baseline, resulting in a very imprecise pooled estimate (MD 20.15, 95% CI -12.08 to 52.38, I^2 = 82%; Jeri 2002; Tice 2003; Analysis 1.2). A small trial (Jeri 2002) reported that a significantly greater proportion of women described hot flush severity ranging from moderate to severe to none or light in the Promensil group (RR 17.06, 95% CI 1.1 to 264.5; Analysis 1.3). One trial found no difference in the change in vasomotor score from baseline to end of study (MD 0.02, 95% CI -0.29 to 0.32; Tice 2003; Analysis 1.4).

Figure 4. Forest plot of comparison: 1 Promensil versus placebo, outcome: 1.1 Incidence of hot flushes (number/d).



Other red clover extracts (not included in the meta-analyses): One trial using a dose of 80 mg of red clover (Imhof 2006) found significant benefit for daily frequency of hot flushes and night sweats and for the mean percentage of decrease in these symptoms (P = 0.0001). Another study that assessed an unspecified red clover extract (same dose) reported benefits for hot flush and night sweat severity (as assessed by the Kupperman Index; Hidalgo 2005). After treatment, 15% of women taking 80 mg of red clover reported hot flushes compared with 98.1% of women taking placebo; values for night sweats were 30.2% and 92.5% for red clover and placebo, respectively (P < 0.05). The authors claimed that these values represented severity "as expressed as a percentage," but it is not clear what they meant. The other two studies assessing the efficacy of red clover (Del Giorno 2010; Geller 2009) found no difference between groups when treatment was given for 12 months.

Secondary outcomes: safety

Results are reported separately for Promensil and other red clover extracts.

One large trial of Promensil versus placebo assessed adverse events (Tice 2003). It reported no differences in the proportions of women who experienced any adverse event (RR 0.95, 95% CI 0.65 to 1.40). Also, no differences were found between groups in rates of specific adverse events, such as respiratory tract infection, headache, myalgia, nausea, arthralgia, diarrhoea and vaginal spotting. Two other studies (not included in the meta-analysis) also did not find differences between groups with respect to adverse events.

Three trials assessed the effects of treatment on endometrial thickness (Baber 1999; Geller 2009; Imhof 2006). One trial (included in the meta-analysis) found no difference in endometrial thickness after 12 weeks of treatment with Promensil. The other two trials reported different findings: One reported a significant decrease of 15% in endometrial thickness in women treated with red clover compared with zero change in women treated with placebo (SD of change not given, P < 0.001; Imhof 2006), and the other found no evidence of a significant difference between groups (Geller 2009). One study that assessed an unspecified red clover extract reported significant changes in all vaginal cytology indexes (karyopyknotic index, cornification index, maturation index) when compared with placebo (P < 0.05) (Hidalgo 2005).

Secondary outcomes: acceptability

No trials assessed the acceptability of treatment.

Sensitivity analyses

Variability in study results appeared to be explained in part by trial quality. One small Peruvian study (n = 30) of poor quality (Jeri 2002) reported highly significant effects for both frequency and severity but gave no details on randomisation method, allocation concealment or baseline comparability. Inclusion of this study in the meta-analyses, combined with findings of other, larger trials of better quality, caused highly significant heterogeneity, and a random-effects model was chosen for presentation of results. Exclusion of this small trial of poor quality from the meta-analyses reduced heterogeneity and the summary effect estimate, suggesting that benefit derived from a dose of 40 mg of Promensil

per day was no longer significant. Another study (van de Weijer 2002) reported a significant benefit of Promensil (at a dose of two tablets per day) but did not provide an indication of the variability around the estimate so could not be included in the meta-analysis. A large trial of good quality (n = 252) (Tice 2003) that compared two types of red clover extract-Promensil (two tablets per day) and Rimostil-versus placebo reported no significant change in the frequency of hot flushes between groups and no significant difference in the change in vasomotor score over the period of the study. One of these studies also compared a higher dose of Promensil (160 mg/d) with placebo, but substitution of these values in the meta-analysis did not alter the results.

Four studies compared other types of red clover extract (Del Giorno 2010; Geller 2009; Hidalgo 2005; Imhof 2006), but findings were inconclusive regarding efficacy. Two of these studies found benefit for 80 mg of red clover, but two others reported no evidence of significant differences associated with a dose of 40 mg or 120 mg of red clover at the end of 12 months of treatment. Variation in the findings was explained to some extent by differing quality of the trials. Results from larger studies of better quality appeared to conflict with those from smaller studies of poorer quality.

Genistein

Five studies assessed the effects of predominantly genistein extracts on outcomes (Crisafulli 2004; D'Anna 2007; Evans 2011; Ferrari 2009; Sammartino 2003). Genistein doses ranged from 30 mg to 60 mg per day. Duration of treatment with genistein ranged from 12 weeks to two years.

Primary outcome: efficacy

All four studies assessing primary efficacy-two with unclear risk of bias and two with low risk of bias-reported that genistein significantly improved the frequency of hot flushes when compared with placebo (Crisafulli 2004; D'Anna 2007; Evans 2011; Ferrari 2009). One study also found that the duration of hot flushes was reduced compared with placebo (although this is not an outcome of this review). The Crisafulli study also compared genistein with continuous hormone therapy; it reported a 24% mean reduction in daily hot flushes with genistein compared with placebo ($P < 0.05$) and a 30% reduction in daily hot flushes with HT compared with genistein ($P < 0.05$). The other three studies reported a mean percentage reduction in daily hot flushes from baseline ranging from 41% to 61% with genistein in comparison with a mean reduction ranging from 7% to 29% with placebo. Two studies of 12 weeks' duration found no evidence that the severity or intensity of hot flushes differed between genistein and placebo groups (Evans 2011; Ferrari 2009), but a study of longer duration reported that hot flush severity declined significantly when compared with placebo over two years (D'Anna 2007).

Secondary outcomes: safety

Four studies did not find a significant difference between groups in endometrial thickness after genistein treatment, and one study found no evidence of a significant difference in the vaginal maturation value.

Two studies found no evidence of a significant difference in adverse events between randomly assigned groups. In one study, most of these adverse events were gastrointestinal. No severe adverse events were experienced by participants.

Secondary outcomes: acceptability

The proportion of participants who were satisfied with treatment was similar in both groups in one study (79% with genistein compared with 69% with placebo; Heger 2006).

Sensitivity analyses

The four studies had low or unclear risk of bias. All studies evaluating efficacy consistently reported significant reductions in the frequency of hot flushes at the end of treatment ranging from 12 weeks to two years. Individual trial characteristics were generally fairly similar. Doses of genistein ranged from 56 mg to 60 mg of genistein per day, with one trial using a 30-mg dose. Women generally had at least four hot flushes per day, and two studies reported average numbers of eight and nine hot flushes per day. Reductions in the number of hot flushes with genistein ranged from 24% to 56% against placebo. Placebo response, when reported, was variable; the two-year study reported a reduction from baseline of 7.2%, but two shorter studies of 12 weeks' duration reported reductions of 27% and 29%. Results of the effects of genistein on the severity of hot flushes were more mixed and could not be explained by trial characteristics or quality.

Other phytoestrogens

Three studies compared flaxseed dietary supplement or flaxseed extract versus placebo or control (Colli 2012; Dalais 1998; Lewis 2006); one compared two strengths of hop extract with placebo (Heyerick 2006), one compared a natural supplement containing S-(-)equol, a daidzein metabolite, with placebo in women who were equol nonproducers (Aso 2012) and one compared an extract of *Rheum rhaponticum* (ERr 731) with placebo in perimenopausal women (Heger 2006). Duration of treatment was 12 weeks in most of the studies, but one trial had a duration of 16 weeks and another had a duration of 24 weeks.

Primary outcome: efficacy

All six trials assessed efficacy outcomes. Two trials found no evidence of a difference between groups in frequency or intensity of

hot flushes after flaxseed treatment (Dalais 1998; Lewis 2006), and both Lewis and Colli did not find evidence of a time by interaction effect of hot flush severity or intensity between groups. The study evaluating hop extracts did not find evidence of a significant difference in the Kupperman Index hot flush severity score, although a non-significant trend favoured both hop extract doses (Heyerick 2006). The study comparing S-Equol with placebo found that S-Equol was associated with a significantly larger decrease in hot flush frequency from baseline (62.8%) compared with placebo (23.6%) in women with three or more hot flushes per day and a significant improvement in hot flush severity with S-Equol (61%) compared with placebo (45%) (Aso 2012). Results of the trial were assessed in postmenopausal women with at least one hot flush per day and low rates of equol excretion, as this was considered to reduce the possibility of confounding by background isoflavone intake. Another trial investigating the effects of an extract from the roots of *Rheum rhaponticum* (ERr 731) in perimenopausal women in the Ukraine reported that both the frequency and the severity of moderate to severe hot flushes and sweats (Menopause Rating Scale II and Menoqol vasomotor score) were significantly reduced with ERr 731 compared with placebo (mean decrease of 2.5 points compared with mean decrease of 1.2 points) at week 12 (Heger 2006). Effects were assessed blindly by both participants and investigators.

Secondary outcomes: safety

Three trials assessed endometrial thickness after six months or one year and reported no significant difference between groups (Colli 2012; Crisafulli 2004; Heger 2006). Also no evidence of a change in vaginal maturation index was noted with flaxseed compared with placebo or control (Colli 2012; Dalais 1998). In one trial, women ingesting flaxseed meal withdrew from treatment in greater numbers than those taking flaxseed extract or placebo because of gastrointestinal complaints (Colli 2012), but these differences were not tested statistically.

Secondary outcomes: acceptability

One trial (Heger 2006) reported that 63% of women taking ERr 731 were satisfied with their treatment compared with 32% of women taking placebo (no P value reported).

Sensitivity analyses

Studies using similar interventions in this subgroup were too few for sensitivity analyses to be undertaken.

DISCUSSION

Summary of main results

This review has assessed the effectiveness, safety and acceptability of foods, supplements or extracts containing phytoestrogens when compared with placebo, no treatment and HT in randomised studies completed by the end of July 2013. It has been able to pool only the studies that used Promensil in meta-analyses because of the heterogeneity of the other phytoestrogen interventions.

Primary outcome: efficacy

Dietary soy

Of the 13 included studies that used some type of substance containing dietary soy and had efficacy analyses of any kind, seven studies indicated that no significant differences were seen between the soy intervention group and the control group in terms of primary efficacy outcomes. In studies that reported significant findings, interventions included phytoestrogen-enriched diets, soy milk, fruit drinks with isoflavones and soy powders. Only one trial had low risk of bias, and participants varied in the severity of their flushes at baseline. Sensitivity analyses could not explain the variable results. Thus, the findings from these trials must be considered only tentative, as variability and significant bias influencing the findings cannot be excluded.

Overall, no evidence suggested that a diet with high levels of soy phytoestrogens had a positive effect on hot flush frequency or severity.

Soy extracts

Of the 11 trials that compared soy extracts with placebo, nine had some positive results and two were negative. Five of nine studies found significant improvement in hot flush frequency with soy extract, but one found that soy extract was associated with more hot flushes than were seen with placebo. Four of seven studies found that hot flush severity was significantly reduced with soy extract, but most of these studies were at high risk of bias. One other study at high risk of bias found no difference in the effect of soy extract or hormone therapy on hot flush symptoms (as measured by the Kupperman Index).

Given the variability in the interventions, the severity of hot flushes at baseline and the potential for risk of bias, no overall conclusive evidence showed that soy extracts had a positive effect on hot flush frequency or severity.

Red clover extracts

Five studies assessed the effects of Promensil, and four studies assessed the effects of other red clover extracts. Findings were inconclusive and could largely be explained by risk of bias. The two

larger studies at low risk of bias found no evidence of benefit with red clover extracts.
Overall, no evidence suggested that red clover extracts had a positive effect on hot flush frequency or severity.

Genistein

All four studies found consistent benefit for hot flush frequency with doses of genistein ranging from 30 to 60 mg per day in women with moderate to severe hot flushes, although benefits for hot flush severity were more mixed. Although benefits were found with genistein, they were significantly less than those associated with continuous hormone therapy in one study. These positive findings should be considered tentative as, in two of the four studies, effects on hot flushes were secondary outcomes, and in one study, measurements were made in a subgroup from the total study population, which may have introduced bias (Schulz 2005).
Overall, genistein extracts appeared to significantly reduce the numbers of hot flushes experienced by symptomatic postmenopausal women but to a lesser extent than hormone therapy.

Other phytoestrogens

Among six trials that assessed the effects of other types of phytoestrogens, no evidence of an efficacy difference was noted between flaxseed or linseed diets or extracts and placebo or control in three trials (two of which also contained soy diet arms) or in one trial that assessed a phytoestrogen preparation derived from hops in two different doses in women who had two to five daily flushes. In one trial, ERr 731 was associated with a significant reduction in hot flush and sweating severity symptoms (Menopause Rating Scale II) and in Menoqol vasomotor score compared with placebo. Another trial reported that hot flush frequency and severity were significantly reduced with the S-Equol supplement (a daidzein metabolite) when compared with placebo.
Overall, although benefits were reported from single trials investigating a phytoestrogen extract from the rhubarb plant (ERr 731) and an equol supplement (SE5-OH), data were insufficient to permit determination of whether any other type of phytoestrogen product had significant effects on vasomotor symptoms.

Secondary outcomes

Safety

Data on oestrogenic effects on the endometrium and the vagina and rates of adverse effects were collected in only a few trials and were considered together rather than in subgroups.

Endometrial outcomes

Phytoestrogen products do not appear to have an oestrogen agonistic effect on the endometrium when given for up to one year, in contrast to hormone replacement therapy. No evidence was derived from two studies in the review to suggest that phytoestrogens promote a proliferative endometrium (Balk 2002; Kaari 2006). Most studies reported no difference in endometrial thickness between phytoestrogens and placebo. One study actually found a significant reduction in endometrial thickness from baseline (Imhof 2006). The lack of an oestrogenic effect on the endometrium was further supported by a study comparing phytoestrogens with HT; endometrial thickness significantly changed from baseline with HT, but no change was seen with phytoestrogens (Kaari 2006).

Vaginal outcomes

Evidence of the effects of phytoestrogens on the vaginal maturation index and on pH is mixed. Five placebo-controlled trials found no evidence of a stimulatory effect, but two other studies described a positive oestrogenic effect of increasing cellular mitotic activity, as evidenced by improvement in maturation indices-one with a soy diet versus a wheat diet and the other with a red clover extract (Dalais 1998; Hidalgo 2005). In two studies with a hormone therapy comparator, vaginal cytology values with HT were significantly different from those obtained with soy (Carmigiani 2010; Kaari 2006). Other studies not included in this review, wherein participants were asymptomatic or had breast cancer, have also produced conflicting data. Three studies found evidence of improvement in maturation values (Baird 1995; Chiechi 2003; Uesugi 2004), but three others have not confirmed these results (Duncan 1999; Manonai 2006; Nikander 2005). Characteristics of the individual trials provided no clues that could explain these mixed results. Similarly, one unpublished study described improvement in vaginal pH with a soy extract when compared with placebo (Bicca 2004), and another, much larger study did not find evidence of a difference (Upmalis 2000). In the study that compared soy extract versus HT, vaginal pH improved significantly more with HT than with soy (Kaari 2006). It is hoped that a Cochrane systematic review will be prepared to specifically assess the effects of phytoestrogens on urogenital menopausal symptoms to provide further clarification.

Adverse events

Only three of 17 trials found a significant difference in adverse event rates (Colli 2012; Knight 2001; Levis 2011). The phytoestrogen supplement in the first small trial was give in the form of a powder, and the authors included data on the dislike of the taste of soy powder in the total incidence of adverse events. In this case, the adverse event rate was linked to the type of product used in the soy diet and was more appropriate as a measure of acceptability. Data on the total incidence of adverse effects, with dislike of taste

excluded, were not available. The Levis trial, which investigated the effects of soy on bone loss and on vasomotor symptoms, reported that fracture rates were significantly higher in the group of women consuming soy, but this is likely to be a chance event, as all fractures were associated with a traumatic event rather than with osteoporosis. Women ingesting flaxseed meal as a dietary supplement in another trial were more likely to withdraw from treatment because of gastrointestinal complaints when compared with those given flaxseed extract or placebo (Colli 2012). In a trial that compared soy extract with combined HT (Kaari 2006), women in the latter arm were more likely to experience genital bleeding, which is a common symptom of HT in perimenopausal women. This symptom was not experienced by women who took phytoestrogen supplements. Adverse events were most often collected incidentally during the trials.

Acceptability

Few trials specifically assessed this outcome in spite of the high dropout rate in many of the studies. No evidence was found of a difference in acceptability of any of the phytoestrogen products used when compared with placebo, except for one trial; 63% of those taking ERr 731 were satisfied with their treatment compared with 38% taking placebo.

Summary

In summary, generally no conclusive evidence showed a benefit of phytoestrogen-enriched or -derived products for menopausal vasomotor symptoms, with the exception of products containing a minimum of 30 mg per day of genistein, which have been evaluated for up to two years in four studies. Also, no evidence indicated that products derived from phytoestrogens were associated with stimulation of the endometrium and/or vagina of women with vasomotor symptoms. No evidence suggested an increase in adverse events, and limited data suggest that phytoestrogen supplements were well tolerated.

Overall completeness and applicability of evidence

The review included 43 studies, but variation in components and duration of the intervention and in types of participants and severity of their hot flushes, as well as potential variation in metabolism and absorption among individuals and a high placebo response rate, generally resulted in inconclusive findings. Although some trials reported a significant beneficial effect of phytoestrogen treatment on symptoms, strong evidence was found of a placebo effect, with improvements in frequency ranging from -1% to -59%-similar to the placebo effect found in the Cochrane review of hormone replacement for vasomotor symptoms (MacLennan 1999). When some of the included studies reported significant differences between groups, it was not possible to tease out which of the many variables that differed between included studies might have explained the results.

Studies varied according to the total amount or 'dose' of isoflavone given in the active treatment arm. The rationale for a role for isoflavones is supported by epidemiological evidence from a community-based study, which found that the incidence of hot flushes was inversely related to the quantity of soy foods consumed and the daily intake of isoflavones (Nagata 2001). Studies of Japanese women claim a typical daily consumption of 20 to 54 mg of isoflavones (Nagata 2001; Somekawa 2001). Most of the studies in this review provided treatments with at least 50 mg per day of isoflavones; some used more than 100 mg of isoflavones per day. Examination of the pattern of results within each subgroup did not indicate that trials were more likely to be positive if they used higher doses of isoflavones. Comparison of total isoflavone levels in treatments may not be useful, as the isoflavone profiles of different supplements and extracts differ considerably. Broad groupings in this review into 'types' of phytoestrogens provided no clues as to the best way that phytoestrogens can be delivered for therapeutic effect.

In addition to the heterogeneity of interventions used in the included studies, good evidence of variability was noted in the metabolism and absorption of isoflavones by individuals, which can lead to variations in serum concentrations of parent isoflavones and their metabolites (Rowland 2003; Wiseman 2004). It has been claimed that only 20% to 30% of the general population in the United States possess gut microflorae that convert the isoflavone daidzein to the more oestrogenic dihydroxy isoflavan equol (Setchell 2002) in comparison with 50% to 60% of Asians (NAMS 2011). It has been suggested that 'equol producers' make up a distinct subpopulation that may be associated with the greatest benefit from soy isoflavones for relief of hot flushes, and they may explain anecdotal reports by many women of phytoestrogen effectiveness in relieving hot flushes. The studies included in this review generally did not control or stratify for this added potential source of variation in response to treatment with phytoestrogens, although investigators in one trial stated that isoflavone supplementation improved symptoms only in women with the ability to produce equol. Another recent trial found a significant benefit associated with use of a supplement of S-(-)equol in equol-nonproducing postmenopausal Japanese women. Further research should consider the role of equol production.

In spite of variation in doses, duration and components of phytoestrogen products, extracts containing at least 30 mg of genistein, a type of isoflavone, appeared to reduce both frequency and severity of hot flushes in women, but less so than hormone therapy. A possible rationale is the suggestion that genistein is the most potent isoflavone with regard to receptor binding and transactivation (Muthyala 2004). No evidence of safety concerns in the short term was found. Further research is needed to confirm the efficacy

of high doses of genistein in menopausal women.

Quality of the evidence

The quality of the trials was variable. Although most studies blinded both participants and assessors, less than half reported adequate allocation concealment to protect against selection bias, and high rates of attrition and potential selective outcome reporting in half of the trials suggest that they were at high risk of attrition and reporting bias. Substantial variation in the included studies precluded combining findings in forest plots, and this has limited any definitive conclusions.

Four trials have suggested benefit for the reduction of hot flush frequency and severity from high doses of genistein, but these findings should be considered tentative because of methodological shortcomings in some of the trials. The effect of genistein on menopausal vasomotor symptoms requires verification.

Potential biases in the review process

This review has the following limitations. Because we were unable to pool most of the studies and in many cases had no access to the original data, we accepted the statistical methods used in each study and reported study results in tabular form. Many studies did not use an appropriate statistical method to measure changes in frequency or severity over time; endpoint analysis may have obscured different patterns of response. Some trials used unvalidated menopausal symptom questionnaires to assess severity, and not all scales were similar. For example, the Greene Vasomotor Scale includes hot flushes and night sweats, whereas the vasomotor scale used by Kotospoulos includes hot flushes, lightheadedness and headache.

A second weakness of the review is the potential for publication bias. The search for relevant studies was very comprehensive, and attempts were made to access the grey literature. However, several of the studies waiting assessment are positive studies in abstract form, and their inclusion may paint a different picture. Publication bias usually operates in a differential manner, leading to a higher probability of publication of studies that indicate positive results. Also, some potential for bias may be associated with the need for the review authors to determine which interventions would be considered as phytoestrogens, given the wide variety of sources and doses of phytoestrogenic compounds.

Agreements and disagreements with other studies or reviews

One review has suggested that phytoestrogen products might be more effective in women with more severe flushes at baseline (Huntley 2004). This hypothesis has been supported by another study, which proposed that the effectiveness of phytoestrogens for hot flush relief is seen only in those with five or more hot flushes per day (Messina 2003). Another systematic review and meta-analysis (Howes 2006) also came to the conclusion that women more severely affected by vasomotor symptoms derived a small benefit from isoflavone supplementation and suggested a cut point of around four flushes per day. However, the authors of that review pooled highly variable studies, causing significant statistical heterogeneity, which affects the credibility of effect estimates. These suggestions have not been confirmed by the sensitivity analyses performed in this review, which compared the overall pattern of results with studies that required women to have at least five hot flushes per day. In addition, the North American Menopause Society (NAMS) position paper on isoflavones, which used strict criteria for evaluation of isoflavones, concluded that no linear dose-response relationship was observed (NAMS 2011), and a recent systematic review (Taku 2012) concluded that the effect of baseline frequency of hot flushes is unclear. When included trials show huge variation in characteristics of participants, types of intervention and outcomes measured, it is important to consider the quality of the trials. One of the largest trials (Tice 2003) was a study of good quality with high compliance, a low dropout rate and good generalisability (including a broad cross section of the population). It required that women have at least 35 hot flushes per week to participate, and investigators found no evidence of benefit for Promensil or Rimostil.

The efficacy findings of this review are broadly in accord with those of most systematic reviews assessing the effects of phytoestrogens on menopausal symptoms published over the past decade (Bolanos 2010; Coon 2007; Geller 2005; Glazier 2001; Haimov-Kochman 2005; Howes 2006; Huntley 2004; Jacobs 2009; Krebs 2004; Low Dog 2005; Nedrow 2006; Villaseca 2012; Williamson-H 2006), and this review has included several more recently published studies. In general, most reviews have concluded that phytoestrogen supplementation has no effect or a very mild effect on vasomotor symptoms. However, NAMS, using strict criteria for selection of relevant trials, concluded that soy-based isoflavones are modestly effective in relieving menopausal symptoms, and that their use in women with distressing symptoms is 'reasonable' (NAMS 2011). A recent systematic review reported that soy isoflavone supplements derived by extraction or chemical synthesis were significantly more effective than placebo in reducing the frequency and severity of hot flushes (Taku 2012). This review included trials with a shorter duration of treatment (six weeks) and women with previous breast cancer; these types of studies were excluded from this review. The Taku review authors also acknowledged substantial heterogeneity in their findings and have noted that further research is warranted to clarify the influence of additional factors, such as dose, isoflavone form, baseline hot flush frequency and duration of treatment.

The Taku review has also confirmed the findings of Williamson-H 2006, which focused specifically on soy isoflavone extracts and stratified studies according to the amount of genistein included in

the extract. Findings of this review suggest that supplements that provide at least 15 mg of genistein per day are effective, whereas those providing less genistein are not, and this hypothesis has been supported by the findings of this review. However, this hypothesis has not been supported by the longitudinal Study of Women's Health Across the Nation, which assessed the association between vasomotor symptoms and ethnicity during the menopausal transition in 3,198 women (Gold 2006). Investigators in this study reported that genistein intake in their sample was not related to vasomotor symptoms, and that it did not account for the reduced symptom reporting that they found among Asian women after adjusting for covariates. This hypothesis needs to be further investigated in randomised trials for inclusion in future updates of this review.

The safety of phytoestrogen products has been investigated in another systematic review and assessed in separate subgroups: gynecological or urinary, gastrointestinal, musculoskeletal, neurological or sensory and nonspecific (Tempfer 2009). The review authors concluded that phytoestrogen supplements had a safe side effect profile, along with moderately elevated rates of gastrointestinal side effects. Use of phytoestrogens was not associated with increased risk of endometrial or breast cancer. Most studies in the review were of limited duration. These findings support the conclusion of this review that phytoestrogen-enriched products appear to be safe when used for up to two years. A study of women without hot flushes at baseline (not eligible for inclusion in this review) (Unfer 2004) reported that long-term treatment (up to five years) with soy (150 mg/d isoflavones) was associated with increased occurrence of simple endometrial hyperplasia compared with placebo. This finding has not been confirmed by other studies, but the long-term endometrial safety of high doses of phytoestrogen supplements has not been fully established.

AUTHORS' CONCLUSIONS

Implications for practice

No conclusive evidence shows that phytoestrogen supplements effectively reduce the frequency or severity of hot flushes and night sweats in perimenopausal or postmenopausal women, although benefits reported with concentrates of genistein may be beneficial and should be further investigated. Many of the included studies were of poor quality, and results were inconsistent, providing no guidance on which type of product is likely to be more beneficial. Women need to be reassured that these symptoms usually abate over time. When therapy is desired or required, the use of unspecified phytoestrogen supplements is not based on good quality evidence of benefit, although it is possible that high doses of genistein may offer relief. No evidence shows harmful side effects in the short term resulting from the use of these supplements.

Implications for research

More research is required to test the following hypotheses.

- Supplements containing at least 15 mg of genistein are more effective than supplements containing less than 15 mg of genistein.
- Phytoestrogen supplements are more effective in women with more than five moderate to severe hot flushes per day than in those with mild symptoms.
- Phytoestrogen supplements are more effective in women who are equol producers.

In addition, to enhance comparability, future trials should be based on phytoestrogen products that are well characterised; they should provide strict monitoring of participants throughout the trial, should be well powered and of adequate duration and should use validated measurements of outcome.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Albertazzi 1998

Methods	Design: parallel-group Number randomly assigned: 92 initially plus a further 12 from the reserve randomisation list = 104 Number dropped out: 21 (nine in active group: seven for gastrointestinal symptoms, one for lack of efficacy, one for non-compliance; seven in placebo group: two for gastrointestinal symptoms, three for lack of efficacy, one for non-compliance, one for other reasons) Number lost to follow-up: four (two in each group) Number analysed: 79 Intention-to-treat analysis: no Power calculation: 90% power to detect a difference of three hot flushes per 24 hours (P = 0.05) Duration: 12 weeks Timing: not stated Location: two Italian university hospitals Funding: partial industry funding from Protein Technologies, Missouri
Participants	Inclusion criteria: postmenopausal women requesting treatment for severe hot flushes, six months since last menstruation or six weeks since bilateral oophorectomy, minimum of seven moderate to severe hot flushes or night sweats per 24 hours during two out of four weeks before the study (threshold defined as warmth and sweating preventing normal daily activity), baseline FSH > 50 IU/mL, serum oestradiol < 35 pg/mL Exclusion criteria: use of HT within six weeks of study or other drug used for climacteric symptoms during study period Age, years: active arm 53 (48 to 61), placebo 52 (45 to 62) Recruitment: not stated

Interventions	• Phytoestrogen: Isolated soy protein
	  ○ Formulation: 76 mg isoflavones (genistein 40 mg, daidzein 28 mg) per 60 mag sachet of powder
	• Placebo: 60 g casein powder
	  ○ Dose, duration and timing of administration: one sachet per day for 12 weeks

Outcomes	Menopausal symptoms: change in number of daily moderate and severe hot flushes or night sweats from baseline in each month of treatment; Kupperman Index Compliance: self-report in daily diary and sachet count Adverse effects: reported monthly at follow-up; for each woman, only the worst symptom (in her opinion) was taken into account
Notes	

Risk of bias

Albertazzi 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Investigator site personnel blinded to trial codes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate-12 participants added
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Aso 2012

Methods	Design: parallel-group Number screened for inclusion: 1,211 Number randomly assigned: 160 Number dropped out or withdrew: 34 (placebo group: three dropped out, eight did not comply, 12 met withdrawal criteria; equol group: eight did not comply, three met withdrawal criteria) Intention-to-treat analysis: no Power calculation: not stated Duration: 12 weeks of intervention or placebo, assessments at week 12 and week 18 Location: four clinics/centres in Tokyo, Saitama, Chiba, Fukuoka Funding: Otsuka Pharmaceutical Company Ltd provided the intervention and financial support
Participants	Inclusion criteria: duration of amenorrhoea one to 10 years, oestradiol < 21 pg/mL, FSH > 30 mIU/d, frequency of hot flushes ≥ 1/d, equol non-producer, SMI score ≥ 25, BMI 18.6 to 25, SDS score < 53 Exclusion criteria: surgical menopause, severe menopausal symptoms requiring medical treatment, abnormal vital signs and clinical laboratory tests outside the normal range, current or past reproductive related cancer, thyroid dysfunction or other serious medical conditions, allergy to soy, milk or egg, use of prescription medication for menopausal symptoms, OTC medical agents or health foods for relief of menopausal symptoms Age, years: 53.9 (mean) in placebo group, 53.2 (mean) in equol group Recruited using fliers, advertisements and volunteer lists and registered at a clinical research organisation

Aso 2012 (*Continued*)

Interventions	• Natural S-(-) equol supplement containing 5.0 mg equol (also 1.2 mg daidzein, 1.4 mg genistein, 3.1 mg glycitein, 298 mg protein, 113 mg fat, 375 mg carbohydrate, 56 mg ash and 110 mg fiber • Placebo tablets containing lactose identical to equol tablets ○ Duration and timing of administration: two tablets per day at breakfast and dinner. Compliance measured
Outcomes	Menopausal symptoms (as measured by the modified Climacteric Symptom Evaluation Form Checklist, Visual Analog Scale (VAS), subscales of the Greene Climacteric Scale and somatic symptom scales) Quality of life (as measured by Short Form-36 and VAS)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified permutation block method controlled for study site, years since menopause and BMI
Allocation concealment (selection bias)	Low risk	Computer-generated random permutation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff members and laboratory technicians blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Large proportion of participants dropped out and not analysed
Selective reporting (reporting bias)	Low risk	All plausible outcomes reported

Baber 1999

Methods	Randomisation method: not stated Blinding: double Allocation concealment: not stated Design: cross-over Number screened for inclusion: not stated Number randomly assigned: 51 Number dropped out: eight (seven for personal reasons, one for medical reasons not related to study) Number lost to follow-up: none stated Intention-to-treat analysis: no Power calculation: not stated Duration: three months × 2 Timing: not stated Location: tertiary menopause clinic, Australia Funding: industry (Novogen Ltd, Australia)
Participants	Inclusion criteria: minimum of mean of three hot flushes per day in week preceding trial Exclusion criteria: intercurrent medical problems, HT or antibiotics in previous three months, FSH < 30 mIU/mL, menstruation in previous six months, hysterectomy, vegetarian (> 10 g legumes/d) Age, years: 54 (±4.1) Recruitment method: volunteers. Not further specified
Interventions	• Phytoestrogen: Promensil (red clover extract) ○ Formulation: 40 mg of standardised isoflavones (genistein, daidzein, Fourmentin and Biochemic) per tablet • Placebo tablet ○ Dose, duration and timing of administration: one tablet daily in the morning for three months, one month washout period, then cross-over to opposite arm for three months and two weeks
Outcomes	Menopausal symptoms: daily flush frequency scored on daily diary card Quality of life: Greene Climacteric Scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Allocated randomly and blindly," but method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind

Baber 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind: analysis of data performed by separate group
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout
Selective reporting (reporting bias)	High risk	Adverse events not reported

Balk 2002

Methods	Design: parallel-group Number of women screened: "hundreds" (most not amenorrhoeic for one year) Number randomly assigned: 27 Number dropped out: seven (five in active arm: two for family reasons, three for adverse effects; two in placebo arm: one for lack of efficacy, one disliked taste) Number lost to follow-up: one (active arm) Number analysed: 19 Intention-to-treat analysis: no Power calculation: powered to detect endometrial changes, but baseline proliferation rate underestimated and study thus underpowered for primary outcome Duration: six months Timing: January 1998 to June 2000 Location: university hospital clinic Funding: academic research grants
Participants	Inclusion criteria: postmenopausal women 40 years of age with no vaginal bleeding for one year or over 30 years of age with oophorectomy or premature ovarian failure, omnivorous, intact uterus, normal endometrium on Pipelle biopsy, normal mammogram within previous year Exclusion criteria: tamoxifen usage, endometrial cancer, allergy to soy, hormone therapy on past year, using phytoestrogen supplements (diet logged for two weeks before study) Age, years: active arm 56.8 ± 5.9; placebo arm 57.9 ± 8.2 Recruitment method: primary and tertiary clinics, newspaper and radio advertisements, research institute website
Interventions	• Phytoestrogen: isoflavone ○ Formulation: soy flour and corn cereal (Nutlettes): 3/8-cup serving contains 92 mg of isoflavones. Mixed with placebo cereal (3:1) to increase similarity of taste • Placebo: wheat cereal (Grapenuts) ○ Dose, duration and timing of administration: 100 mg daily (1/2 cup cereal) for three months Given list of soy- and phytoestrogen-containing foods to avoid
Outcomes	Menopausal symptoms: weekly log monitoring nine specific symptoms on 4-point scale Compliance: daily dietary logs, check of unused cereal Adverse effects: weekly log monitored specific symptoms such as nausea, breast tenderness and gastrointestinal effects

Balk 2002 (*Continued*)

Notes	Authors reported that recruitment was difficult. Participants were not required to have menopausal symptoms to be eligible for the study, although these were measured at baseline. Mean symptom score at baseline indicated that, on average, participants had mild to moderate hot flushes and/or night sweats

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated in blocks of six
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Very high dropout (8/27)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Bicca 2004

Methods	Design: parallel-group Number of women screened: 90 Number analysed: 75 Number dropped out: one lost to follow-up in soy group, three lost in placebo group (two adverse events, one other) Intention-to-treat analysis: no Power calculation: yes Duration: 25 weeks Timing: not specified Location: university in Brazil Funding: not specified
Participants	Inclusion criteria: women 42 to 61 years of age, symptomatic and no menses for 12 months Exclusion criteria; oral HT in previous three months, topical HT in previous 30 days, use of medication that could influence the results, concomitant severe disease Mean age, years: 54 in soy group, 52 in placebo group Recruitment method: advertisements

Bicca 2004 (*Continued*)

Interventions	• Standardised soy extract (33 mg/d isoflavones) • Placebo capsule ○ Dose, duration and timing of administration: one capsule per day for 25 weeks.
Outcomes	Decrease in frequency of hot flushes and night sweats; vasomotor symptom intensity; change in vaginal pH
Notes	Study not published

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers kept by separate organisation
Allocation concealment (selection bias)	Low risk	Opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as triple-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as triple-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropout
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Brzezinski 1997

Methods	Design: parallel-group Number screened for inclusion: not stated Number randomly assigned: 145 Number dropped out: 31 (17 in active group: two for unbearable symptoms, 15 for personal reasons; 14 in control group: seven for unbearable symptoms, seven for personal reasons) Number lost to follow-up: none stated Number analysed: 114 Intention-to-treat analysis: no Power calculation: power calculation performed, but anticipated effect size not specified Duration: 12 weeks Timing: not stated Location: menopause clinic in Jerusalem, Israel Funding: academic grants
Participants	Inclusion criteria: perimenopausal and postmenopausal women 43 to 65 years of age, natural or surgical menopause with at least three months of amenorrhoea, FSH > 30 IU, LH > 20 IU, plasma oestradiol < 200 pmol/mL, experiencing hot flushes, night sweats, insomnia, vaginal dryness or dyspareunia Exclusion criteria: acute medical illness, use of gonadal hormones or any medicine known to influence menopausal symptoms or endocrine variables, known or suspected food allergies Age, years: active arm 53.66 (SE 0.74), control arm 51.32 (SE 0.71) Recruitment method: women requesting help for climacteric complaints at outpatient menopause clinic
Interventions	• Phytoestrogens: isoflavones and lignans ○ Formulation: daily consumption of 80 g tofu (approx 75 mg/g daidzein, 200 mg/g genistein), 2 × 200 mL glasses of soy drink (approx 7 mg/g daidzein, 35 mg/g genistein), one teaspoon of miso (40 mg/g daidzein, 35 mg/g genistein), two teaspoons of ground flaxseed (approx 4 mg/g lignans): cooked if unpalatable uncooked • Control diet: regular omnivorous Israeli diet ○ Dose, duration and timing of administration: diet for 12 weeks
Outcomes	Menopausal symptoms: menopause symptoms questionnaire
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number sequence, non-computerised
Allocation concealment (selection bias)	Unclear risk	Unclear

Brzezinski 1997 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported and unlikely
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout
Selective reporting (reporting bias)	High risk	Authors did not report on adverse events

Burke 2003

Methods	Design: parallel-group Number screened for inclusion: 1,571 (1,230 ineligible: main reasons: lack of menopausal symptoms (293), refusal to stop HT (241), cycle not perimenopausal (206)) Number randomly assigned: 241 Number dropped out: none stated Number lost to follow-up: none stated Number analysed: 211 (30 had data missing from symptom diaries) Intention-to-treat analysis: no Power calculation: Duration: two years Timing: August 1996 to August 1997 Location: Wake University Clinic,Carolina, USA Funding: soy supplements supplied by industry (Soy Technologies, St Louis, Missouri, USA)
Participants	Inclusion criteria: perimenopausal women (no more than one menstrual period in three months before randomisation), at least one vasomotor symptom per day, not using HT for three months before recruitment, willingness to participate in one-week run-in with isoflavone-free supplement Exclusion criteria: acute MI or stroke within previous six months, history of breast or endometrial cancer, invasive cancer within previous five years, active thromboembolic disease, previous osteoporosis-related fractures treated with hormones, low baseline bone density, previous exposure to diethylboestrol, dyslipidaemia, endometrial biopsy showing hyperplasia, consumption of soy products on a daily basis and unwillingness to reduce consumption to once a week Age, years: mean 50.8 (SE 0.2) Recruitment method: “recruited from the community”

Interventions	• High-dose phytoestrogens: isoflavones
	  ○ Formulation: 25 g soy protein (58 mg isoflavones) in a drink
	• Medium dose phytoestrogens: isoflavones
	  ○ Formulation: 25 g soy protein (42 mg isoflavones) in a drink

Burke 2003 (*Continued*)

	• Control: 25 mg soy protein, washed to remove isoflavones (maximum 4 mg isoflavones) in a drink ○ Dose, duration and timing of administration: one 25 g ready-to-drink beverage daily, chocolate or orange flavoured, for two years
Outcomes	Menopausal symptoms: hot flushes, night sweats recorded in monthly calendar with daily entry field: participants asked to record number and severity of symptoms for one full week per month Compliance: compliance calendars
Notes	37 women (18%) took HT during trial: 16 in high-dose group (25%), 11 in middle group (16%), 10 in control group (13%). Data analysed with and without these women, and pattern of results not affected

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Moderate dropout: missing data from questionnaires because not filled in
Selective reporting (reporting bias)	High risk	Authors did not report on all prespecified outcomes

Campagnoli 2005

Methods	Design: cross-over Number of women screened: not stated Number randomly assigned: 36 Number analysed: 29 Number dropped out: seven (not clear which group: three medical reasons, four family reasons) Intention-to-treat: no Power calculation: yes: 95% power to detect at least a 20% greater reduction in hot flushes in active arm compared with placebo Duration: 12 + 12 weeks Timing: November 1999 to December 2000 Location: hospital in Torino, Italy Funding: Medestea International (manufacturer of active treatment)
Participants	Inclusion criteria: minimum of five moderate to severe hot flushes/d, good general health, 45 to 58 years, BMI 18 to 28, surgical menopause (bilateral oophorectomy for at least three months or in spontaneous menopause with no menses for over six months) , menopausal hormone profile (oestradiol < 30 pg/mL, FSH > 40 UI/L) Exclusion criteria: use of drugs that influence vasomotor symptoms, hormone therapy or tibolone in previous six months, consumption of soy-based food more than once per week, use of drugs that might reduce absorption of isoflavones Mean age of completers, years: 51 Recruitment method: menopause clinic
Interventions	• Standardised soy extract 200 mg (Soy select) capsules (60 mg/d isoflavones) • Placebo capsules ○ Dose, duration and timing of administration: two capsules per day in two doses for 12 weeks, then switched to alternate treatment without a washout period
Outcomes	Number of hot flushes per week after treatment (at end of first phase of study)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Schedule prepared by the manufacturer of the product using computer-generated randomisation list and distributed sequentially
Allocation concealment (selection bias)	Low risk	Adequate: investigators blind to treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind

Campagnoli 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout
Selective reporting (reporting bias)	Low risk	All potential outcomes reported

Carmigiani 2010

Methods	Design: parallel-group Number of women screened: 1,520 Number of women randomly assigned: 60 Number of women analysed: 60 Number of dropouts or lost to follow-up: Intention-to-treat: yes Power calculation: yes, 16 subjects required in each group to reach power of 90%, assuming a difference of three hot flushes in a 24-hour period and SD of 3.8 hot flushes/d Duration: 16 weeks Timing: January to October 2007 Location: two menopause outpatient clinics at the Centre for Women's Integrated Healthcare of the University of Campinas, Campinas, Sao Paolo, Brazil Funding: Sao Paolo Foundation for the Support of Research
Participants	Inclusion criteria: postmenopausal women between 40 and 60 years of age who had LMP > 12 months previously; FSH > 30 mUI/mL and oestradiol levels < 20 pg/mL; more than eight hot flushes in 24 hours; not using any form of hormonal treatment during previous six months; not currently using any lipid-lowering drugs, antidiabetic drugs, soybean-derived products or herbal supplements Exclusion criteria: previous hysterectomy; chronic gastrointestinal disorder; contraindication to hormone therapy; patients participating in a conflicting clinical trial; known allergy or hypersensitivity to soy or cow's milk; not willing to cease consumption of soy products for the term of the trial Mean age, years: 53 in HT and soy groups; 51 in placebo group Recruitment method: menopause outpatient clinic
Interventions	• Oestradiol 1 mg + 0.5 mg norethisterone acetate • Dietary soy supplementation (containing 90 mg of isoflavone) • Placebo
Outcomes	Primary: menopause rating scale. Also side effects, endometrial thickness, maturation index and compliance
Notes	
Risk of bias	

Carmigiani 2010 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation list with numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded for the duration of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor was gynecologist, who did not participate in the screening process or dispense drugs
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout or lost to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Cheng 2007

Methods	Design: parallel-group Number of women screened: not reported Number of women randomly assigned: 60 Number of women analysed: 51 (two dropped out during the first month, seven continued treatment but missed some examinations) Intention-to-treat: no Power calculation for sample size: no Duration: 12 weeks Timing: not stated Location: Sweden; other details not reported Funding: Stockholm County Council, Swedish Cancer Society, European Union Specific Targeted Research Project and Susan G. Komen Breast Cancer Foundation
Participants	Inclusion criteria: postmenopausal women, at least one year since last menstruation, FSH levels > 30 IU/mL, at least six months without taking hormone therapy. All women experienced hot flashes and night sweats Exclusion criteria: not stated Age, years: between 49 and 69; mean age placebo group 56.9 ± 4.2; isoflavone group 58.4 ± 5.0 Recruitment method: not stated
Interventions	• Isoflavones 60 mg daily in a fruit drink (n = 26) • Placebo (oatmeal drink) (n = 25) Women were encouraged not to alter dietary, alcohol or physical activity habits

Cheng 2007 (*Continued*)

Outcomes	Compliance, endometrial thickness, lipoprotein levels, hormone levels, immunohistochemistry, vasomotor symptoms	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomly assigned by computer to two groups'
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Treatment was blinded both to the women and doctor'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assume that the doctors evaluated outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Two dropped out during the first month and seven women continued treatment but missed some of the examinations. ITT analysis was not conducted for all outcomes
Selective reporting (reporting bias)	High risk	Some prespecified outcomes not reported in the results section

Colli 2012

Methods	Design: parallel-group randomised placebo-controlled trial Number of women randomly assigned: 90 Number of women analysed: 75 Intention-to-treat analysis: no Power calculation for sample size: no Duration: six months Timing: October 2009 to March 2010 Location: gynaecology service in Parana, Brazil Funding: Conselho Nacional de Desenvolvimiento Cientifico e Tecnologico
Participants	Inclusion criteria: women 46 to 68 years of age; FSH > 40 mIU/L, oestradiol < 30 pg/mL, amenorrhoea > 12 months; climacteric symptoms Exclusion criteria: one or more contraindications to the use of synthetic HT, use of any synthetic HT in the past six months; use of antibiotics in past six months; signs of gastrointestinal malabsorption syndrome

	Mean age of participants, years: 54 to 57 Recruitment: from gynaecology clinic
Interventions	• Flaxseed extract (two 500-mg capsules daily, with each capsule containing 50 mg of standardised lignan) • Flaxseed meal (two tbsp (45 g) of ground whole flaxseed corresponding to 270 mg lignan) • Placebo (two 500-mg capsules of collagen daily) ○ Capsules taken in the morning before the first meal, and ground flaxseed mised with milk, yogurt or juice
Outcomes	• Hot flash score (intensity) • Kupperman Index score • Vaginal epithelial maturation value • Endometrial thickness • Adverse events
Notes	Group 2 was not blinded, as the women took a different product from placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly distributed": method not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Group 1 blinded but group 2 not blinded (non-identical placebo)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial dropouts with no reasons stated and uneven between groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Crisafulli 2004

Methods	Design: parallel-group Number randomly assigned: 90 Number dropped out: seven (no reasons given) Number lost to follow-up: zero Number analysed: 90 Intention-to-treat analysis: yes Power calculation: 90% power to detect a 2.5-mm difference in endometrial thickness among the three treatment groups (P = 0.05) Duration: 12 months Timing: not stated Location: university clinic in Italy Funding: not stated
Participants	Inclusion criteria: healthy and ambulatory; 47 to 57 years of age; not undergone surgically induced menopause; no menstrual period in the preceding year; FSH > 50 IU/L; serum 17B-oestradiol level of 100 pmol/L or less Exclusion criteria: clinical/laboratory abnormalities that suggested cardiovascular, hepatic or renal disorders; coagulopathy; use of oral or transdermal oestrogen, progestin, androgen or other steroids in the preceding year; smoking more than 10 cigarettes/d Age, years: mean in placebo group 51; mean in other two groups 52 Recruitment: referred by university department
Interventions	• Phytoestrogen genistein (54 mg/d) • Continuous HT (1 mg/d 17B-oestradiol plus norethisterone acetate) • Placebo (identical tablets) All participants had a four-week stabilisation diet (isocaloric, fat restriction) before treatment
Outcomes	Menopausal symptoms: daily number of hot flushes at three, six and 12 months Adverse effects: endometrial thickness at six and 12 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer software
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind (participants and investigators)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind

Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropout but no reasons given
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

D'Anna 2007

Methods	Design: parallel-group Number randomly assigned: 265 (substudy of larger trial) Number dropped out: by year one, 10/125 in genistein group (after six months of follow-up) and 8/122 in placebo group (four after three months and four after six months). Reasons given for dropping out were mainly gastrointestinal side effects but also presence of other diseases, loss to follow-up and inadequate interaction with the woman's family doctor. None withdrew because of treatment inefficacy. By year two, 16/125 in genistein group and 13/122 in placebo group Number analysed: year one: 247; year two: 236 Intention-to-treat analysis: no Power calculation for sample size: yes: difference of at least 20% between groups required 97 participants in each group Duration: one and two years (two publications) Timing: not stated Location: two separate university centres in Italy Funding: Italian Ministry of Scientific Research and Technology and University of Messina, Italy
Participants	Inclusion criteria: 50 to 70 years old; postmenopausal; FSH > 50 IU/L; serum oestradiol < 100 pmol/L. In the substudy of 247 participants, only women with vasomotor symptoms were evaluated Exclusion criteria: clinical or laboratory abnormalities that suggested various disorders; coagulopathy; use of oral or transdermal oestrogen, progestin, androgen or other steroids; use of bisphosphonates, cholesterol-lowering therapy or cardiovascular medications in previous six months; smoking > 10 cigarettes/d; BMD of the femoral neck > 0.795 g/cm^3 Age, years: mean 53 in both groups Recruitment: women referred from university departments
Interventions	• Phytoestrogen genistein twice per day (each tablet contained 27 mg of total isoflavone) • Placebo twice per day
Outcomes	Number and severity of hot flushes Endometrial thickness
Notes	The study is a substudy of a larger study evaluating bone loss and CVD prevention. The substudy consisted of women with vasomotor symptoms, and characteristics of participants did not differ from those in the parent study
Risk of bias	

D'Anna 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computerised database"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although dropouts were minimal at both one and two years, outcomes were measured in a subgroup of the total study population
Selective reporting (reporting bias)	Unclear risk	Side effects were presumably collected, as the authors stated that treatments were "well tolerated" but the results were not reported

Dalais 1998

Methods	Design: cross-over Number randomly assigned: 52 Number dropped out: eight (seven for personal reasons, one for lack of compliance) Number lost to follow-up: none stated Number analysed: 44 Intention-to-treat analysis: no Power calculation: yes, 80% chance of detecting a 40% decrease in hot flush rate Duration: 2 × 12 weeks with a four-week washout period Timing: not stated Location: Australia Funding: industry support (George Weston foods)
Participants	Inclusion criteria: postmenopausal women 45 to 65 years of age, FSH > 40 IU/mL, > 14 hot flushes/wk, 12 months of amenorrhoea, non-smoking, non-vegetarian Exclusion criteria: antibiotics or hormone therapy during preceding three months Age, years: mean 53.6 to 54.6 Recruitment method: not stated
Interventions	• High-phytoestrogen diet: isoflavone. Formulation: 45 g daily of soy grits, totalling 52.64 (SD 8.68) mg of isoflavones daily (genistein and daidzein) • High-phytoestrogen diet: mammalian lignan precursors. Formulation: 45 g daily

Dalais 1998 (*Continued*)

	of linseed (secoisolariciresinol and matairesinol) • Low-phytoestrogen diet: wheat. Formulation: 45 g daily of kibbled wheat ○ Dose, duration and timing of administration: four slices of bread or two rolls (or equivalent combinations) substituted for daily bread intake for two 12-week periods Participants completed a food diary for two weeks before randomisation and were asked to repeat the same two-weekly diet and to note in their hot flush diary if they diverged from it
Outcomes	Measures of frequency and severity of menopausal symptoms Measures of change in quality of life
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate
Selective reporting (reporting bias)	High risk	Adverse events not measured

Del Giorno 2010

Methods	Design: parallel-group Number randomly assigned: 120 Number dropped out: eight because they did not take more than 80% of drug and 12 for personal reasons (not given per group) Number analysed: 100 Intention-to-treat analysis: no Power calculation: yes, 80% power, beta 10%, 38 participants per group Duration: follow-up at four, eight and 12 months Timing: December 2005 to December 2008 Location: University of Sao Paolo, Brazil Funding: not stated
Participants	Inclusion criteria: 45 to 65 years of age with menopausal symptoms; > 12 months amenorrhoea; FSH > 30 mIU/mL; oestradiol < 30 pg/mL Exclusion criteria: diabetes mellitus; CVD; hypersensitivity to drugs used in the study; oestrogen-dependent cancer; liver failure; nephropathy; systemic lupus erythematosus; porphyia; altered cervicovaginal cytology; osteoporosis; endometrial thickness > 6 mm; uterine volume > 200 cm^3; BI-RADS category 3, 4 or 5 mammograms; hormone treatment with sex steroids or phytoestrogens in past six months Mean age, years: 56 in phytoestrogen group; 55 in placebo group Recruitment: from outpatient clinic
Interventions	• *Trifolium pratense* (red clover) 40 mg • Placebo
Outcomes	Vasomotor symptom score (Kupperman): sexual satisfaction (as measured by GRISS questionnaire)
Notes	Vasomotor symptoms not further defined

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer program"
Allocation concealment (selection bias)	Low risk	"Sample blinding codes" not disclosed during study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as "double-blind"

Del Giorno 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout; appears that women were allocated to groups after dropouts were excluded
Selective reporting (reporting bias)	High risk	Insufficient information on outcomes assessed

Evans 2011

Methods	Design: parallel-group Number randomly assigned: 84 Number dropped out: by 4 weeks, n = 2 (in genistein group); by 12 weeks, n = 14 more (eight in genistein group, six in placebo group). Reasons were given Number analysed: 82 Intention-to-treat analysis: yes, modified; all those who had at least four weeks of treatment for efficacy Power calculation: yes, 42 participants per group required to detect a clinically important difference of 35% at 5% level of significance and 80% power Duration: four, eight and 12 weeks of follow-up Timing: not stated Location: five study sites in southwestern Ontario, Canada Funding: DSM Nutritional Products (manufacturer of the genistein tested)
Participants	Inclusion criteria: minimum of 40 hot flushes/wk; between ages of 40 and 65 years; physiological state of natural or surgical menopause (amenorrhoeic for $\geq$ three months + serum FSH > 35 IU/mL or > 42 days post surgery) Exclusion criteria: clinical or laboratory abnormalities; use of conventional hormone therapy or selective oestrogen receptor modulators within four weeks of study start; known allergy or hypersensitivity to soy, peanuts, purified isoflavones, genistein, lactose and/or cow's milk; consumed soy products within four weeks before screening visit; unpredictable vaginal bleeding; uterine fibroids or endometriosis that required treatment; untreated polycystic ovarian syndrome; history of abnormal PAP smear; use of gonadotropin agonists within 24 weeks; glucocorticoids or chronic high-dose prednisone or equivalent for the past 12 weeks Mean age, years: 53 Recruitment: not stated
Interventions	• Genistein (geniVida) 30 mg once daily • Placebo once daily
Outcomes	Primary: percentage change in number of daily hot flushes from pretreatment to week 12 Secondary: duration and severity of daily hot flushes, Greene Climacteric Scale score; FSH, 17B-oestradiol, endometrial thickness
Notes	
Risk of bias	

Evans 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list"
Allocation concealment (selection bias)	Low risk	"Sealed envelopes for each randomisation number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patient, Medical Directors and research staff blinded to the treatment assignment for the duration of the trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patient, Medical Directors and research staff blinded to the treatment assignment for the duration of the trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified intention-to-treat analysis: very low dropout by week four
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Faure 2002

Methods	Design: parallel-group Number randomly assigned: 75 Number dropped out: 17 for inefficacy (six from active group, 11 from placebo group) Number lost to follow-up: three (placebo group) Number analysed: 75 Intention-to-treat analysis: yes (missing data imputed by "last observation carried forward" principle), also per-protocol analysis Power calculation: 630 in each study arm required to give 90% power to detect a difference of three hot flushes per day, assuming a standard deviation of 3.8 hot flushes/d (P = 0.05) Duration: 16 weeks Timing: not stated Location: outpatient clinic, Nimes, France Funding: industry funded (Arkopharma Laboratories)
Participants	Inclusion criteria: postmenopausal women requesting treatment for hot flushes, at least six months since last menstrual period, minimum of seven moderate to severe hot flushes or night sweats during two weeks before study. Baseline FSH > 40 IU/L and serum oestradiol < 35 pg/mL Exclusion criteria: use of any other drug for treatment of climacteric symptoms during study period, HT within six weeks before the study Age, years: active group 53 (SD 5.6), placebo group 53.9 (SD 4.1) Recruitment: not reported

Faure 2002 (*Continued*)

Interventions	• Phytoestrogen: isoflavone ○ Formulation: Phytosa: soy extract 325 mg capsules containing 17.5 mg total isoflavones (genistein, daidzein, biochanin and formononetin) • Placebo (cellulose microcrystalline and sodium magnesium stearic) ○ Dose, duration and timing of administration: 2 × 2 tablets daily for 16 weeks
Outcomes	Menopausal symptoms: daily diary card recording number of moderate/severe hot flushes and night sweats Adverse events recorded at each follow-up
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	High dropout rates but missing data imputed
Selective reporting (reporting bias)	Unclear risk	Insufficient information on one of the prespecified outcomes: adverse events

Ferrari 2009

Methods	Design: parallel-group Number randomly assigned: 180 Number dropped out: 30/85 in genistein group (three before treatment intake); 29/95 in placebo group (one before treatment intake). Detailed reasons given Number analysed: 170 (exclusions were those with violation of selection criteria at entry) Intention-to-treat analysis: yes, modified; women excluded with violation of selection criteria at entry Power calculation: yes, 20% reduction in frequency of hot flushes for isoflavone group compared with placebo group-required 176 participants Duration: 12 weeks Timing: September 2004 to April 2006 Location: 16 different hospitals in Italy Funding: not stated
Participants	Inclusion criteria: women 40 to 65 years of age; reporting a minimum of five moderate to severe hot flushes per day over the last seven days of the run-in period; absence of menstruation for at least six months or six weeks after bilateral oophorectomy; FSH $\geq$ 30 IU/mL; 17B-oestradiol $\leq$ 40 pg/mL Exclusion criteria: HT or any other hormone therapy in last three months before inclusion or one month if participant had been treated with megestrol acetate, clonidine, vitamin E, phenobarbital, ergotamine or antidepressant drugs; presence of suspected or confirmed breast nodule; severe liver or renal dysfunction; type 1 or 2 diabetes mellitus; heart failure NYHA class II to IV, severe neurological disease; history of drug abuse or alcoholism; known hypersensitivity to soy or soy derivatives Mean age, years: 53 in isoflavone group; 55 in placebo group Recruitment: not reported
Interventions	• Extract of soy phytoestrogens: isoflavone content 80 mg with high doses of genistein (60 mg); one tablet daily • Identical placebo Initial two-week run-in period, then a baseline visit
Outcomes	Average number of hot flushes in last seven days compared with baseline; improvement in hot flushes; change in severity of hot flushes; satisfaction; Kupperman Index; compliance; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list. . .generated by blocks of four patients"
Allocation concealment (selection bias)	Low risk	Randomisation done off-site, with consecutive random numbers

Ferrari 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	High dropout but modified intention-to-treat analysis, with the only exclusions those who violated inclusion criteria
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Geller 2009

Methods	Design: parallel-group Number randomly assigned: 67 (black cohosh treatment arm not included) Number dropped out: seven (reasons given) Number analysed: 67 Intention-to-treat analysis: yes, all women who had been in study for at least three months Power calculation: yes, for primary outcomes only, comparing each treatment with placebo: 22 women per arm, treatments would reduce vasomotor symptoms by approx 60% with anticipated placebo effect of 35% Duration: 12 months Timing: February 2003 to December 2007 Location: two university medical centres in the USA Funding: Office of Dietary Supplements, National Center for Complementary and Alternative Medicine, National Institute for General Medical Sciences and Office for Research on Women's Health
Participants	Inclusion criteria: experiencing at least 35 vasomotor symptoms per week, perimenopausal or postmenopausal with intact uterus, amenorrhoea for longer than six months to < 10 years, FSH > 40 mIU/mL, hormone therapy not contraindicated, able to give informed consent Exclusion criteria: previous hysterectomy, < 35 vasomotor symptoms/wk, last menstrual period > 10 years, positive pregnancy test or breastfeeding, BMI > 38 kg/m^2, previous history of endometrial hyperplasia or neoplasia, previous history of cancers of the reproductive tract or breast cancer, history or presence of myocardial infarction or stroke, history of severe recurrent depression or severe psychiatric disturbances, history or presence of cerebrovascular accident, severe varicose veins, sickle cell anaemia, history of alcohol or drug abuse, abnormal vaginal bleeding of undetermined cause, untreated or uncontrolled hypertension defined as systolic blood pressure > 165 mmHg or diastolic > 95 mmHg, concurrent administration of medication-containing oestrogen/progestin, SERM, St John's Wort, bisphosphonates or dietary phytoestrogens, history of migraine associated with hormone use, history or presence of deep vein thrombosis, thrombophlebitis or thromboembolic disorder, current participation in any other clinical trial within 30 d of enrolment, >5 alcoholic drinks per week, smoker, diabetes, abnormal

Geller 2009 (*Continued*)

	transvaginal ultrasound defined as > 7 mm thickness, abnormal endometrial biopsy or mammogram, vegans Mean age, years: 52 in placebo and red clover groups; 53 in hormone therapy group Recruitment: not reported
Interventions	• 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (n = 23) • Black cohosh (128 mg/d) (n = 21) • Red clover (398 mg/d including 120-mg isoflavones) (n = 22) • Placebo (n = 22) ○ Women consumed two capsules each evening Women taking oral hormone therapy had a two-month washout period, and women using transdermal patches had a one-month washout period
Outcomes	Primary outcome: relief of vasomotor symptoms Secondary outcomes: relief of somatic symptoms, mood changes, sexual dysfunction, health-related quality of life, use of validated questionnaires, adverse events Participants completed diaries
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Random, computer-generated code'
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was by intention-to-treat Placebo = one dropout due to life changes; CEE/MPA = four dropouts due to two adverse events, one relocation and one life change; black cohosh = two dropouts, one loss to follow-up and one lack of efficacy; red clover = two dropouts due to lack of efficacy
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes reported, but insufficient information on adverse effects

Han 2002

Methods	Design: parallel-group Number screened for inclusion: not stated Number randomly assigned: 82 Number of dropouts: two (one from each arm, one due to poor response, one due to nausea-not stated which arms they were on) Number analysed: 80 Intention-to-treat analysis: no Power calculation: none stated Duration: four months Timing: August 1999 to February 2000 Location: university clinic, Brazil Funding: unclear. Investigators acknowledge the co-operation of a doctor employed by food supplement manufacturer Eugenbio
Participants	Inclusion criteria: women 45 to 55 years of age; "in menopause" at least 12 months, no hormonal treatment for at least 12 months, intact uterus, FSH > 25 U/L, oestradiol < 20 pg/mL, having hot flushes Exclusion criteria: taking lipid-lowering drugs, antidiabetic medications, soybean-derived products or herbal supplements; uncontrolled hypertension, stroke or transient ischaemic attack, cancer diagnosed within past five years, previous myocardial infarction Age, years: mean active arm 48 (SE 1.1), placebo arm 49 (SE 1.3) Recruitment method: not stated
Interventions	• Phytoestrogen: isoflavone capsules ○ Formulation: soy protein 50.3 mg and isoflavone 33.3 mg (genistein 23.3 mg, daizein 6.2 mg, glycitein in aglycone form 3.8 mg) per capsule • Placebo ○ Dose, duration and timing of administration: one capsule eight hourly (= 100 mg isoflavone daily) for four months
Outcomes	Menopausal symptoms: hot flashes (Kupperman Index) Compliance: examination of prescriptions/pills Endometrial thickness
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generator
Allocation concealment (selection bias)	Low risk	Numbered coded envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded researchers and participants

Han 2002 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes recorded by an independent gynaecologist
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropout
Selective reporting (reporting bias)	High risk	Adverse events not reported

Hanachi 2008

Methods	Design: parallel-group Number randomly assigned: 37 Number dropped out: not reported Number analysed: assume this is 37 Intention-to-treat analysis: not reported Power calculation for sample size: not reported Duration: three months Timing: not stated Location: not stated Funding: not stated
Participants	Inclusion criteria: non-smokers; free from diseases; not on any type of hormone treatment during previous 12 months; not currently using lipid-lowering drugs, antidiabetic medications, soybean-derived products or herbal supplements; intact uterus; FSH > 25 U/L; oestradiol < 100 pg/mL; presence of hot flushes Exclusion criteria: history of uncontrolled hypertension, stroke or transient ischemic attack, cancer diagnosed less than five years ago, previous myocardial infarction Mean age, years: 52 Recruitment method: not stated
Interventions	• Soy milk product (12.5 g soy protein with genistein 13 mg and daidzein 4.13 mg day 1) • Soy milk + exercise (one hour walking per day) • Control
Outcomes	Kupperman Index (hot flushes); lipids
Notes	Baseline values not given, only percentage decrease from baseline. Control values also not given. Nature of control not described

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomly assigned', but no other description provided

Hanachi 2008 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Does not appear there were any dropouts
Selective reporting (reporting bias)	High risk	Outcomes not clearly described

Heger 2006

Methods	Design: parallel-group, multi-centre Number of women randomly assigned: 110 Number of dropouts: n = 16 in ERr 731 group (one lack of efficacy, three violations of smoking ban, three adverse events, two organisational reasons, seven other reasons); n = 48 in placebo group (31 lack of efficacy, one violation of smoking ban, one adverse events, 16 other reasons) Number analysed: n = 109 (one woman refused to take the intervention) Intention-to-treat: yes, modified-only the women who took the interventions Power calculation: yes, using a group sequential design according to O'Brien and Fleming Duration: 12 weeks Timing: February 2003 to May 2004 Location: nine gynaecological outpatient departments in the Ukraine Funding: Health Research Services Ltd, Germany, and Chemisch-Pharmazeutische Fabrik Goeppingen, Carl Muller, Apotheker, GmbH u Co KG, Goeppingen, Germany (manufacturer of the supplement)
Participants	Inclusion criteria: climacteric complaints with MRS II total score > 22 points; perimenopause, defined as 45 to 55 years of age with cycle irregularity during the past 12 months or LMP at least three but no longer than 12 months ago Exclusion criteria: regular cycles during the past three months; mandatory indication for HT; treatment with drugs containing oestrogen/progestogen during past six months or any other Rx in past three months; PAP smear class III/IV and/or endometrial hyperplasia; known or suspected hypersensitivity to experimental intervention; concomitant medications that might influence trial results; BMI < 18 kg/m^2 or > 30 kg/m^2 and/or abnormal eating habits; wish to become pregnant or to be breast-feeding; previous or existing major diseases; previous or existing psychiatric disorders including depression; smoking, moderate alcohol intake, coffee/chocolate intake of 500 mg or more of caffeine per day and/or suspected drug abuse; participation in another clinical trial during past six months; incompetence or incapability of understanding the trial Mean age, years: 49 Recruitment method: from outpatient departments (women seeking treatment for cli-

Heger 2006 (*Continued*)

	macteric complaints)
Interventions	• One tablet (250 mg) of ERr 731 per day-containing 4 mg of *Rheum rhaponticum* dry extract-identical to the product Phytoestrol N • One tablet of placebo per day
Outcomes	Primary • Change in total score of MRS II (this outcome not extracted in this review) Secondary • Changes in individual symptoms of MRS II: number and severity of hot flushes; number of bleeding/spotting days; intensity of bleeding; time until onset of Rx effect; scores on the Integrative Medicine Outcomes Scale, Clinical Global Impressions, MENQOL; satisfaction with Rx; changes in climacteric complaints; health-related quality of life; endometrial biopsy findings; investigations of vagina, breast, cervix; tolerability of medication; adverse effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer generated randomisation list with a balanced 1:1 randomisation using a block size of 4"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators and data monitoring committee-all blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators and data monitoring committee-all blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One woman did not take the intervention and was not included. When discontinuations were reported, the LOCF method was used for missing data
Selective reporting (reporting bias)	Low risk	Most prespecified outcomes reported; authors stated that an additional paper will report on the remaining outcomes

Heyerick 2006

Methods	Design: parallel-group Number of women screened: 84 Number randomly assigned: 67 Number of dropouts: 18% (12/67): four in high-phytoE group (three no efficacy, one other), one in low-phytoE group (no efficacy), seven in placebo group (all no efficacy) Number analysed: 55 Intention-to-treat analysis: no Power calculation: not reported Duration: 12 weeks Timing: December 2003 to April 2004 Location: Ghent, Belgium Funding: IWT-Vlaanderen in Belgium; Biodynamics, Belgium
Participants	Inclusion criteria: healthy, 45 to 60 years of age, intact uterus, no menses for past 12 months, at least two to five hot flushes per day, abstention from HT for past three months Exclusion criteria: score < 2 on Kupperman Hot Flush Index Mean age, years: 52 in placebo and low-dose groups; 53 in high-dose group Recruitment method: not stated
Interventions	• Hop extract (100 μg/d 8-prenylnaringenin) • Hop extract (250 μg/d 8-prenylnaringenin) • Placebo Dose, duration and timing of administration: one capsule a day for 12 weeks
Outcomes	Hot flush score on Kupperman Index (severity)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	On-line randomiser
Allocation concealment (selection bias)	Low risk	Random codes kept separate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout
Selective reporting (reporting bias)	High risk	Adverse events not measured

Hidalgo 2005

Methods	Design: cross-over Number of women screened: not stated Number randomly assigned: 60 Number of dropouts: 12% (7/60): not clear which group: five no reason, two adverse events Intention-to-treat analysis: no Power calculation: yes, but insufficient Duration: 12 weeks, seven-day washout, then another 12 weeks on alternate treatment Timing: July 2003 to August 2004 Location: Guayaquil, Ecuador Funding: Melbrosin International (provision of intervention and control)
Participants	Inclusion criteria: over 40 years of age, no menses for past 12 months, non-users of HT, moderate to severe menopausal symptoms (Kupperman Index score $\geq$ 15, basal determination Exclusion criteria: no consent, indication of non-compliance, conventional HT, isoflavone supplements, thyroid medication or history of thyroid disease, medication that could interfere with vasomotor symptoms and/or lipid serum levels Mean age, years: 51 Recruitment method: clinical database, private practice or from the general population through advertising and flyers
Interventions	• Red clover extract (80 mg/d isoflavones) • Placebo Dose, duration and timing of administration: Participants acted as their own control-two capsules a day of the randomly assigned treatment for 90 days, a seven-day washout period, then alternate treatment for a further 90 days
Outcomes	Hot flush and night sweat Kupperman scores (severity) expressed as percentages Vaginal cytology
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generation
Allocation concealment (selection bias)	Low risk	Opaque containers with investigators blinded to codes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias)	Low risk	Stated as double-blind

Hidalgo 2005 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear whether dropouts likely to influence results
Selective reporting (reporting bias)	High risk	Adverse effects not measured

Imhof 2006

Methods	Design: cross-over Number of women screened: not stated Number randomly assigned: 113 Number dropped out: four (three in active arm and one in placebo arm-all started hormone therapy) Number analysed: 109 Intention-to-treat analysis: yes-modified, based only on the women who started the trial and excluded the women who started hormone treatment Power calculation: not reported Timing: not stated Location: general hospital and study centre in Vienna, Austria Funding: Melbrosin International (manufacturer of interventions)
Participants	Inclusion criteria: postmenopausal (no menses for > 12 months), 40+ years, negative pregnancy test, willingness for adherence to control dates and to take prescribed medications, moderate to severe menopausal symptoms (Kupperman Index ≥ 15) Exclusion criteria: constant ET, known isoflavone hypersensitivity Mean age, years: 55 in active arm and 54 in placebo arm Recruitment method: menopause clinic
Interventions	• Red clover extract (MF11RCE) (80 mg/d isoflavones) • Placebo capsules ○ Dose, duration and timing of administration: two capsules per day for 12 weeks, seven-day washout period and crossed over to other treatment for next 12 weeks
Outcomes	Endometrial thickness, daily hot flush and night sweat frequency and side effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not described

Imhof 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropout
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Jeri 2002

Methods	Design: parallel-group Number screened for inclusion: not stated Number randomly assigned: 30 Number dropped out: none stated Number lost to follow-up: none stated Number analysed: 30 Intention-to-treat analysis: not mentioned Power calculation: not stated Duration: 16 weeks Timing: not stated Location: Peru Funding: not stated
Participants	Inclusion criteria: healthy, non-vegetarian women; postmenopausal for longer than one year; younger than 60 years of age; FSH level > 30 mIU/mL; having at least five hot flushes daily, averaged over one week; not using HT, antidepressants or other medications, or soy or other oestrogen-active plant products for the past 16 weeks Exclusion criteria: Age, years: 51 Other characteristics of participants: All were Hispanic "with a middle class income and good education" Recruitment method: not reported
Interventions	• Phytoestrogen: Promensil ○ Formulation: 40 mg of standardised isoflavones (genistein, daidzein, formonetin and biochanin) per tablet • Placebo ○ Dose, duration and timing of administration: one tablet daily
Outcomes	Menopausal symptoms: hot flush frequency and severity recorded at beginning and end of study
Notes	

Jeri 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Apparently no dropouts
Selective reporting (reporting bias)	High risk	Adverse events not reported

Jou 2008

Methods	Design: parallel-group Number randomly assigned: 96 Number dropped out: 4/30 in placebo group (one unwell and three for personal reasons) , 2/34 in the equol-producing group (personal reasons), one in the non-equol-producing group (personal reasons) Number analysed: 89 Intention-to-treat analysis: no Power calculation for sample size: 81 participants (27 per group) would have 85% power to detect a difference of 10 in total Kupperman score between groups Duration: six months Timing: April to December 2005 Location: clinics at hospital and university in Taiwan Funding: not stated
Participants	Inclusion criteria: healthy menopausal women (confirmed by FSH $\geq$ 40 mIU/mL); did not receive hormone therapy during previous year; Kupperman Index score > 0 Exclusion criteria: taking medications containing hormones; major systemic disease such as diabetes mellitus, hypertension, hypothyroidism, chronic renal disease, breast disease, CVD, cancer Mean age, years: 54 Recruitment method: from gynaecology clinics

Jou 2008 (*Continued*)

Interventions	• Soy germ extract powder twice per day-135 mg isoflavones (1 g = 10.9 mg daidzein and 2.85 mg genistein) in two separate subgroups: equol producers (n = 34) and non-equol producers (n = 32) • Placebo (roasted wheat powder) (n = 30)
Outcomes	Hot flushes as measured by Kupperman Index together with other symptoms
Notes	Hot flush status at baseline not reported. Menopausal symptom score at baseline not comparable between groups (higher in the equol-producing group)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Random number generator'
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropout
Selective reporting (reporting bias)	High risk	Adverse events not reported

Kaari 2006

Methods	Design: parallel-group Number of women screened: 150 Number randomly assigned: 79 Number of dropouts: 14% (11/79): seven from soy group (three medical, four personal) , four from ET group (one medical, one no reason, one scared of biopsy, one personal) Number analysed: 68 Intention-to-treat analysis: no Power calculation: not reported Duration: 24 weeks Timing: July 2001 to November 2002 Location: University of Sao Paolo, Brazil Funding: ACHE Laborotorio Ldta (made the intervention)
Participants	Inclusion criteria: ≥ 45 years, good overall health, no menses for past 12 months, FSH ≥ 30 mU/mL, intact uterus, endometrial thickness < 5 mm, atrophic endometrium (biopsy) Exclusion criteria: strict vegetarian, high-fiber/high-soy diet, regular consumption of vitamin and mineral supplementation > Recommended Dietary Allowances, antibiotic or hormone use in past six months, history of chronic disorders (incl benign breast disease), regular use of medication known to interfere with study endpoints, BMI > 30 Mean age, years: 54 Recruitment method: menopause clinic
Interventions	• Standardised soy extract 300 mg (120 mg/d isoflavones) • Oestrogen replacement therapy (CEE 0.625 mg + placebo) ○ Dose, duration and timing of administration: two capsules per day
Outcomes	In those who were symptomatic at baseline: percentage of participants who reported any reduction in hot flush severity (Kupperman score) Endometrial thickness Endometrial proliferation Adverse events
Notes	Participants were recruited from a menopause clinic, but 18% of soy group and 26% of ET group were asymptomatic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer software
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind

Kaari 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Moderate dropout
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Khaodhiar 2008

Methods	Design: parallel-group Number of women screened: 235 recruited and 191 randomly assigned Number of dropouts: 49/191 (26%) dropped out, were lost to follow-up or were excluded (not clear which group they came from: 30 unable to comply with protocol or lost to follow-up, eight withdrew because they started taking other meds, two were withdrawn because they resumed menstruation, two were withdrawn because of abnormal liver function tests, two discontinued because of side effects, five did not complete their diaries) Number analysed: 142 Intention-to-treat analysis: no Power calculation: yes, 50 women per group for 80% power to detect differences in hot flush activity of 0.58 SD, average shift of 1.2 hot flushes/d or a hot flush score of 3 units/d Duration: 12 weeks Timing: not stated Location: medical centre in Harvard Medical School, Boston, USA Funding: Nichimo Co Ltd, Japan-manufacturer of daidzein-rich isoflavone aglycone extract
Participants	Inclusion criteria: postmenopausal, no menses for past six months, 38 to 60 years of age, between five and 15 hot flushes per day Exclusion criteria: active smoker; use of dietary supplements containing soy isoflavones, vitamin E, flaxseed or red clover; use of HT or any medication for hot flushes within past six weeks; BMI $\geq$ 40; history of breast, endometrial or cervical cancer; positive pregnancy test; history of undiagnosed vaginal bleeding, thromboembolic disease, cardiovascular disease, liver or kidney disease, diabetes mellitus or major illness Mean age, years: between 52 and 54 in the three groups Recruitment method: referring physicians at the medical centre and newspaper advertisements
Interventions	• Extract of isoflavones prepared from soy germ fermentation with Koji fungus, 40 mg/d (n = 48) • Soy extract (see above) 60 mg/d (n = 49) • Placebo (n = 45) (isoflavone quantity not known) ○ Dose, duration and timing of administration: one tablet per day in the morning for 12 weeks

Outcomes	Mean change from baseline to week 12 in frequency of hot flushes (daily diary) Severity of hot flushes (measured morning and evening on a scale of 1 to 4) (daily diary) Outcomes were measured as percentage change for both	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided on method of randomisation
Allocation concealment (selection bias)	Unclear risk	No details provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis-30 women withdrew from study as unable to comply with protocol or lost to follow-up (not clear from which group); eight withdrew because they started to take other medications or supplements, two women resumed menses after randomisation and were excluded, two women were withdrawn after randomisation because of abnormal liver function tests, two women in the 60-mg isoflavone group withdrew because of side effects and five women did not complete hot flush diaries and were excluded Number analysed: 142 had analysable data
Selective reporting (reporting bias)	Unclear risk	Insufficient data on adverse events and quality of life

Knight 1999

Methods	Design: parallel-group Number screened for inclusion: not stated Number randomly assigned: 37 initially. When one woman dropped out after randomisation and before commencing treatment, another was recruited to the same treatment Number dropped out: two in high-dose group withdrawn on GP advice Number lost to follow-up: Number analysed: 35 Intention-to-treat analysis: no Power calculation: not reported Duration: 12 weeks Location: hospital outpatient clinic, Sydney, Australia Funding: industry funded (Novogen, Australia)
Participants	Inclusion criteria: postmenopausal women (bilateral oophorectomy or amenorrhoea for least six months with typical symptoms of menopause, FSH > 40 IU/L), having at least three hot flushes daily, 40 to 65 years of age Exclusion criteria: HT use within previous six weeks, allergy to isoflavones, current bowel, liver or gallbladder disease, diabetes requiring medication, malignancy other than skin cancers, contraindications to HT use, vegetarians, regular soy product users, taking liver enzyme-inducing medications Age, years: high dose 51.1 (± 8.8), medium dose 54.5 (± 4.4), placebo 53.1 (± 2.5) Recruitment method: through university department of obstetrics and gynaecology
Interventions	• Phytoestrogen: isoflavones: one Promensil tablet plus three placebo tablets • Phytoestrogen: isoflavones: four Promensil tablets ○ Formulation: Each Promensil tablet contained 40 mg total isoflavones (genistein 4.0 mg, daidzein 3.5 mg and their methylated precursors biochanin 24.5 mg and formonetin 8.0 mg) • Placebo four tablets identical to active tablets ○ Dose, duration and timing of administration: four tablets daily (packed in individual sachets) for 12 weeks Participants advised not to alter their usual diet during the study
Outcomes	Menopausal symptoms: daily flush diary Quality of life: Greene Menopause Scale Compliance: pill counts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random number generator
Allocation concealment (selection bias)	Low risk	Randomisation performed remotely by external statistician

Knight 1999 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropout
Selective reporting (reporting bias)	High risk	Adverse events not reported

Knight 2001

Methods	Design: parallel-group Number screened for inclusion: not stated Number randomly assigned: 24 Number dropped out: three (from active arm-all disliked taste) Number lost to follow-up: one (from placebo arm) Number analysed: 20 Intention-to-treat analysis: no Power calculation: not stated Duration: 12 weeks Timing: not stated Location: Australia Funding: industry funded (Protein Technology Industries)
Participants	Inclusion criteria: postmenopausal women (bilateral oophorectomy or amenorrhoea for least six months with typical symptoms of menopause, FSH > 40 IU/L), having at least three hot flushes daily, 45 to 60 years of age Exclusion criteria: HT use within previous six weeks; allergy to isoflavones; current bowel, liver or gallbladder disease; diabetes requiring medication; malignancy other than skin cancers; contraindications to HT use; vegetarians; regular soy product users (> once a week), taking liver enzyme-inducing medications Age, years: Recruitment method: two university hospital obstetrics and gynaecology clinics
Interventions	• Phytoestrogen: isoflavones ○ Formulation: Take Care powder four scoops or 60 g in each sachet, containing total isoflavones 134.4 mg (genistein, daidzein, glycetein) • Placebo: isocaloric casein-based beverage packed in sachet ○ Dose, duration and timing of administration: one sachet per day made into a drink, for 12 weeks Participants advised not to alter their usual diet during the study

Knight 2001 (*Continued*)

Outcomes	Menopausal symptoms: flush count Quality of life: Greene Menopause Scale Compliance: sachet counts Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly permuted blocks of six, using computerised random number generator
Allocation concealment (selection bias)	Low risk	Randomisation performed remotely-external statistician
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Moderate dropout, which could influence findings-25% in active arm
Selective reporting (reporting bias)	High risk	Adverse events not reported

Kotsopoulos 2000

Methods	Design: parallel-group Number screened for inclusion: not stated Number randomly assigned: 94 Number dropped out: 19 (10 on active treatment, nine on placebo, because of adverse effects) Number lost to follow-up: none Number analysed: 73 (two excluded from analysis as FSH in normal range) Intention-to-treat analysis: no Power calculation: not stated Duration: three months Timing: not stated Location: Australia Funding: academic research grant

Kotsopoulos 2000 (*Continued*)

Participants	Inclusion criteria: 50 to 75 years of age, postmenopausal (12 months of amenorrhoea and FSH > 20 U/L) Exclusion criteria: taking antibiotics within three months before study, receiving HT during 12 months before study, smoker, vegetarian, ingesting phytoestrogens or soy-based products Mean age, years: 59 Recruitment method: subgroup of a larger trial
Interventions	• Phytoestrogen: isoflavones ○ Formulation: soy dietary supplements containing 118 mg isoflavones daily (daidzein, genistein, glycitein and their respective glycosides: 2.11 mg total isoflavones per g of protein or 1.72 mg aglycone per g of protein); in powder form for mixing into a drink • Placebo powder (casein) ○ Dose, duration and timing of administration: drinks drinks daily for three months
Outcomes	Menopausal symptoms: validated questionnaire to record psychological, vasomotor, musculoskeletal, genitourinary and other symptoms on 4-point scale. Completed at baseline and after treatment Compliance: returned sachet count Adverse effects: recorded adverse effects causing women to drop out
Notes	No requirement for vasomotor symptoms was given for eligibility for the study. 80% of participants had mild symptoms at baseline, and analyses were undertaken in this subgroup of women

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Levis 2011

Methods	Design: parallel-group Number randomly assigned: 248 Number dropped out: 11 in soy group (but they completed all study visits) and 12 in placebo group (but they completed all study visits) Number lost to follow-up: 23 in soy group (18 before 12 months, five between 12 and 24 months), 43 in placebo group (40 before 12 months and three between 12 and 24 months) Number analysed: 182 (99 in soy group and 83 in placebo group) Intention-to-treat analysis: no Power calculation: yes, 80% power to detect a 4% or greater difference in BMD of the lumbar spine, with the assumption that the control group will lose 4% to 5% of bone mass. Target total sample size was 306 with 15% attrition rate expected Duration: two years Timing: July 2004 to March 2009 Location: University of Miami Miller School of Medicine, South Florida, USA Funding: National Institute of Arthritis, Musculoskeletal and Skin Diseases
Participants	Inclusion: women 45 to 60 years of age, menopausal for longer than 12 months but less than five years; or absence of menses for six to 12 months and FSH > 40 IU/L Exclusion: osteoporotic fractures, a bone mineral density T score in the lumbar spine or total hip of < -2, BMI of 32 or higher, abnormal mammogram findings, cancer in previous 10 years (except skin cancer), taking bone active drugs, corticosteroids, or herbal products. Taking menopausal hormone therapy within six months before trial Mean age, years: 53 ± 3.3 in soy group; 52 ± 3.3 in placebo group Recruitment method: from South Florida area by direct mailings, posters and presentations to community organisations
Interventions	• Isoflavones 200 mg daily from soy protein (4 × 50-mg tablets) (n = 122). Each 200-mg dose contained 91 mg genistein, 103 mg daidzein • Placebo tablets (n = 126) Treatment for two years taken in the morning before breakfast. Additional calcium supplements were provided to participants as required. Followed up at baseline and at 12 and 24 months
Outcomes	Bone mineral density Bone collagen Menopausal symptoms Vaginal oestrogenisation Serum lipids Thyroid function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence in blocks of ten

Levis 2011 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and study personnel masked to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and study personnel masked to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 66 participants were lost to follow-up (26.6%)-18.8% from the soy group and 34.1% in the placebo group
Selective reporting (reporting bias)	Unclear risk	Quality of life was indicated as a secondary outcome in the protocol but was not reported in the 2011 paper and was not a primary outcome of this review. Not all of the exclusion criteria were listed in the paper

Lewis 2006

Methods	Randomisation method: separate site prepared randomisation codes Blinding: double Allocation concealment: adequate Design: parallel-group Number of women screened: 792 Number randomly assigned: 99 Number of dropouts: 12% (12/99): two in soy group (one could not accept Rx, one adverse event), five in flaxseed group (two could not accept Rx, one adverse event, one medical, one personal), five in placebo group (one could not accept Rx, one adverse event, two medical, one protocol violation) Number analysed: 87 Intention-to-treat analysis: no Power calculation: not reported Duration: 16 weeks Timing: not stated Location: Toronto and Calgary, Canada Funding: Canadian Institutes of Health Research
Participants	Inclusion criteria: 45 to 60 years old, natural menopause with last menses in previous one to eight years, Menoquol vasomotor score > 3.0 Exclusion criteria: medical or surgical menopause; inflammatory bowel disease; malabsorption syndrome; uncontrolled thyroid disorder; known allergy or intolerance to muffin ingredients or any serious and active medical or social condition likely to affect quality of life during the study; no ET in past three months; no phytoestrogens, steroids or antibiotics in past month Mean age, years: 53

Lewis 2006 (*Continued*)

	Recruitment method: mailings to family practice, to previous participants of menopause workshops and to gynaecologists and family physicians
Interventions	• Flaxseed muffins (50 mg/d lignans) • Soy muffins (42 mg/d isoflavones) • Placebo muffins (low levels of lignans and no isoflavones) Dose, duration and timing of administration: one muffin per day
Outcomes	Primary: Menoquol vasomotor score (0 to 6) Secondary: number of flushes per day Severity of flushes (0 to 6) Gastrointestinal side effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Separate site prepared the randomisation codes
Allocation concealment (selection bias)	Low risk	Separate site ensured concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Moderate dropout-not balanced between groups
Selective reporting (reporting bias)	Unclear risk	Inadequate data on side effects

Nahas 2007

Methods	Design: parallel-group Number randomly assigned: 80 Number dropped out: four (two in each group-reasons given) Number analysed: 76 Intention-to-treat analysis: no Power calculation: not reported Duration: 10 months Timing: not stated Location: Climacterium Outpatient Service of the Department of Gynecology in Sao Paolo University Funding: Ativus Farmaceutica Brazil and Fundacao Lucentis de Apoio a Cultura, Ensino, Pesquisa e Extensao
Participants	Inclusion: postmenopausal, 45 years of age or older with good overall health, spontaneous amenorrhoea for at least 12 months, FSH level > 40 mIU/mL, average of five or more vasomotor symptoms per day Exclusion: strict vegetarian; high-fiber or high-soy diet; history of breast cancer, endometrial carcinoma, cardiovascular disease, thromboembolic disorders, undiagnosed vaginal bleeding, chronic alcoholism or chronic gastrointestinal diseases. Not on hormonal therapy or phytoestrogens for previous six months Mean age, years: 55.7 Recruitment method: from outpatient menopause clinic at university
Interventions	• Soy isoflavones extract (n = 40) 250 mg (Glycine max AT) corresponding to 100 mg/d of isoflavones, administered twice daily in capsules containing 125 mg soy extract plus 50 mg of isoflavones each (50% genistein and 35% daidzein) • Placebo (n = 40): two lactose tablets daily Followed up for 10 months with evaluations at baseline and at four, seven and 10 months
Outcomes	Kupperman Menopausal Index Daily diary of hot flushes Symptoms Body mass index Vaginal cytology (maturational value, pH) Transvaginal ultrasonography (endometrial thickness) Adverse events Mammography Lipids, plasma levels of isoflavones
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomly assigned to one of two groups'. Computer randomised

Nahas 2007 (*Continued*)

Allocation concealment (selection bias)	Low risk	Centralised computerised randomisation using software by a statistician who was unaware of the study protocol
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Isoflavone group: Two withdrew because of flatulance and epigastralgia; control group: two withdrew because of depression and family problems and not wishing to continue
Selective reporting (reporting bias)	Low risk	Original protocol was not viewed, but outcomes listed in the methods section of the paper were reported in the results

Penotti 2003

Methods	Design: parallel-group Number randomly assigned: 62 Number dropped out: 13 did not complete six months of treatment (six in active group: one because of diarrhoea and five because of persistent hot flushes; seven in placebo group because of persistent hot flushes) Number analysed: 49 at six months Number lost to follow-up: nil Intention-to-treat analysis: no Power calculation: not stated Duration: six months Timing: not stated Location: outpatient menopause clinics, Italy Funding: not stated
Participants	Inclusion criteria: postmenopausal for at least six months; 45 to 60 years of age; FSH and 17-B E2 levels within postmenopausal range; experiencing at least seven hot flushes daily (evaluated by participant diary completed over 15 days prerandomisation); computerised bone mineralometry score greater than -2.5 at level of lumbar spine Exclusion criteria: serious disease such as hypertension, heart disease, diabetes, renal disease, peripheral vascular disease Age, years: 52.5 (49 to 58) Recruitment method: from outpatient menopause clinic at gynaecology department

Penotti 2003 (*Continued*)

Interventions	• Phytoestrogen: isoflavone tablets ○ Formulation: 36 mg soy-derived isoflavones (5.5 mg genistein, 18 mg daidzein, 12.5 mg glyciteine) and 48-mg soy saponine per tablet • Placebo: 0.5 g talc and 0.5 mg microcrystalline cellulose ○ Dose, duration and timing of administration: two tablets daily, one before lunch and one before dinner, for six months
Outcomes	Menopausal symptoms: mean (=/-SD) daily number of hot flushes per month
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers list, balanced in blocks of 10
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout
Selective reporting (reporting bias)	High risk	Adverse events not measured

Radhakrishnan 2009

Methods	Design: parallel-group Number randomly assigned: 100 Number dropped out: 15 (six in soy group and nine in control group) Number analysed: 85 Intention-to-treat analysis: no Power calculation: yes, 7% decrease in cholesterol with 80% power and 20% withdrawal rate Duration: six months Timing: not stated Location: Department of Obstetrics and Gynecology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India Funding: Dupont Protein Technology International-manufactured soy and protein supplements
Participants	Inclusion: last menstruation at least 12 months previous or six weeks since bilateral oophorectomy; FSH level 40 mIU/mL; unwillingness to take or intolerance to HT; not currently taking lipid-lowering drugs, antidiabetic medications or herbal supplements; discontinued HT more than three months previously Exclusion: unexplained vaginal bleeding, hypertension, diabetes, liver dysfunction, renal or cardiac disease, active thromboembolic disease, deep vein thrombosis, coronary artery disease, cerebrovascular accident or past history of thromboembolic disease associated with oestrogen use; present or past oestrogen-dependent malignancy such as breast or endometrial carcinomas, known peanut/legume allergy Mean age, years: 48.07 ± 5.44 in the soy group; 49.71 ± 7.27 in the placebo group Recruitment method: from outpatient clinic
Interventions	• Soy group (n = 50): sachets containing 25 g of isoflavone-rich soy protein isolate with 75 mg of isoflavones in powder form, sweetened with aspartase with mild vanilla flavour • Placebo group (n = 50): sachets containing 25 mg of milk protein, which looked and tasted identical to the soy supplement ○ Both sachets contained equal amounts of elemental calcium (900 mg) and other trace elements and vitamins ○ Followed up at baseline and at three and six months
Outcomes	Kupperman Menopausal Index Karyopyknotic Index Maturation value Endometrial thickness Laboratory investigations Bone mineral density Acceptability of treatment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Radhakrishnan 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomly assigned using computer-generated randomised numbers in blocks of 10
Allocation concealment (selection bias)	Low risk	Precoded sachets were provided by DUPONT Protein Technology International
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15 stopped the trial prematurely during the initial two months: six in the study group and nine in the control group. Main reasons were gastrointestinal side effects and food intolerance. Three cases in each group were lost to follow-up
Selective reporting (reporting bias)	Low risk	Original protocol not viewed. Outcomes listed in the methods sections were reported in the results

Sammartino 2003

Methods	Design: cross-over (no washout) Number of women screened: not stated Number randomly assigned: 70 Number of dropouts: seven (three in genistein group: two no compliance, one personal; four in calcium group: three no compliance, one personal) Number analysed: 63 Intention-to-treat analysis: no Power calculation: not reported Duration: one year Timing: not stated Location: menopause clinic at university department in Naples, Italy Funding: not stated
Participants	Inclusion criteria: minimum number of seven moderate to severe hot flushes (including night sweats)/d (defined), postmenopausal (hormones in the menopausal range: FSH > 40 IU/L; oestradiol < 20 pg/mL); no menses for 12 months Exclusion criteria: neoplastic, metabolic and infectious diseases; concomitant use of any drug; BMI > 30; past or concomitant use of HRT or any other drug used for menopausal symptoms; endometrial thickness > 5 mm or endometrial abnormalities Mean age, years: 52 in both groups

Sammartino 2003 (*Continued*)

	Recruitment method: menopause clinic
Interventions	• Genistein • Calcium supplements ○ Dose, duration and timing of administration: 36 mg/d (two tablets) genistein and 3.3 g calcium phosphate + 8 mg/d cholecalciferol for 12 cycles of 28 days
Outcomes	Endometrial thickness and adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study not blinded, but lack of blinding unlikely to affect measurement of the main outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study not blinded, but lack of blinding unlikely to affect measurement of the main outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced between groups and unlikely to affect results
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

St Germain 2001

Methods	Design: parallel-group Number screened for inclusion: 1,000 (of whom 102 passed first screening. Subsequently, 22 found to be ineligible, six could not tolerate treatment, one died, one had a family member die, two had medical conditions preventing continuance, one was non-compliant) Number randomly assigned: 69 Number dropped out: nil Number lost to follow-up: nil Number analysed: 69 Intention-to-treat analysis: no Power calculation: not stated Duration: 24 weeks Timing: not stated Location: Human Metabolic Unit, Iowa State University, USA Funding: academic grants and industry donations of muffin ingredients and laboratory tests
Participants	Inclusion criteria: perimenopausal women, one or both ovaries remaining, FSH at least 30 IU/L, BMI 20 to 31,experiencing at least 10 hot flushes or night sweats per week, within 12 months of last menstrual cycle Exclusion criteria: smokers, any chronic disease such as known cardiovascular disease or osteoporosis, long-term medication use, taking HT at time of study or during the previous 12 months Age, years: median 50 (42 to 62) Recruitment method: not reported
Interventions	• High phytoestrogen: isoflavone ○ Formulation: 40 g daily of isoflavone-rich soy protein (80.4 mg/d aglycone components) plus daily vitamin/mineral supplement • Low phytoestrogen: isoflavone ○ Formulation: 40 g daily of isoflavone-poor soy protein (4.4 mg/d aglycone products) plus daily vitamin/mineral supplement • Placebo (whey protein) plus daily vitamin/mineral supplement ○ Dose, duration and timing of administration: one jumbo muffin daily, containing half the daily dose of protein, plus protein powder to be consumed as food or drink. Muffin and flour to be used as a meal replacement-not as a supplement Participants advised to avoid food items containing soy isoflavones and not to take their own supplements
Outcomes	Menopausal symptoms: Menopausal Index of hot flushes, night sweats and other symptoms Measures of change in quality of life: Compliance: self-reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

St Germain 2001 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appears that all randomly assigned participants were analysed
Selective reporting (reporting bias)	High risk	Adverse effects not reported

Tice 2003

Methods	Design: parallel-group, active arms versus placebo Number screened: 1,191 (principal reasons for ineligibility: too few hot flushes (251), not interested (216) and medical conditions/medications (192)) Number randomly assigned: 252 Number dropped out: six (two taking Promensil (one too busy, one no improvement), two taking Rimostil (one nauseated, one on physician's advice), two taking placebo (one feared possible placebo, one too busy)) Number lost to follow-up: Number analysed: 252 Intention-to-treat analysis: yes (also per-protocol analysis) Power calculation: 90% power to detect at least a 15% greater reduction in hot flush frequency in the active arm compared with placebo; 25% placebo effect anticipated Duration: 12 weeks Timing: November 1999 to March 2001 Location: three US academic clinical research sites Funding: industry (Novogen Inc)
Participants	Inclusion criteria: women 45 to 60 years of age, experiencing at least 35 hot flushes/wk, FSH level 30 mIU/mL, documented bilateral oophorectomy or at least two consecutive months of amenorrhoea before enrolment, with at least six months of amenorrhoea during the year before entry Exclusion criteria: vegetarian, ate soy products > once a week, taking medications affecting isoflavone absorption or hormonal preparations during previous three months, significant gastrointestinal disease, > two alcoholic beverages per day, allergic to red clover, consumed < 80% of expected study tablets during the two-week placebo run-in Age, years: 52.3 (SD 2.8 to 3.4 in different arms) Recruitment method: newspaper and radio advertising, flyers, directed mailings

Tice 2003 (*Continued*)

Interventions	• Phytoestrogen: isoflavones ○ Formulation: Promensil tablets, containing average of 41 mg total isoflavones per tablet (range 37 to 43 mg), with higher proportion of biochanin A and genistein than Rimostil • Phytoestrogen: isoflavones ○ Formulation: Rimostil tablets, containing average of 28.6 mg of total isoflavones per tablet (range 25.6 to 31.4 mg) with higher proportions of formononetin and daidzein than Promensil • Placebo: contained < 0.04 mg total isoflavones per tablet ○ Dose, duration and timing of administration: two tablets once daily for 12 weeks
Outcomes	Menopausal symptoms: daily diary cards for recording hot flushes and night sweats Quality of life: Greene Climacteric Scale Compliance: pill count Adverse effects: assessed at follow-up, specific method unclear
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated in random blocks of six, stratified by centre
Allocation concealment (selection bias)	Low risk	Allocation schedule maintained remotely, at pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind: participants and researchers
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind: participants and researchers
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants analysed
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Upmalis 2000

Methods	Design: parallel-group Number screened for inclusion: not stated Number randomly assigned: 177 Number dropped out: 40 (21 in active arm: one did not take supplement, nine ineligible, 11 violated protocol, one had urinary tract infection; 18 in placebo arm: one did not take supplement, four ineligible, 13 violated protocol) Number lost to follow-up: 15 (nine in active group, six in placebo group) discontinued before week 12 Number analysed: 122 (for efficacy) Intention-to-treat analysis: no Power calculation: not stated Duration: 12 weeks Timing: not stated Location: 15 outpatient sites in USA Funding: industry funded (Advanced Care Products)
Participants	Inclusion criteria: postmenopausal women experiencing average of at least five hot flushes per day, over 50 years of age, in good health, weight within ± 35% range for BMI, FSH at least 40 mIU/mL, oestradiol level 25 pg/mL or less, no menses for at least six months, discontinued HT at least 60 days before study entry Exclusion criteria: history of breast cancer, hyperplasia, endometrial carcinoma or cervical neoplasia, positive pregnancy test, undiagnosed abnormal vaginal bleeding, bilateral oophorectomy or hysterectomy, thromboembolic disorders, cardiovascular disease, liver disease, chronic alcoholism, medication hypersensitivity, allergy to dietary supplement ingredients, uncontrolled addiction, severe depression, acute systemic infection or abnormal laboratory values Age, years: mean 55 Recruitment method: not stated
Interventions	• Phytoestrogen: isoflavone ○ Formulation: soy isoflavone extract tablet (50 mg genistein and daidzein daily, approximately 25 g of each) • Placebo ○ Dose, duration and timing of administration: two tablets at bedtime for 12 weeks Intake of other soy products and dietary supplements restricted during the study
Outcomes	Menopausal symptoms: daily diary card for number and severity of hot flushes and night sweats; 3-point scale for severity Compliance: check of unused medication at week six and week 12 Endometrial thickness Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Upmalis 2000 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Very high rate of dropout
Selective reporting (reporting bias)	High risk	Quality of life prespecified as an outcome in the methods section but not reported on in the results section

van de Weijer 2002

Methods	Design: parallel-group Number screened for inclusion: 42 (six ineligible, 24 did not return to clinic, tqo recorded inadequate data in diary during screening phase) Number randomly assigned: 30 Number dropped out: six (three in each group, mainly because of lack of efficacy) Number lost to follow-up: nil Number analysed: 26 Intention-to-treat analysis: no Power calculation: not stated Duration: 12 weeks Timing: not stated Location: university clinic, The Netherlands Funding: industry funded (Novogen Ltd, Australia)
Participants	Inclusion criteria: postmenopausal women 49 to 65 years of age with at least 12 months' amenorrhoea, average of > five hot flushes daily Exclusion criteria: HT or antibiotics within 12 weeks of study entry, undiagnosed vaginal bleeding, active liver or renal disease, history of allergy to foodstuffs, cardiovascular disease or thromboembolism Age, years: active arm 52.5 (SD 5.2), placebo 54.2 (SD 7.4) Recruitment method: not stated
Interventions	• Phytoestrogen: isoflavones ○ Formulation: Promensil 40-mg tablets (daidzein, genistein, biochanin, formononetin) • Placebo tablets

	○ Dose, duration and timing of administration: two tablets each morning for 12 weeks Participants given list of foods to avoid, including legumes and isoflavone supplements
Outcomes	Menopausal symptoms: daily diary for number of hot flushes, list of 21 symptoms to score on 4-point scale Measures of change in quality of life
Notes	Baseline hot flush count = average count of last seven days from four-week screening phase

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blank envelopes containing allocation shuffled, numbered consecutively, then given consecutively to participants
Allocation concealment (selection bias)	Low risk	Participants took envelope to pharmacy, where number in envelope was matched with batch number of medication
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and researchers blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both participants and researchers blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition > 10% and unbalanced between groups
Selective reporting (reporting bias)	High risk	Adverse events not reported

Ye 2012

Methods	Design: parallel-group Number of women randomly assigned: 90 Number of women analysed: 84 (two withdrew in low-dose group; four withdrew in high-dose group because of adverse events, traffic accident and emigration) Intention-to-treat analysis: yes-last observation carried forward used for missing data Power calculation: not stated Duration: six months Timing: not stated Location: Sun Yat-sen University, Guangzhou, China Funding: Guangzhou Sciences and Technology Bureau, Department of Health of Guangdong Province and extract provided by pharmaceutical company
Participants	Inclusion criteria: Chinese, between 45 and 60 years of age, within the five-year period after natural menopause (12 months since last menstrual cycle), BMI < 30 kg/m^2, FSH > 30 IU/L, Kupperman Climacteric Scale score > 15 Exclusion criteria: detectable diseases such as chronic diseases of the kidney, liver, heart or endocrine system; cancer; diabetes; taking medications known to affect bone health or lipid metabolism Mean age of participants, years: 52 to 53 Recruitment method: advertisements in local media
Interventions	• Low-dose isoflavones 84 mg daily • High-dose isoflavones 126 mg daily • Placebo (starch) ○ Three identical capsules taken morning and evening after meals. Participants were asked to stop taking other dietary supplements. Food frequency questionnaire administered at baseline and after treatment to check on dietary intake
Outcomes	• Hot flushes • Kupperman Index • Serum lipids
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation (SPSS)
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not applicable as hot flushes assessed by participants

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for dropouts and missing data imputed by last observation carried forward
Selective reporting (reporting bias)	Unclear risk	Adverse events not measured

Aglycone: unconjugated parent form of isoflavone.
Dropouts: did not complete treatment as per protocol; reason for dropping out and/or outcome reported.
Intention-to-treat analysis: all randomly assigned women included in analysis, in the groups to which they were assigned.
Greene Climacteric Scale: measures quality of life in women experiencing symptoms attributed to menopause (11 psychological symptoms, seven somatic, two vasomotor, one sexual, on a 4-point scale ranging from none to severe).
Kupperman Index: numerical conversion index of 11 menopausal symptoms on a 4-point scale from no complaints to severe.
Per-protocol analysis: analysis according to treatment actually received.
Lost to follow-up: women whose reasons for withdrawing and/or outcomes are unknown or are not reported.
Abbreviations
SDS: Self Depression Scale.
BMI: Body mass index.
SMI: Simplified Menopausal Index.
HT: Hormone therapy.
ET: Oestrogen therapy.
FSH: Follicle-stimulating hormone.
LMP: Last menstrual period.
MRS II: Menopause Rating Scale II.
LOCF: Last observation carried forward.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albert 2001	No control group
Albertazzi 2005	Duration of trial only 6 weeks.
Aly 2009	Used Black Cohosh
Amato 2005	Low prevalence of menopausal symptoms
Atkinson 2003	About half of the women in each group had hot flushes but this was not a requirement for participation in the study
Bai 2007	Used Black Cohosh
Baird 1995	The study assessed oestrogenicity of dietary soy but did not assess any of the primary outcomes in this review, frequency or severity of vasomotor symptoms

(*Continued*)

Cancellieri 2007	The soy intervention included other plant extracts. It was not possible to separate out the effects of phytoestrogens alone
Carranza-Lira 2001	Only one month of treatment
Caserta 2005	Not clear if women symptomatic at baseline and did not state that the two groups were randomised
Chandeying 2007	No details on the dosage of phytoestrogens in the product and both groups received some form of oestrogen therapy
Chandeying 2007a	Dose comparison study
Chiechi 2003	Analyses effects of soy-rich diet on vaginal epithelium of asymptomatic postmenopausal women. Symptomatic women excluded
Cianci 2012	Combination treatment: isoflavones and berberine combined
Cohn 2009	Not clear if intervention is a phytoestrogen
Colacurci 2004	There is no evidence that the control group was randomised.
Dodin 2005	Women had very mild symptoms of hot flushes at baseline - women requesting treatment for hot flushes unlikely to agree to be randomised to the trial - only a subset of women analysed
Duffy 2003	Women had low incidence of symptoms - aim of study to assess effects on cognitive function
Duncan 1999	No outcomes of interest - outcomes were physiological rather than clinical
Ehsanpour 2012	Trial duration only 8 weeks
Erkkola 2010	Only treated for 8 weeks in first arm of crossover
Hale 2001	Women did not have vasomotor symptoms at baseline
Harding 1996	Treatment only given for 2 months
Hochanadel 1999	Only cognitive outcomes assessed; no flush outcomes or endometrial safety outcomes
Ishiwata 2009	A proportion of women were premenopausal at baseline (39/134) - not clear if they were symptomatic at baseline
Jenks 2012	Treatment for only 8 weeks
Jou 2005	Treatment for only 6 weeks.
Katz 2007	Treatment was only for 6 weeks

(*Continued*)

Kok 2005	Participants were asymptomatic and effects measured on quality of life, not vasomotor symptoms
Kolarov 2001	Does not appear to be randomised.
Krzysztof 2007	Study not randomised
Lamlertkittikul 2004	This was a dose finding study with no control group
Manonai 2006	No evidence that women had vasomotor symptoms at baseline.
Manonai 2008	Dosage study
Mittal 2011	Not clear if symptomatic at baseline - cannot separate out the effects of isoflavone on vasomotor symptoms
Murkies 1995	It was not possible to determine the level of phytoestrogens in the experimental intervention
Nahas 2004	38% of the participants had breast cancer.
Nasrin 2011	Women were treated for only 6 weeks
Newton 2006	The soy intervention was not standardised and was included with another preparation, a multibotannical tablet, so it was difficult to separate out the individual effects of soy alone. Also, women were given only dietary soy counseling and there was no measurement of their actual soy consumption
Nikander 2005	Women had a history of breast cancer
Palacios 2010	Women were asymptomatic at the start of the trial and no control group - designed to assess endometrial safety
Pedro 2012	No evidence that the participants had hot flushes at baseline
Pop 2008	This was not a randomised trial. The women were randomly stratified based on equol production to placebo or soy group
Pruthi 2012	Treated for only 6 weeks
Quaas 2012	No evidence of hot flushes at baseline in the participants
Quella 2000	Participants had breast cancer.
Rotem 2007	Combination treatment with black cohosh, dong quai, milk thistle, red clover, American ginseng and chaste-tree berry
Russo 2003	The intervention was a composite of phytoestrogens and black cohosh. It was not possible to determine whether effects solely due to phytoestrogens

(*Continued*)

Sammartino 2006	The intervention was a combination of isoflavones, lignans and cimicifugua racemosa. The effects of phytoestrogens alone could not be separated out
Scambia 2000	Co-intervention of HT. First part of the trial, soy vs placebo, only for 6 weeks
Schwen 2010	Animal model
Secreto 2003	About 10% of the participants had breast cancer
Steinberg 2011	Women were not symptomatic
Uesugi 2004	The participants in the study were a mixture of asymptomatic and symptomatic women. Data were not available separately just for symptomatic women. Treatment also only for 4 weeks
Unfer 2004	Participants were asymptomatic.
van Patten 2002	Women had breast cancer
Verhoeven 2005	Intervention was a combination of phytoestrogens and black cohosh. It was not possible to separate out the effects of phytoestrogens alone
Virojchaiwong 2011	Head to head study
Washburn 1999	Treatment given for only 6 weeks.
Woo 2003	Low prevalence of menopausal vasomotor symptoms
Xue 2004	Outcome was a composite of menopausal symptoms. Effects on vasomotor symptoms could not be separated
Yang 2012	No control group - comparison of 2 different strengths of soy extract

Characteristics of studies awaiting assessment *[ordered by study ID]*

Agrawal 2005

Methods	Randomised placebo-controlled trial in menopause clinic of a hospital in India
Participants	Not reported
Interventions	• Phytoestrogens given as a supplement in the form of capsules • Placebo
Outcomes	Quality of life, hot flushes, night sweats, urinary outcomes, psychological symptoms, sexual desire, dyspareunia
Notes	Author contacted and awaiting reply

Baker 2011

Methods	Double-blind placebo-controlled randomised study (abstract)
Participants	Symptomatic perimenopausal and postmenopausal women (n = 51)
Interventions	• Licogen (liquorice extract) 100 mg (n = 20) • Licogen 50 mg (n = 21) • Placebo (n = 10)
Outcomes	Number and severity of hot flushes, nighttime wakenings, vaginal dryness, endometrial thickness
Notes	Abstract published in 2011; author contacted

Garcia-Martin 2012

Methods	Parallel-group double-blind randomised trial
Participants	Postmenopausal Spanish women (n = 99)
Interventions	• Milk product with soy isoflavones (50 mg/d) • "Product control"-assume that this is placebo, as the authors state that the trial is double-blind
Outcomes	• Menopausal symptoms • Vasomotor symptoms • Quality of life (Cervantes scale) • Bone metabolism • Bone mass
Notes	Author contacted for full text of the publication

Mucowski 2013

Methods	Randomised placebo-controlled trial
Participants	Menopausal women (n = 110), secondary analysis of WISH trial in women who reported at least seven weekly hot flushes of any level at baseline
Interventions	• Isoflavone soy protein (ISP) supplementation • Placebo
Outcomes	Composite flushing score (frequency times intensity)
Notes	Secondary analysis of larger trial. Author contacted for data

Nahidi 2009

Methods	Randomised double-blind clinical trial
Participants	Menopausal women referred to healthcare centres (n = 68)
Interventions	• Licorice root extract (n = 34) • Placebo (n = 34)
Outcomes	Number of nocturnal hot flushes
Notes	Author contacted

Paixao 2005

Methods	Double-blind randomised study, duration 12 months
Participants	Menopausal women (n = 34) with age ranging from 38 to 54 years
Interventions	• Genistein 100 mg/d (n = 17) • Placebo (n = 17)
Outcomes	Climacteric symptoms (as measured by Kupperman's Menopausal Index), endometrial thickness (as measured by vaginal echography)
Notes	

Sekhavat 2012

Methods	Not reported
Participants	Not reported
Interventions	Not reported
Outcomes	Not reported
Notes	Awaiting translation to determine whether study meets eligibility criteria

Stanosz 2006

Methods	Randomised study, duration 12 months
Participants	Women in the early postmenopausal period (n = 71)
Interventions	• Two tablets of Soyfem twice a day, 400 mg extract, 104 mg genistein (n = 22) • One tablet of Soyfem, one tablet of placebo twice a day, 200 mg extract, 52 mg genistein (n = 26) • Two tablets of placebo twice a day

Outcomes	Kupperman Index
Notes	Not clear whether vasomotor symptoms alone measured

DATA AND ANALYSES

Comparison 1. Promensil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hot flushes (number/d)	5	300	Mean Difference (IV, Random, 95% CI)	-0.93 [-1.95, 0.10]
1.1 40 mg/d	3	105	Mean Difference (IV, Random, 95% CI)	-1.45 [-2.26, -0.64]
1.2 80 mg/d	2	195	Mean Difference (IV, Random, 95% CI)	-0.76 [-3.28, 1.77]
2 Change in frequency of hot flushes (% reduction)	2	199	Mean Difference (IV, Random, 95% CI)	20.15 [-12.08, 52.38]
3 Improvement in hot flush severity rate	1	27	Risk Ratio (M-H, Fixed, 95% CI)	17.06 [1.10, 264.52]
4 Change in vasomotor score from baseline to end of study/vasomotor severity-Kupperman subscale	1	165	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.29, 0.32]
5 Endometrial thickness (mm) after treatment	1	51	Mean Difference (IV, Fixed, 95% CI)	0.06 [-4.94, 5.06]
6 Adverse event rates	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.65, 1.40]
7 Incidence of specific adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Cold or upper respiratory tract infection (URTI)	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.30, 1.42]
7.2 Headache	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.17, 1.27]
7.3 Myalgia	1	169	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.58, 3.62]
7.4 Nausea	1	169	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.26, 3.91]
7.5 Arthralgia	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.27, 2.66]
7.6 Diarrhoea	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.94]
7.7 Vaginal spotting	1	169	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.26, 8.85]

Analysis 1.1. Comparison 1 Promensil versus placebo, Outcome 1 Incidence of hot flushes (number/d).

Review: Phytoestrogens for menopausal vasomotor symptoms

Comparison: 1 Promensil versus placebo

Outcome: 1 Incidence of hot flushes (number/d)

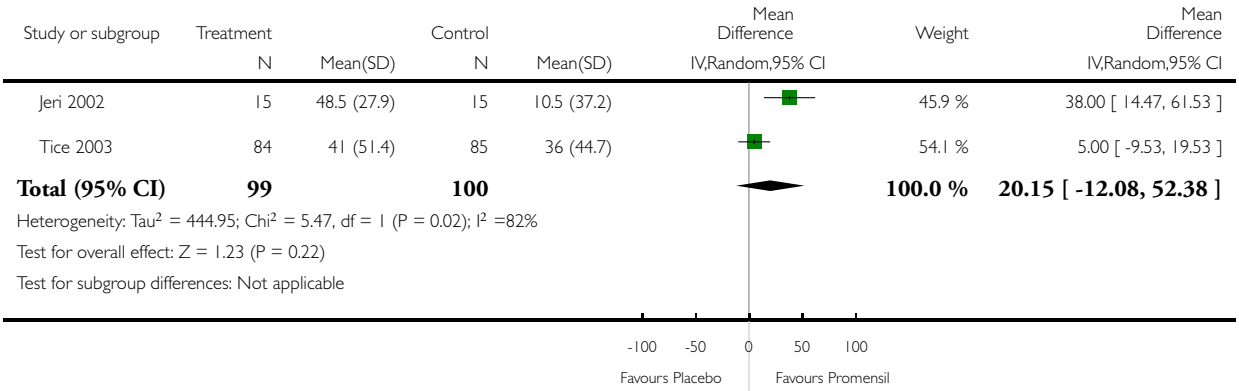
Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 40 mg/d							
Baber 1999	25	4.83 (16.8)	26	3.95 (13.4)		1.5 %	0.88 [-7.48, 9.24]
Jeri 2002	15	3.6 (1.16)	15	5.1 (1.16)		47.9 %	-1.50 [-2.33, -0.67]
Knight 1999	12	4.9 (4.8)	12	5.8 (4.5)		6.8 %	-0.90 [-4.62, 2.82]
Subtotal (95% CI)	**52**		**53**			**56.2 %**	**-1.45 [-2.26, -0.64]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.40$, df = 2 (P = 0.82); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.52 (P = 0.00043)							
2 80 mg/d							
Tice 2003	84	5.1 (4.21)	85	5 (3.53)		36.5 %	0.10 [-1.07, 1.27]
van de Weijer 2002	15	3.35 (3)	11	6.04 (5.5)		7.3 %	-2.69 [-6.28, 0.90]
Subtotal (95% CI)	**99**		**96**			**43.8 %**	**-0.76 [-3.28, 1.77]**
Heterogeneity: $Tau^2 = 2.04$; $Chi^2 = 2.10$, df = 1 (P = 0.15); $I^2 = 52\%$							
Test for overall effect: Z = 0.59 (P = 0.56)							
Total (95% CI)	**151**		**149**			**100.0 %**	**-0.93 [-1.95, 0.10]**
Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 5.83$, df = 4 (P = 0.21); $I^2 = 31\%$							
Test for overall effect: Z = 1.77 (P = 0.076)							
Test for subgroup differences: $Chi^2 = 0.26$, df = 1 (P = 0.61), $I^2 = 0.0\%$							

Analysis 1.2. Comparison 1 Promensil versus placebo, Outcome 2 Change in frequency of hot flushes (% reduction).

Review: Phytoestrogens for menopausal vasomotor symptoms

Comparison: 1 Promensil versus placebo

Outcome: 2 Change in frequency of hot flushes (% reduction)

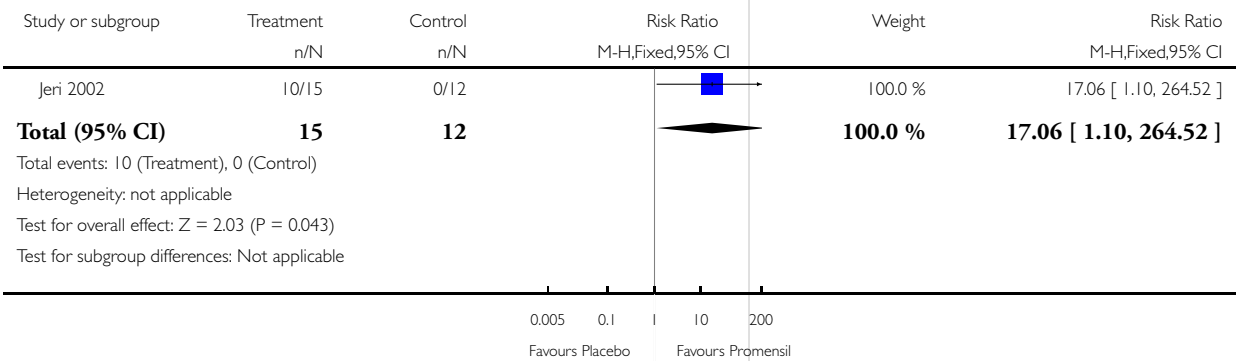


Analysis 1.3. Comparison 1 Promensil versus placebo, Outcome 3 Improvement in hot flush severity rate.

Review: Phytoestrogens for menopausal vasomotor symptoms

Comparison: 1 Promensil versus placebo

Outcome: 3 Improvement in hot flush severity rate

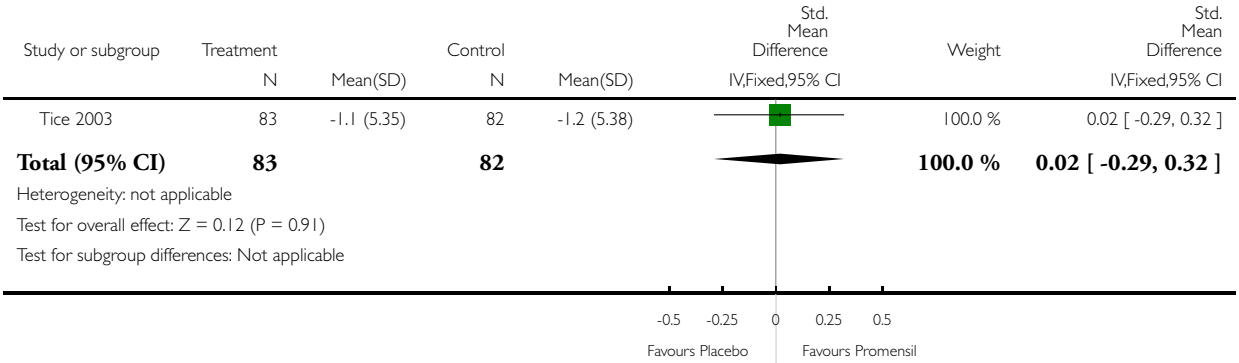


Analysis 1.4. Comparison 1 Promensil versus placebo, Outcome 4 Change in vasomotor score from baseline to end of study/vasomotor severity-Kupperman subscale.

Review: Phytoestrogens for menopausal vasomotor symptoms

Comparison: 1 Promensil versus placebo

Outcome: 4 Change in vasomotor score from baseline to end of study/vasomotor severity—Kupperman subscale

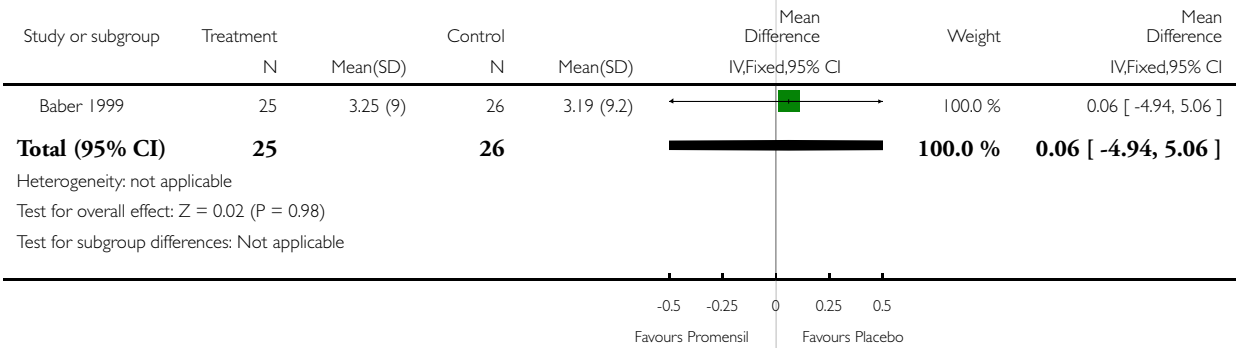


Analysis 1.5. Comparison 1 Promensil versus placebo, Outcome 5 Endometrial thickness (mm) after treatment.

Review: Phytoestrogens for menopausal vasomotor symptoms

Comparison: 1 Promensil versus placebo

Outcome: 5 Endometrial thickness (mm) after treatment



Analysis 1.6. Comparison 1 Promensil versus placebo, Outcome 6 Adverse event rates.

Review: Phytoestrogens for menopausal vasomotor symptoms

Comparison: 1 Promensil versus placebo

Outcome: 6 Adverse event rates

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tice 2003	31/84	33/85		100.0 %	0.95 [0.65, 1.40]
Total (95% CI)	**84**	**85**		**100.0 %**	**0.95 [0.65, 1.40]**
Total events: 31 (Treatment), 33 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.80)					
Test for subgroup differences: Not applicable					

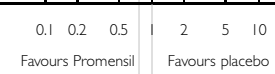
Analysis 1.7. Comparison 1 Promensil versus placebo, Outcome 7 Incidence of specific adverse events.

Review: Phytoestrogens for menopausal vasomotor symptoms

Comparison: 1 Promensil versus placebo

Outcome: 7 Incidence of specific adverse events

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cold or upper respiratory tract infection (URTI)					
Tice 2003	9/84	14/85		100.0 %	0.65 [0.30, 1.42]
Subtotal (95% CI)	**84**	**85**		**100.0 %**	**0.65 [0.30, 1.42]**
Total events: 9 (Treatment), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.08 (P = 0.28)					
2 Headache					
Tice 2003	5/84	11/85		100.0 %	0.46 [0.17, 1.27]
Subtotal (95% CI)	**84**	**85**		**100.0 %**	**0.46 [0.17, 1.27]**
Total events: 5 (Treatment), 11 (Control)					



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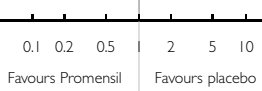
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 1.50 (P = 0.13)					
3 Myalgia					
Tice 2003	10/84	7/85		100.0 %	1.45 [0.58, 3.62]
Subtotal (95% CI)	**84**	**85**		**100.0 %**	**1.45 [0.58, 3.62]**
Total events: 10 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
4 Nausea					
Tice 2003	4/84	4/85		100.0 %	1.01 [0.26, 3.91]
Subtotal (95% CI)	**84**	**85**		**100.0 %**	**1.01 [0.26, 3.91]**
Total events: 4 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.99)					
5 Arthralgia					
Tice 2003	5/84	6/85		100.0 %	0.84 [0.27, 2.66]
Subtotal (95% CI)	**84**	**85**		**100.0 %**	**0.84 [0.27, 2.66]**
Total events: 5 (Treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.29 (P = 0.77)					
6 Diarrhoea					
Tice 2003	2/84	3/85		100.0 %	0.67 [0.12, 3.94]
Subtotal (95% CI)	**84**	**85**		**100.0 %**	**0.67 [0.12, 3.94]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
7 Vaginal spotting					
Tice 2003	3/84	2/85		100.0 %	1.52 [0.26, 8.85]
Subtotal (95% CI)	**84**	**85**		**100.0 %**	**1.52 [0.26, 8.85]**
Total events: 3 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.64)					



ADDITIONAL TABLES

Table 1. Summary of findings: efficacy outcomes

Trial	No.	Intervention	Comparison	Duration	Efficacy outcomes	Results (between-group comparison)	Overall risk of bias
SOY DIETARY SUPPLEMENTS							
Albertazzi 1998	104	60 g soy powder (76 mg isoflavones)	Placebo (60 g casein)	12 weeks	Number of flushes/d after treatment; percentage decrease in number of flushes	At end of study, significant difference between placebo and soy: -1.59 (-1.95 to -1.2; P < 0.01), representing mean reduction of 1.6 flushes/d in soy group compared with placebo. 45% reduction in flushes with soy versus 30% reduction with placebo (P < 0.01)	Unclear
Balk 2002	27	Soy and corn flour cereal (100 mg/d isoflavones)	Placebo (wheat cereal)	24 weeks	Hot flush and night sweat symptom score after Rx (1 to 4)	NS all outcomes	High
Brzezinski 1997	145	Phytoestrogen-enriched diet (individualised by dietician) (isoflavone amount not given)	Control-regular diet (avoiding phytoestrogens)	12 weeks	MSQ hot flush severity reduction subscore (0 to 3)	Greater reduction with PE-rich diet (P = 0.004; no CI given)	High
Burke 2003	241	(1) soy drink 1 (42 mg/d isoflavones); (2) soy drink 2 (58 mg/d isoflavones)	Placebo (soy drink with isoflavones removed)	2 years	Number and severity of flushes/sweats per day after Rx (symp-	NS all outcomes	High

Table 1. Summary of findings: efficacy outcomes (*Continued*)

					tom diary); also subgroup analysis in women with 4+ symptoms/d at baseline		
Carmigiani 2010	60	(1) oestradiol 1 mg + 0.5 mg norethisterone acetate; (2) dietary soy supplementation (90 mg isoflavone) in powder form + placebo tablet	Placebo (identical powder and placebo tablets)	16 weeks	Somatic score (hot flushes, heart discomfort, sleeping problems and muscle and joint problems) on the Menopause Rating Scale	Reduction in somatic symptoms was -45.6% with HT and -49.8% with dietary soy compared with -28.6% with placebo	Low
Cheng 2007	60	(1) isoflavones 60 mg daily in fruit drink	Placebo (oatmeal drink)	12 weeks	Hot flush and night sweat scores	Significant reduction in hot flush score with isoflavones compared with placebo	High
Dalais 1998	52	(1) soy diet (53 mg/d isoflavones); (2) linseed diet (high in isoflavones-quantity not given)	Placebo (wheat diet (low isoflavones))	12 weeks + 12 weeks	Percentage decrease in number of hot flushes	NS: 22% reduction with soy; 41% reduction with linseed; 51% reduction with wheat	High
Hanachi 2008	37	(1) soy milk product (12.5 g soy protein with 13 mg genistein and 4.13 mg daidzein); (2) soy milk product + exercise	Control	12 weeks	Hot flush score on Kupperman Index	Hot flushes significantly improved with both soy interventions compared with control	High
Knight 2001	24	Soy powder 60 g/d for beverage (134.4 mg/d isoflavones)	Placebo (casein powder for beverage)	12 weeks	Number of flushes per week after Rx	NS: 29 flushes/wk in soy group; 46 flushes/wk in placebo group (reduction in	High

Table 1. Summary of findings: efficacy outcomes (*Continued*)

						both from baseline)	
Kotsopoulos 2000	94	Soy powder for beverage (118 mg/d isoflavones)	Placebo (casein powder for beverage)	12 weeks	Hot flush symptom score (severity) (0 to 3) after Rx	NS: 0.77 score with soy; 0.83 score with placebo	High
Lewis 2006	99	(1) soy flour muffins (42 mg/d isoflavones); (2) flaxseed muffins (50 mg/d lignans)	Placebo (wheat flour muffins (low lignans and no isoflavones))	16 weeks	Menoquol vasomotor score; number of flushes per day; severity of flushes (1 to 7 scale) after Rx	NS: all outcomes	Unclear
Radhakrishnan 2009	100	(1) soy sachets (25 mg isoflavone soy protein isolate containing 75 mg isoflavones in powder form)	Placebo powder	6 months	Number of daily hot flushes; karyopyknotic index; maturation value; endometrial thickness; acceptability of treatment; adverse events	Significantly greater proportion of women had reduction in hot flushes with soy (84%) when compared with placebo (60%) but no significant difference in hot flush score between groups	Unclear
St Germain 2001	69	(1) soy protein + (80.4 mg/d isoflavones); (2) soy protein - (4.4 mg/d isoflavones) in muffins and powder for cooking	Placebo (whey protein)	24 weeks	Percentage of participants perceiving a decrease in (1) frequency, (2) duration and (3) severity of flushes; number of flushes per week after Rx; number of sweats per week after Rx	NS	High
SOY EXTRACT							
Bicca 2004	75	Standardised soy ex-	Placebo capsules	25 weeks	Greene Vasomotor Sub-	NS: Greene Vasomotor Scale;	Low

Table 1. Summary of findings: efficacy outcomes (*Continued*)

		tract (33 mg/d isoflavones)			scale (intensity); percentage who experienced a decrease in frequency of flushes and sweats from baseline	74% with soy versus 43% with placebo had decrease in number of hot flushes (P = 0.007); 68% with soy versus 46% with placebo had decrease in number of night sweats (P = 0.049). NS: severity of symptoms	
Campagnoli 2005	36	Standardised soy extract (soy select) (60 mg/d isoflavones)	Placebo capsules	12 weeks + 12 weeks	Number of flushes per week after Rx	NS	High
Faure 2002	75	Standardised soy extract capsules (70 mg/d isoflavones)	Placebo capsules	16 weeks	Percentage decrease in flushes per day; percentage of 'responders' (participants who had reduction of at least 50%)	61% decrease with soy versus 21% reduction with placebo (P value not reported); 66% of soy group were responders versus 34% in placebo group (P < 0.005). Repeated measures analysis confirmed the soy-placebo treatment effect	Unclear
Han 2002	80	Soy capsules (100 mg/d isoflavones)	Placebo capsules	16 weeks	Kupperman Vasomotor Symptom Score (severity)	Vasomotor score 8.2 in soy group versus 9.9 in placebo group (P < 0.01)	High
Jou 2008	96	Soy germ extract powder (3 g) twice per day (135 mg isoflavones - 1 g = 10.9	Placebo (roasted wheat powder)	6 months	Hot flushes as measured by Kupperman Index	Reduction in hot flush score of 79% in equol producers, 35% in non-equol pro-	High

Table 1. Summary of findings: efficacy outcomes (*Continued*)

		mg daidzein and 2.85 mg genistein) in equol producers and non-producers				ducers and 78% in placebo group. Results from equol producers significantly different from placebo by repeated measures analysis	
Kaari 2006	79	Soy extract capsules (S40/Ach-1) (120 mg/d isoflavones)	Oestrogen + placebo capsules	24 weeks	Percentage of participants reporting reduction (subgroup)	NS	High
Khaodhiar 2008	147	Soy extract capsule (isoflavone quantity not known) (1) 40 mg/d; (2) 60 mg/d	Placebo capsules	12 weeks	Percentage reduction in frequency of hot flushes (from daily diary), percentage reduction in severity of hot flushes (daily diary)	52% and 51% reduction in hot flush frequency in 40-mg and 60-mg soy groups at 12 weeks compared with 39% reduction with placebo (NS). When both treatment groups were combined, an average reduction of 52% was seen in hot flush frequency per day in women taking soy compared with women taking placebo (P = 0.048)	Unclear
Levis 2011	248	Isoflavone tablets 200 mg from soy protein (each tablet 91 mg genistein, 103 mg	Placebo tablets	2 years	Menopausal symptoms (hot flushes and night sweats) were secondary outcomes	Soy isoflavone group: 48.4% had hot flushes; 31.7% in placebo group had hot	Unclear

Table 1. Summary of findings: efficacy outcomes (*Continued*)

		daidzein)				flushes	
Nahas 2007	80	Soy extract (isoflavones 100 mg)	Placebo capsules	10 months	Change in daily hot flush number; change in hot flush severity score	Significant reduction from baseline in number of daily hot flushes in both groups and significantly greater in soy versus placebo. Hot flush severity significantly reduced in soy extract group when compared with placebo	Low
Penotti 2003	62	Soy tablets (72 mg/d isoflavones)	Placebo tablets	24 weeks	Number of flushes per day after Rx	NS	High
Upmalis 2000	177	Standardised soy extract tablets (50 mg/d of genistein and daidzin)	Placebo tablets	12 weeks	Percentage change in flush severity per week; percentage change in flush frequency per week; percentage change in sweat frequency per week	34% change in severity with soy versus 21% change in severity with placebo (P = 0.01); NS for percentage change in frequency (P = 0.078 repeated measures analysis); NS for change in reduction of night sweats	High
Ye 2012	90	Soy germ isoflavone extract powder in capsules in two doses (84 mg and 126 mg of isoflavones)	Placebo capsules	24 weeks	Hot flush frequency and percentage change per week	44.3% and 48.5% change in hot flushes from baseline in the 84-mg and 126-mg isoflavone groups, respectively, compared with 27.8% change in placebo group	Unclear

Table 1. Summary of findings: efficacy outcomes (*Continued*)

						(P < 0.01)	
RED CLOVER EXTRACTS							
Baber 1999	51	Promensil (standardised red clover extract) (40 mg/d isoflavones)	Placebo tablets	12 weeks + 12 weeks	Number of flushes per day after Rx; percentage flush reduction	NS	High
Del Giorno 2010	120	*Trifolium pratense* (red clover) 40 mg	Placebo	12 months	Vasomotor symptoms (Kupperman Index)	NS between groups	High
Geller 2009	67	(1) 0.625 mg CEE + 2.5 mg MPA; (2) Black cohosh (128 mg/d); (3) Red clover (398 mg/d including 120 mg isoflavones)	Placebo	12 months	Vasomotor symptoms (hot flushes and night sweats); frequency of hot flushes; intensity of hot flushes	NS: black cohosh and red clover versus placebo	Unclear
Hidalgo 2005	60	Red clover supplement capsules (80 mg/d isoflavones)	Placebo capsules	12 weeks + 12 weeks	Kupperman Index score for hot flushes and sweats (severity) (expressed as percentage)	Hot flushes: 15% with red clover versus 98% with placebo; night sweats: 30% with red clover versus 93% with placebo; P value not given	High
Imhof 2006	109	Red clover extract capsules (80 mg/d isoflavones)	Placebo capsules	90 days + 7 days washout + 90 days	Hot flush daily frequency, night sweats daily frequency Mean percentage decrease in hot flushes and night sweats	Mean (SD) daily frequency (hot flushes) in red clover group (3.1 (3.5)); in placebo group (10.1 (5.5)) Mean (SD)	Unclear

Table 1. Summary of findings: efficacy outcomes (*Continued*)

						daily frequency (night sweats) in red clover group (1.5 (2.1)); in placebo group (5.0 (2.6)) Mean percentage decrease in hot flushes in red clover group 73.5%; in placebo group 8.2% Mean percentage decrease in night sweats in red clover group 72.2%; in placebo group 0.9% All differences significant (P = 0.0001)	
Jeri 2002	30	Promensil (standardised red clover extract) (40 mg/d isoflavones)	Placebo tablets	16 weeks	Percentage reduction in number of flushes per day; severity of flushes per day (scale)	Frequency: 49% reduction with red clover versus 11% reduction with placebo (P < 0.001); severity: reduction from 2.53 to 1.33 with red clover versus no reduction with placebo (P < 0.001)	High
Knight 1999	37	Promensil (standardised red clover extract) (40 mg/d isoflavones)	Placebo tablets	12 weeks	Number of flushes per day	NS	Low
Tice 2003	252	(1) Promensil (standardised red clover ex-	Placebo tablets	12 weeks	Number of flushes per day; per-	Number of flushes per day NS; percentage	Low

Table 1. Summary of findings: efficacy outcomes (*Continued*)

		tract) (82 mg/d isoflavones-two tablets); (2) Rimostil (standardised red clover extract) (57 mg/d isoflavones-two tablets)			centage reduction in flushes; rate of reduction over time	reductions NS; Promensil had faster reduction over time versus placebo (P = 0.03)	
van de Weijer 2002	30	Promensil (standardised red clover extract) (80 mg/d isoflavones-two tablets)	Placebo tablets	12 weeks	Number of flushes per day; median percentage change in number of flushes	3.4 flushes/d with Promensil versus 6 flushes/d with placebo (P value not reported); 44% reduction with Promensil versus 0% reduction with placebo (P = 0.01; variation not reported)	High
GENISTEIN							
Crisafulli 2004	90	(1) genistein extract (54 mg/d isoflavones); (2) continuous HT (17B-ostradiol 1 mg/d + norethisterone acetate)	Placebo tablets	1 year	Percentage change in number of flushes per day	24% reduction with genistein when compared with placebo (P < 0.01); 30% reduction with HT when compared with genistein (P < 0.05)	Unclear
D'Anna 2007	247	Genistein extract twice per day (each tablet containing 27 mg total isoflavone)	Placebo twice per day	2 years	Number and severity of hot flushes	Significant reduction in frequency (56.4%) and severity (37.5%) of hot flushes compared with placebo	Unclear
Evans 2011	84	Genistein (geniVida) 30 mg once daily	Placebo	12 weeks	Percentage change in number of daily hot	Significant reduction in frequency (51.2%	Low

Table 1. Summary of findings: efficacy outcomes (*Continued*)

					flushes; duration and severity of daily hot flushes	vs 27.2%) and duration of hot flushes (12 minutes/ d vs 23 minutes/ d) at the end of treatment compared with placebo. NS severity of hot flushes	
Ferrari 2009	180	Soy isoflavone extract (80 mg) with high dose of genistein (60 mg)	Placebo	12 weeks	Change in daily frequency of hot flushes; improvement (as assessed by investigator)	Significant reduction in number of hot flushes in genistein group (41.2%) when compared with placebo (29.3%); improvement in genistein group 56.7% and in placebo group 53.1% (P value not reported)	Low
OTHER PHYTOESTROGENS							
Aso 2012	160	Natural S-(-)equol supplement twice per day (5.0 mg equol, 1.2 mg daidzein, 1.4 mg genistein)	Placebo	12 weeks	Change in frequency and severity of hot flushes	Significant reduction in frequency of hot flushes with equol supplement (62.8%) compared with placebo (23.6%) in women with more than three hot flushes per day. Significant improvement in severity of hot flushes	High

Table 1. Summary of findings: efficacy outcomes (*Continued*)

						with equol supplement (61.2%) when compared with placebo (45%)	
Colli 2012	90	Flaxseed extract (1 g/d) (at least 100 mg secoisolariciresinol diglucoside (SDG)) and flaxseed meal (90 g/d) (at least 270 mg SDG)	Placebo (1 g/d collagen)	24 weeks	Intensity of hot flush score (Kupperman Index)	In both flaxseed groups, hot flush intensity score was reduced significantly from baseline, but no significant difference was seen in the placebo group. Comparison of groups by ANOVA showed no significant difference between groups at end of study	High
Dalais 1998	52	See above for results in the flaxseed arm					High
Heger 2006	110	Extract of ERr 731, an extract of the roots of *Rheum rhaponticum*	Placebo	12 weeks	Changes in number and severity of hot flushes	Number and frequency of hot flushes significantly reduced with ERr 731 compared with placebo ($P < 0.0001$) (average of 5.5 fewer per day compared with 0 fewer per day)	Unclear
Heyerick 2006	67	(1) Hop extract 1 (100 μg 8-prenylnaringenin); (2) Hop extract 2 (250 μg 8-prenylnarin-	Placebo capsules	12 weeks	Kupperman hot flush score (severity)	NS at the end of the study period	High

Table 1. Summary of findings: efficacy outcomes (*Continued*)

		genin) (Menohop)					
Lewis 2006	99	See above for results in the flaxseed arm					Unclear

CEE: conjugated equine oestrogen.
MPA: medroxyprogesterone acetate.

Table 2. Summary of findings: safety outcomes

Trial	No.	Intervention	Comparison	Duration	Safety outcomes	Results (between-group comparison)	Overall risk of bias
SOY DIETARY SUPPLEMENTS							
Albertazzi 1998	104	60 g soy powder (76 mg isoflavones)	Placebo (60 g casein)	12 weeks	Adverse events	NS	Unclear
Balk 2002	27	Soy and corn flour cereal (100 mg/d isoflavones)	Placebo (wheat cereal)	24 weeks	Endometrial stimulation; adverse events	Endometrial stimulation: NS (all participants had atrophic endometrium) . Adverse events: NS	High
Carmigiani 2010	60	(1) oestradiol 1 mg + 0.5 mg norethisterone acetate; (2) dietary soy supplementation (90 mg isoflavone) in powder form + placebo tablet	Placebo (identical powder and placebo tablets)	16 weeks	Endometrial thickness, vaginal maturation value; side effects	NS: side effects, endometrial thickness or vaginal maturation value with soy compared with placebo	Low
Cheng 2007	60	(1) isoflavones 60 mg daily in fruit drink	Placebo (oatmeal drink)	12 weeks	Endometrial thickness	No difference in endometrial thickness	High

Table 2. Summary of findings: safety outcomes (*Continued*)

Dalais 1998	52	(1) soy diet (53 mg/d isoflavones); (2) linseed diet (high in isoflavones-quantity not given)	Placebo (wheat diet-low isoflavones)	12 weeks + 12 weeks	Vaginal maturation index (percentage increase from baseline)	Increase of 103% with soy diet (P = 0.03), 6% increase with linseed (NS), 11% increase with placebo (NS)	High
Knight 2001	24	Soy powder 60 g/d for beverage (134.4 mg/d isoflavones)	Placebo (casein powder for beverage)	12 weeks	Adverse events; vaginal maturation index	Total adverse events: 75% with soy versus 17% with placebo (P < 0.001); vaginal maturation index NS	High
Kotsopoulos 2000	94	Soy powder for beverage (118 mg/d isoflavones)	Placebo (casein powder for beverage)	12 weeks	Adverse events	Total adverse events: NS	High
Radhakrishnan 2009	100	(1) Soy sachets (25 mg isoflavone soy protein isolate containing 75 mg isoflavones in powder form)	Placebo powder	6 months	Karyopyknotic index; maturation value; endometrial thickness; adverse events	No difference in vaginal cytology, endometrial thickness or adverse events	Unclear
SOY EXTRACTS							
Bicca 2004	75	Standardised soy extract (33 mg/d isoflavones)	Placebo capsules	25 weeks	Vaginal maturation index; vaginal pH (percentage with improvement)	Maturation: NS; pH: 21% with soy versus 11% with placebo had improvement in pH (P = 0.008)	Low
Campagnoli 2005	36	Standardised soy extract (Soyselect) (60 mg/d isoflavones)	Placebo capsules	12 weeks + 12 weeks	Vaginal maturation index	NS	High

Table 2. Summary of findings: safety outcomes (*Continued*)

Faure 2002	75	Standardised soy extract capsules (7 mg/d isoflavones)	Placebo capsules	16 weeks	Adverse events	NS	Unclear
Han 2002	80	Soy capsules (100 mg/d isoflavones)	Placebo capsules	16 weeks	Endometrial thickness	NS	High
Kaari 2006	79	Soy extract capsules (S40/Ach-1) (120 mg/d isoflavones)	Oestrogen + placebo capsules	24 weeks	Vaginal pH; vaginal maturation index; endometrial thickness; endometrial stimulation; adverse events	pH: 5.5 in soy group versus 4.8 in HT group (P = 0.0012); maturation index: significant difference in intermediate and superficial cell frequency in ET group when compared with soy group (P value not given); endometrial thickness: 5.9 mm in HT group versus 3.0 mm in soy group (significant; P value not given); non-atrophic endometrium: 54% in HT group versus 88% in soy group (P < 0.01); adverse events: 17% genital bleeding in HT group versus 0% in soy group	High
Khaodhiar 2008	207	Soy extract capsules (isoflavone quantity not known)-two different doses:	Placebo	12 weeks	Adverse events	Very few events reported-no group comparisons reported	Unclear

Table 2. Summary of findings: safety outcomes (*Continued*)

		(1) 40 mg/d; (2) 60 mg/d					
Levis 2011	248	Isoflavone tablets 200 mg from soy protein (each tablet 91 mg genistein, 103 mg daidzein)	Placebo tablets	2 years	Adverse events	7/99 had fractures in soy group compared with 1/83 in placebo group (P = 0.03)	Unclear
Nahas 2007	80	Soy extract (isoflavones 100 mg)	Placebo capsules	10 months	Median endometrial thickness (mm); maturation value; vaginal pH; adverse events	2.4 mm in intervention group and 2.8 mm in placebo group (NS) NS in vaginal outcomes and adverse events	Low
Penotti 2003	62	Soy tablets (72 mg/d isoflavones)	Placebo tablets	24 weeks	Endometrial thickness	NS	High
Upmalis 2000	177	Standardised soy extract tablets (50 mg/d of genistin and daidzin)	Placebo tablets	12 weeks	Adverse effects; vaginal pH; vaginal maturation index; endometrial thickness	Adverse events: 34% (30/89) of soy group reported 70 events versus 45% (39/86) in placebo group reported 79 events (no P value); pH: NS; maturation index NS; endometrial thickness: NS	High
RED CLOVER EXTRACTS							
Baber 1999	51	Promensil	Placebo	12 weeks + 12 weeks	Endometrial thickness	NS	High
Geller 2009	67	(1) 0.625 mg CEE + 2.5 mg MPA;	Placebo	12 months	Endometrial thickness;	NS	Unclear

Table 2. Summary of findings: safety outcomes (*Continued*)

		(2) black cohosh (128 mg/d); (3) red clover (398 mg/d including 120 mg isoflavones)			adverse events		
Hidalgo 2005	60	Red clover supplement capsules (80 mg/d isoflavones)	Placebo	12 weeks + 12 weeks	Vaginal cytology (karyopyknotic index, cornification index, maturation index)	Significant changes ($P < 0.05$) in all indexes when compared with placebo	High
Imhof 2006	113	Red clover extract capsules (80 mg/d isoflavones)	Placebo	12 weeks + 12 weeks	Endometrial thickness	Significant decrease in thickness with red clover (15%) but not with placebo (placebo values not given) ($P < 0.001$) No side effects reported	Unclear
Tice 2003	252	(1) Promensil (standardised red clover extract) (82 mg/d isoflavones- two tablets); (2) Rimostil (standardised red clover extract) (57 mg/d isoflavones-two tablets)	Placebo	12 weeks	Adverse events	NS	Low
GENISTEIN EXTRACTS							
Crisafulli 2004	90	(1) genistein extract (54 mg/d isoflavones); (2) continuous HT (17B-oestradiol 1 mg/d + norethis-	Placebo	1 year	Endometrial thickness	NS	Unclear

Table 2. Summary of findings: safety outcomes (*Continued*)

		terone acetate)					
D'Anna 2007	247	Genistein extract twice per day (each tablet containing 27 mg total isoflavone)	Placebo twice per day	2 years	Endometrial thickness; vaginal maturation values	NS	Unclear
Evans 2011	84	Genistein (geniVida) 30 mg once daily	Placebo	12 weeks	Endometrial thickness; adverse events	NS	Low
Ferrari 2009	180	Soy isoflavone extract (80 mg) with high dose of genistein (60 mg)	Placebo	12 weeks	Adverse events	NS	Low
Sammartino 2003	70	Genistein extract tablets (quantity of isoflavones not given)	Placebo tablets	1 year	Endometrial thickness	NS	Unclear
OTHER PHYTOESTROGENS							
Colli 2012	90	Flaxseed extract (1 g per day) (at least 100 mg secoisolariciresinol diglucoside (SDG)) and flaxseed meal (90 g per day) (at least 270 mg SDG)	Placebo (1 g per day collagen)	24 weeks	Endometrial thickness; vaginal epithelial maturation value	NS	High
Dalais 1998	52	See above for results in the linseed arm					High
Heger 2006	110	Extract of ERr 731, an extract of the roots of *Rheum rhaponticum*	Placebo	12 weeks	Endometrial thickness; adverse events	NS	Unclear

Table 2. Summary of findings: safety outcomes (*Continued*)

Sammartino 2003	70	Genistein extract tablets (quantity of isoflavones not given)	Placebo tablets	1 year	Endometrial thickness	NS	Unclear

HT: Hormone therapy.

Table 3. Summary of findings: acceptability outcomes

Trial	No.	Intervention	Comparison	Duration	Outcomes	Results (between-group comparison)
Albertazzi 1998	104	60 g soy powder (76 mg/d isoflavones)	Placebo	12 weeks	Withdrawal due to adverse events	20% in soy group versus 23% in placebo group (P value not reported)
Ferrari 2009	180	Soy isoflavone extract (80 mg) with high dose of genistein (60 mg)	Placebo	12 weeks	Satisfaction rates	79. 1% in genistein group; 69.1% in placebo group (P value not reported)
Heger 2006	110	Extract of ERr 731, an extract of the roots of *Rheum rhaponticum*	Placebo	12 weeks	Satisfaction rates	63% in ERr 731 group satisfied at end of treatment; 32% in placebo group (P value not reported)
Knight 2001	24	Soy powder 60 g/d for beverage (134.4 mg/d isoflavones)	Placebo	12 weeks	Withdrawal due to adverse events	25% in soy group versus 8% in placebo group (P value not reported)
Kotsopoulos 2000	94	Soy powder for beverage (118 mg/d isoflavones)	Placebo	12 weeks	Withdrawal due to adverse events or inability to tolerate treatment	20% in soy group versus 18% in placebo group (P value not given)
Radhakrishnan 2009	100	Soy sachets (25 mg isoflavone soy protein isolate containing 75 mg isoflavones in powder form)	Placebo powder	6 months	Acceptability of treatment according to taste, odor or bulk of preparation	Not reported

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp perimenopause/ or exp postmenopause/ (17644)
2 postmenopaus$.ti,ab,sh. (41580)
3 menopaus$.ti,ab,sh. (43511)
4 exp Climacteric/ or exp Hot Flashes/ or exp Menopause/ (46568)
5 hot flash$.ti,ab. (1560)
6 hot flush$.ti,ab. (1646)
7 climacteric.ti,ab. (3594)
8 (vagina$ adj3 atroph$).ti,ab,sh. (586)
9 (vagina$ adj3 dry$).ti,ab. (645)
10 endometri$.ti,ab. (62890)
11 or/1-10 (133776)
12 Phytoestrogens/ (2493)
13 phytoestrogen$.ti,ab. (2979)
14 Soy Foods/ (813)
15 soy$.ti,ab. (35598)
16 exp isoflavones/ or coumestrol/ or genistein/ or pterocarpans/ or rotenone/ (13154)
17 linseed.mp. or Flax/ (2037)
18 isoflavon$.ti,ab. (5734)
19 red clover.ti,ab. (715)
20 daidzein.ti,ab. (2323)
21 promensil.ti,ab. (8)
22 or/12-21 (50378)
23 11 and 22 (2078)
24 randomized controlled trial.pt. (337111)
25 controlled clinical trial.pt. (85195)
26 randomized.ab. (252126)
27 placebo.tw. (143456)
28 clinical trials as topic.sh. (162463)
29 randomly.ab. (184559)
30 trial.ti. (108477)
31 (crossover or cross-over or cross over).tw. (54671)
32 or/24-31 (825664)
33 exp animals/ not humans.sh. (3782187)
34 32 not 33 (761678)
35 23 and 34 (686)
36 2012$.ed. (638938)
37 35 and 36 (43)

Appendix 2. EMBASE search strategy

1 exp “menopause and climacterium”/ or climacterium/ or early menopause/ or menopause/ or postmenopause/ (76520)
2 postmenopaus$.ti,ab. (47787)
3 menopaus$.ti,ab. (43440)
4 climacter$.ti,ab. (4494)
5 exp Hot Flush/ (9977)
6 hot flush$.ti,ab. (2262)
7 hot flash$.ti,ab. (2066)
8 (vagina$ adj3 atroph$).ti,ab,sh. (777)
9 (vagina$ adj3 dry$).ti,ab,sh. (1100)

10 endometri$.ti,ab. (75307)
11 or/1-10 (176874)
12 exp PHYTOESTROGEN/ (4474)
13 phytoestrogen$.ti,ab. (3724)
14 plant estrogen$.ti,ab. (69)
15 Daidzein/ or Isoflavone Derivative/ or Genistein/ or Soybean Oil/ or Soybean/ or Isoflavone/ or Soybean Protein/ or soy$.mp. (57048)
16 COUMESTROL DERIVATIVE/ or COUMESTROL/ (662)
17 coumestrol.ti,ab. (404)
18 pterocarpan$.ti,ab,sh. (274)
19 rotenone$.ti,ab,sh. (5229)
20 linseed.ti,ab,sh. (1785)
21 red clover.ti,ab,sh. (947)
22 daidzein.ti,ab,sh. (4250)
23 promensil.ti,ab,sh. (14)
24 or/12-23 (66860)
25 11 and 24 (3465)
26 Clinical Trial/ (871161)
27 Randomized Controlled Trial/ (328650)
28 exp randomization/ (59349)
29 Single Blind Procedure/ (16360)
30 Double Blind Procedure/ (110736)
31 Crossover Procedure/ (34922)
32 Placebo/ (204401)
33 Randomi?ed controlled trial$.tw. (78497)
34 Rct.tw. (9931)
35 random allocation.tw. (1183)
36 randomly allocated.tw. (17608)
37 allocated randomly.tw. (1829)
38 (allocated adj2 random).tw. (711)
39 Single blind$.tw. (12516)
40 Double blind$.tw. (130405)
41 ((treble or triple) adj blind$).tw. (280)
42 placebo$.tw. (178872)
43 prospective study/ (213060)
44 or/26-43 (1272542)
45 case study/ (16909)
46 case report.tw. (230790)
47 abstract report/ or letter/ (843460)
48 or/45-47 (1086430)
49 44 not 48 (1237229)
50 25 and 49 (1414)
51 limit 50 to yr="2012 -Current" (45)

Appendix 3. PsycINFO search strategy

1 exp menopause/ (2681)
2 postmenopaus$.tw. (1757)
3 menopaus$.tw. (3373)
4 perimenopaus$.tw. (440)
5 climacteric.tw. (392)
6 hot flash$.tw. (268)
7 hot flush$.tw. (152)
8 (vagina$ adj3 atroph$).tw. (26)
9 (vagina$ adj3 dry$).tw. (99)
10 or/1-9 (4865)
11 Phytoestrogens.tw. (58)
12 soy.tw. (217)
13 linseed.tw. (8)
14 isoflavon$.tw. (96)
15 red clover.tw. (6)
16 daidzein.tw. (28)
17 promensil.tw. (0)
18 or/11-17 (312)
19 10 and 18 (60)
20 limit 19 to yr="2012 -Current" (5)

Appendix 4. AMED search strategy

1 exp climacteric/ or exp menopause/ or exp postmenopause/ (499)
2 postmenopaus$.tw. (374)
3 menopaus$.tw. (657)
4 exp Climacteric/ (499)
5 hot flash$.tw. (47)
6 hot flush$.tw. (33)
7 climacteric.tw. (49)
8 (vagina$ adj3 atroph$).tw. (2)
9 (vagina$ adj3 dry$).tw. (10)
10 or/1-9 (890)
11 exp Phytoestrogens/ (54)
12 phytoestrogen$.tw. (132)
13 Soy Foods/ (12)
14 soy$.tw. (226)
15 exp isoflavones/ (96)
16 linseed.tw. (7)
17 isoflavon$.tw. (278)
18 red clover.tw. (14)
19 daidzein.tw. (53)
20 promensil.tw. (0)
21 or/11-20 (514)
22 10 and 21 (68)
23 limit 22 to yr="2012 -Current" (1)

Appendix 5. CENTRAL search strategy

1 exp perimenopause/ or exp postmenopause/ (3249)
2 postmenopaus$.ti,ab,sh. (7655)
3 menopaus$.ti,ab,sh. (4117)
4 exp Climacteric/ or exp Hot Flashes/ or exp Menopause/ (5212)
5 hot flash$.ti,ab. (325)
6 hot flush$.ti,ab. (570)
7 climacteric.ti,ab. (573)
8 (vagina$ adj3 atroph$).ti,ab,sh. (113)
9 (vagina$ adj3 dry$).ti,ab. (116)
10 endometri$.ti,ab. (3122)
11 or/1-10 (13074)
12 Phytoestrogens/ (148)
13 phytoestrogen$.ti,ab. (171)
14 Soy Foods/ (67)
15 soy$.ti,ab. (1349)
16 exp isoflavones/ or coumestrol/ or genistein/ or pterocarpans/ or rotenone/ (468)
17 linseed.mp. or Flax/ (111)
18 isoflavon$.ti,ab. (514)
19 red clover.ti,ab. (35)
20 daidzein.ti,ab. (139)
21 promensil.ti,ab. (7)
22 or/12-21 (1716)
23 11 and 22 (516)
24 limit 23 to yr="2007 -Current" (174)

Appendix 6. MDSG search strategy

Keywords CONTAINS "menopausal"or"*Menopause"or"perimenopause"or"perimenopausal"or "Postmenopausal"or "postmenopause"or"climacteric "or "vasomotor"or"hot flashes"or "hot flushes"or"vaginal atrophy"or "vaginal dryness"or Title CONTAINS "menopausal"or"*Menopause"or"perimenopause"or"perimenopausal"or "Postmenopausal"or "postmenopause"or"climacteric "or "vasomotor"or"hot flashes"or "hot flushes"or"vaginal atrophy"or "vaginal dryness"
AND
Keywords CONTAINS "Phyto-Female complex" or"phytoestrogen"or "phytoestrogens" or"phytosterols"or "soy" or"soy-protein diet" or"soy-nut diet" or"soybean"or "soybeans"or "soyfem preparation" or"soymilk" or"isoflavones" or"isoflavonoids" or"red clover"or "daidzein"or "promensil" or Title CONTAINS "Phyto-Female complex" or"phytoestrogen"or "phytoestrogens" or"phytosterols"or "soy" or"soy-protein diet" or"soy-nut diet" or"soybean"or "soybeans"or "soyfem preparation" or"soymilk" or"isoflavones" or"isoflavonoids" or"red clover"or "daidzein"or "promensil"

WHAT'S NEW

Last assessed as up-to-date: 30 July 2013.

Date	Event	Description
31 October 2013	New citation required and conclusions have changed	Fourteen new trials added in the 2013 update of the review (two of which were longer follow-ups of previously included trials). Three previously included trials were ex-

(*Continued*)

		cluded in the 2013 update because additional information indicated that the women did not have troublesome hot flushes at baseline. Conclusions changed: Genistein extracts appeared to offer a benefit for hot flushes, but confirmation through more research is needed
31 October 2013	New search has been performed	New studies added and review conclusions changed.

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 4, 2007

Date	Event	Description
14 May 2008	Amended	Converted to new review format.
27 July 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Anne Lethaby registered the title; undertook searches, selection of studies, data extraction, quality assessment and data entry; and wrote the review.

Julie Brown undertook searches, selection of studies, data extraction, contact with authors and quality assessment and commented on the final version of the review.

Jane Marjoribanks undertook selection of studies, data extraction, quality assessment and preparation of tables and commented on the final version of the review.

Fredi Kronenberg undertook selection of studies, data extraction and quality assessment and commented on both the protocol and the final review.

Helen Roberts provided clinical input and commented on the final version of the review.

John Eden commented on the final version of the review.

DECLARATIONS OF INTEREST

Anne Lethaby provided advice and suggestions to the author of the unpublished Brazilian study (Bicca 2004) that has been included in this review. She is included as an author of that unpublished paper.

John Eden is an author of two of the included studies (Knight 1999; Knight 2001).

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Hot Flashes [*drug therapy]; Isoflavones [therapeutic use]; Phytoestrogens [*therapeutic use]; Randomized Controlled Trials as Topic; Soybeans; Sweating [*drug effects]; Trifolium

MeSH check words

Female; Humans