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[Intervention Review]

Phytoestrogens for vasomotor menopausal symptoms

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ABSTRACT

Background

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

Objectives

To assess the efficacy, safety and acceptability of foods and supplements based on high levels of phytoestrogens for reducing hot flushes and night sweats in postmenopausal women.

Search methods

Searches were undertaken of the following electronic databases: the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of randomised trials, Cochrane Register of Controlled Trials (CENTRAL) (March 2007), MEDLINE (1966 to March 2007), EMBASE (1980 to March 2007), AMED (1985 to March 2007), PsycINFO (1986 to March 2007) and CINAHL (1982 to March 2007). Attempts were made to access grey literature by letters to pharmaceutical companies and searches of ongoing trial registers. Reference lists of included trials were also searched.

Selection criteria

Studies were included if they were randomised, had peri- or postmenopausal participants with vasomotor symptoms, a duration of at least 12 weeks and where the intervention was a food or supplement with high levels of phytoestrogens (and not combined with other herbal treatments). Trials of women who had breast cancer or a history of breast cancer were excluded.

Data collection and analysis

Selection of trials, data extraction and quality assessment were undertaken by at least two authors. Most of the trials were too dissimilar to combine in meta-analysis and their results are provided in table format. Studies were grouped into broad categories: dietary soy, soy extracts, red clover extracts and other types of phytoestrogen. Five trials used Promensil, a red clover extract; these trials were combined in a meta-analysis and summary effect measures were calculated.

Main results

Thirty trials comparing phytoestrogens with control met the inclusion criteria. Very few trials had data suitable for combining in meta-analysis. Of the five trials with data suitable for pooling that assessed daily frequency of hot flushes, there was no significant difference overall in the frequency of hot flushes between Promensil (a red clover extract) and placebo (WMD=-0.6, 95% CI -1.8 to 0.6). There was no evidence of a difference in percentage reduction in hot flushes in two trials between Promensil and placebo (WMD=20.2, 95% CI -12.1 to 52.4). Individual results from the remaining trials were compared. Some of the trials found that phytoestrogen treatments alleviated the frequency and severity of hot flushes and night sweats when compared to placebo but many of the trials were of low quality and were underpowered. There was a strong placebo effect in most trials with a reduction in frequency ranging from 1% to 59% with placebo. There was no indication that the discrepant results were due to the amount of isoflavone in the active treatment arm, the severity of vasomotor symptoms or trial quality factors. There was also no evidence that the treatments caused oestrogenic stimulation of the endometrium (an adverse effect) when used for up to two years.

Authors' conclusions

There is no evidence of effectiveness in the alleviation of menopausal symptoms with the use of phytoestrogen treatments.

PLAIN LANGUAGE SUMMARY

Phytoestrogens for vasomotor menopausal symptoms

Hormone replacement 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 for the shortest possible time because of concerns about increased risk of some chronic diseases. Many women have started using therapies that they perceive as 'natural' and safe but they often do not have good information about the potential benefits and risks. This review has evaluated the benefits, risks and acceptability of treatments based on phytoestrogens, a group of plant-derived chemicals that are thought to prevent or treat diseases. Phytoestrogens are found in a wide variety of plants some of which are foods, particularly soy, red clover and alfalfa. Most of the trials in this review were small, of short duration and poor quality. Some trials found a slight reduction in hot flushes and night sweats with phytoestrogen-based treatment but overall there was no indication that phytoestrogens worked any better than no treatment. There was no evidence of harm with short term use.

BACKGROUND

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

Hot flushes are described as the sudden feeling 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). The 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 of concern in themselves because they can disrupt sleep patterns and alter daily activities, which can then lead to fatigue and decreased quality of life (NAMS 2004). Hot flushes are thought to result from both the brain's response to diminished hormones and the hormonal fluctuations that occur during the menopausal transition, which then leads to instability of thermoregulatory mechanisms (that regulate temperature) in the hypothalamus (Freedman 2001; Kronenberg 1987).

Vasomotor symptoms can affect up to 80% of women in Western countries (Freeman 2007; Thompson 1973) but the incidence and the severity is variable in different populations (Freeman 2007; Gold 2006; Lock 1991). Fewer than 5% to 10% of women in Japan are affected (Freeman 2007; Gold 2006; Lock 1988) and the incidence in other South-East Asian countries is also much lower than for Western women (Boulet 1994; Freeman 2007). Up to 40% of Western women are affected severely enough with these symptoms to seek medical help (Freeman 2001; Gold 2006).

Most therapies designed to combat menopausal vasomotor symptoms aim to supplement levels of circulating oestrogen (Sikon 2004). The treatment of choice is hormone replacement therapy (HRT) but, despite its effectiveness for symptom reduction, there has been a marked and global decline in the prescription and use of HRT because of concerns over long-term use (Bestul 2004; Haas 2004; Travers 2006). HRT was also being prescribed to prevent the onset of cardiovascular events as women grew older. The longer-term apparent benefits of HRT were first questioned with the publication of three trials (Hulley 1998; Roussouw 2002; Viscoli 2001). The first report of the Women's Health Initiative trial (WHI), in 2002, indicated that the risks of combined HRT and unopposed oestrogen therapy outweighed the benefits (Roussouw 2002). Combined therapy was linked with an 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). Direct extrapolation of the data from WHI to perimenopausal women is problematic because of the greater average age of women in the WHI trial; however, concerns about risk have continued to reduce HRT use. Contraindications to HRT include a family history or increased risk of cardiovascular disease, blood clotting disorders, venous thromboembolism or certain hormone-sensitive cancers (Anderson 2003; Grady 2000). Many women report adverse side effects when taking HRT (Bakken 2004; Bjorn 1999); common side effects include breast tenderness, bloating and genital bleeding. Regulatory bodies around the world are now advocating that HRT should only be prescribed in the smallest dose and for the shortest possible time (Europ Med Ag 2006; NZGG 2004; UK CSM 2003).

The potential health risks of HRT and the further uncertainty surrounding actual benefits to be gained from it have caused many women to seek non-medical alternatives (Blair 2005; Newton 2002). 'Natural' therapies appear to be very popular among women; a survey of 866 women aged 45 to 65 years reported that 61% agreed or strongly agreed with a statement that natural approaches are better than hormone pills for menopausal symptoms (Newton 2002). However, there is a lack of good information on the risks and benefits of these approaches. Another survey 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).

Therapies based on phytoestrogens are among the most common of the alternatives to HRT. 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 amounts, 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 (Cassidy 1993; Cassidy 1994). Isoflavones are among the most oestrogenically potent and the major dietary isoflavones, genistein and daidzein, are found almost exclusively in legumes including soy, chick peas, lentils and beans (Cassidy 1993). The urinary excretion of equol, a weak oestrogen, in humans eating soy-supplemented diets can greatly exceed the concentration of urinary endogenous oestrogens and this enhances the plausibility of human physiological health effects (Setchell 1984). Other classes of phytoestrogen, 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 and it is postulated that the high intake among Asian women may account for the lower rates of some menopausal symptoms. 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. The findings of this study are contradicted by 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). It is thus not clear whether frequent soy consumption explains the lower rate of hot flushes

among different ethnic groups. Red clover (Trifolium pretense) is another source of isoflavones; it 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). There have been no specific examples of toxicity for human in countries where soy is consumed regularly (Setchell 1997). It is generally considered difficult for humans to consume the amount of isoflavones from natural soy foods to reach the toxicological levels that induce pathological effects recorded in animals.

Current use of phytoestrogen products among women with vasomotor symptoms is high; an American cross-sectional analysis of over 2000 women (Study of Women's Health Across the Nation (SWAN)) reported that among women with vasomotor symptoms, 11% 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 either no benefit compared with placebo or a very slight reduction in the frequency of daily hot flushes. Government agencies and health organisations have also scrutinised the effect of phytoestrogens, particularly isoflavones (AFSSA 2005; Com Tox 2003). The North American Menopause Society position statement on the treatment of menopause-associated vasomotor symptoms suggests that women should consider trying isoflavone supplementation if their menopausal flushing does not respond to other interventions (NAMS 2004). However, they acknowledge that the evidence base for their recommendation is poor.

The aim of this review was to assess the efficacy, safety and acceptability of food products or dietary supplements containing phytoestrogens on vasomotor menopausal symptoms.

OBJECTIVES

To determine the efficacy, safety and acceptability of food products or dietary supplements containing high levels of phytoestrogens for the amelioration of vasomotor menopausal symptoms (such as hot flushes and night sweats).

We wished to test the following hypotheses
1 Treatment with phytoestrogens is more effective than placebo in reducing the incidence (frequency and severity) of vasomotor menopausal symptoms.
2 Treatment with phytoestrogens is more effective than no treatment in reducing the incidence (frequency and severity) of vasomotor menopausal symptoms.
3 Treatment with phytoestrogens is as effective as hormone replacement therapy in reducing the incidence (frequency and severity) of menopausal symptoms.
4 Treatment with phytoestrogens is associated with a low incidence of adverse events and good adherence to treatment.
5 Treatment with phytoestrogens causes less stimulation to the endometrium than hormone replacement therapy (either combined oestrogen-progestogen therapy or unopposed oestrogen therapy).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled comparisons of food products or dietary supplements containing high levels of phytoestrogens (for example at least 30 mg/day of isoflavones) versus placebo, HRT, 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 being in the 45 to 55 year age range, who have menstruated within the last 12 months and who are seeking treatment for menopausal vasomotor symptoms
- Postmenopausal women, defined as women who are more than 45 years of age, who have not menstruated for more than 12 months and who are seeking treatment for menopausal symptoms

This includes women who have had bilateral oophorectomy (removal of both ovaries).

Source of recruitment

*The participants could be recruited from any healthcare setting or the community and could have had either spontaneous or a surgical menopause.

Exclusion criteria

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

Types of interventions

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

Types of outcome measures

Studies were included if they measured vasomotor symptoms in a sub scale 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.

Studies were also included that measured individual symptoms, for example severity or frequency, or both, of hot flushes and night

sweats (evaluated subjectively by participants, usually in daily diaries).

Studies were included if they measured specific safety outcomes: measures of physiological oestrogenicity of the endometrium and vagina. There are other possible safety outcomes that 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 there is evidence of a beneficial effect on symptoms.

Primary outcomes

- Change in vasomotor menopausal symptom scores
- Change in frequency or severity of individual symptom scores e.g. hot flushes and night sweats

Secondary outcomes

- Adverse events
- Acceptability of therapy (withdrawal because of adverse events)
- Stimulation of the endometrium (endometrial thickness, rates of atrophic endometrium)
- Vaginal stimulation (pH, maturation value)

Search methods for identification of studies

All publications which described randomised trials of interventions containing phytoestrogens versus placebo, hormone therapy, no treatment or food products with low levels of phytoestrogens for the treatment of menopausal symptoms were obtained using the search strategy developed by the Trials Search Coordinator of the Menstrual Disorders and Subfertility Group. Details of the search strategies are as follows.

(1) MEDLINE (1966 to February 2007)
1 exp perimenopause/ or exp postmenopause/ (11143)
2 postmenopaus$.ti,ab,sh. (27419)
3 menopaus$.ti,ab,sh. (32022)
4 exp Climacteric/ or exp Hot Flashes/ or exp Menopause/ (34350)
5 hot flash$.ti,ab. (841)
6 hot flush$.ti,ab. (1072)
7 climacteric.ti,ab. (2573)
8 (vagina$ adj3 atroph$).ti,ab,sh. (359)
9 (vagina$ adj3 dry$).ti,ab. (378)
10 endometri$.ti,ab. (44653)
11 or/1-10 (93334)
12 Phytoestrogens/ (1432)
13 phytoestrogen$.ti,ab. (1716)
14 Soy Foods/ (267)
15 soy$.ti,ab. (22618)
16 exp isoflavones/ or coumestrol/ or genistein/ or pterocarpans/ or rotenone/ (8827)
17 linseed.mp. or Flax/ (1142)
18 isoflavon$.ti,ab. (2998)
19 red clover.ti,ab. (389)
20 daidzein.ti,ab. (1311)
21 promensil.ti,ab. (5)
22 or/12-21 (32056)
23 11 and 22 (1134)
24 randomized controlled trial.pt. (229481)
25 controlled clinical trial.pt. (74116)
26 Randomized controlled trials/ (46944)
27 random allocation/ (56812)
28 double-blind method/ (89516)
29 single-blind method/ (10609)
30 or/24-29 (389441)
31 clinical trial.pt. (431918)
32 exp clinical trials/ (186631)
33 (clin$ adj25 trial$).ti,ab,sh. (125917)
34 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh. (88774)
35 placebos/ (25762)
36 placebo$.ti,ab,sh. (112355)
37 random$.ti,ab,sh. (478353)
38 Research design/ (46062)
39 or/31-38 (847992)
40 animal/ not (human/ and animal/) (3032479)
41 30 or 39 (854870)
42 41 not 40 (783796)
43 23 and 42 (441)
44 43 not review$.ti,ab. (376)
45 44 not cancer$.ti,ab,sh. (279)
46 (2006$ or 2007$).ed. (747107)
47 45 and 46 (53)
48 from 47 keep 1-53 (53)

(2)EMBASE (1980 to February 2007)
1 exp "menopause and climacterium"/ or climacterium/ or early menopause/ or menopause/ or postmenopause/ (36573)
2 postmenopaus$.ti,ab. (24221)
3 menopaus$.ti,ab. (20905)
4 climacter$.ti,ab. (1812)
5 exp Hot Flush/ (4864)
6 hot flush$.ti,ab. (1173)
7 hot flash$.ti,ab. (790)
8 (vagina$ adj3 atroph$).ti,ab,sh. (275)
9 (vagina$ adj3 dry$).ti,ab,sh. (442)
10 endometri$.ti,ab. (36898)
11 or/1-10 (85387)
12 exp PHYTOESTROGEN/ (2469)
13 phytoestrogen$.ti,ab. (1767)
14 plant estrogen$.ti,ab. (37)
15 Daidzein/ or Isoflavone Derivative/ or Genistein/ or Soybean Oil/ or Soybean/ or Isoflavone/ or Soybean Protein/ or soy$.mp. (24083)
16 COUMESTROL DERIVATIVE/ or COUMESTROL/ (426)
17 coumestrol.ti,ab. (214)
18 pterocarpan$.ti,ab,sh. (103)
19 rotenone$.ti,ab,sh. (2325)
20 linseed.ti,ab,sh. (683)
21 red clover.ti,ab,sh. (324)
22 daidzein.ti,ab,sh. (2025)
23 promensil.ti,ab,sh. (14)
24 or/12-23 (28426)
25 11 and 24 (1563)
26 Controlled study/ or randomized controlled trial/ (2355685)
27 double blind procedure/ (62924)
28 single blind procedure/ (6391)
29 crossover procedure/ (18301)
30 drug comparison/ (81250)
31 placebo/ (94966)
32 random$.ti,ab,hw,tn,mf. (359179)
33 latin square.ti,ab,hw,tn,mf. (1055)
34 crossover.ti,ab,hw,tn,mf. (32126)
35 cross-over.ti,ab,hw,tn,mf. (11162)
36 placebo$.ti,ab,hw,tn,mf. (143096)

37 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask $)).ti,ab,hw,tn,mf. (104982)
38 (comparative adj5 trial$).ti,ab,hw,tn,mf. (5490)
39 (clinical adj5 trial$).ti,ab,hw,tn,mf. (472326)
40 or/26-39 (2829668)
41 nonhuman/ (2844329)
42 animal/ not (human/ and animal/) (12841)
43 or/41-42 (2847931)
44 40 not 43 (1660512)
45 25 and 44 (753)
46 45 not review$.ti,ab,sh. (535)
47 (2006$ or 2007$).em. (715142)
48 46 and 47 (113)
49 from 48 keep 1-113 (113)

(3) AMED: Allied and Complementary Medicine (1985 to March 2007)
1 exp perimenopause/ or exp postmenopause/ (0)
2 postmenopaus$.ti,ab,sh. (289)
3 menopaus$.ti,ab,sh. (513)
4 exp Climacteric/ or exp Hot Flashes/ or exp Menopause/ (394)
5 hot flash$.ti,ab. (27)
6 hot flush$.ti,ab. (16)
7 climacteric.ti,ab. (29)
8 (vagina$ adj3 atroph$).ti,ab,sh. (2)
9 (vagina$ adj3 dry$).ti,ab. (8)
10 endometri$.ti,ab. (74)
11 or/1-10 (736)
12 Phytoestrogens/ (47)
13 phytoestrogen$.ti,ab. (84)
14 Soy Foods/ (3)
15 soy$.ti,ab. (148)
16 exp isoflavones/ or coumestrol/ or genistein/ or pterocarpans/ or rotenone/ (71)
17 linseed.mp. or Flax/ (5)
18 isoflavon$.ti,ab. (172)
19 red clover.ti,ab. (12)
20 daidzein.ti,ab. (39)
21 promensil.ti,ab. (0)
22 or/12-21 (360)
23 11 and 22 (52)
24 randomized controlled trial.pt. (863)
25 controlled clinical trial.pt. (59)
26 Randomized controlled trials/ (1293)
27 random allocation/ (288)
28 double-blind method/ (370)
29 single-blind method/ (0)
30 or/24-29 (2733)
31 clinical trial.pt. (947)
32 exp clinical trials/ (2875)
33 (clin$ adj25 trial$).ti,ab,sh. (2824)
34 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask $)).ti,ab,sh. (1446)
35 placebos/ (495)
36 placebo$.ti,ab,sh. (1936)
37 random$.ti,ab,sh. (8431)
38 Research design/ (1635)
39 or/31-38 (12853)
40 animal/ not (human/ and animal/) (188)
41 30 or 39 (12922)
42 41 not 40 (12920)
43 23 and 42 (15)
44 from 43 keep 1-15 (15)

(4) PsycINFO (1986 to March 2007)
1 exp "menopause and climacterium"/ or climacterium/ or early menopause/ or menopause/ or postmenopause/ (1676)
2 postmenopaus$.ti,ab. (943)
3 menopaus$.ti,ab. (1964)
4 climacter$.ti,ab. (323)
5 hot flush$.ti,ab. (85)
6 hot flash$.ti,ab. (130)
7 (vagina$ adj3 atroph$).ti,ab,sh. (9)
8 (vagina$ adj3 dry$).ti,ab,sh. (52)
9 endometri$.ti,ab. (136)
10 phytoestrogen$.ti,ab. (29)
11 plant estrogen$.ti,ab. (3)
12 Daidzein/ or Isoflavone Derivative/ or Genistein/ or Soybean Oil/ or Soybean/ or Isoflavone/ or Soybean Protein/ or soy$.mp. (202)
13 coumestrol.ti,ab. (5)
14 pterocarpan$.ti,ab,sh. (0)
15 rotenone$.ti,ab,sh. (20)
16 linseed.ti,ab,sh. (2)
17 red clover.ti,ab,sh. (4)
18 daidzein.ti,ab,sh. (8)
19 promensil.ti,ab,sh. (0)
20 placebo/ (1710)
21 random$.ti,ab,hw,tn,mf. (65117)
22 latin square.ti,ab,hw,tn,mf. (350)
23 crossover.ti,ab,hw,tn,mf. (2851)
24 cross-over.ti,ab,hw,tn,mf. (936)
25 placebo$.ti,ab,hw,tn,mf. (19043)
26 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask $)).ti,ab,hw,tn,mf. (11549)
27 (comparative adj5 trial$).ti,ab,hw,tn,mf. (272)
28 (clinical adj5 trial$).ti,ab,hw,tn,mf. (8212)
29 or/1-9 (2982)
30 or/10-19 (248)
31 or/20-28 (86925)
32 29 and 30 (22)
33 31 and 32 (9)
34 from 33 keep 1-9 (9)

(5) CINAHL: Cumulative Index to Allied and Nursing Health Literature (1982 to March 2007)
1 exp "menopause and climacterium"/ or climacterium/ or early menopause/ or menopause/ or postmenopause/ (4114)
2 postmenopaus$.ti,ab. (2450)
3 menopaus$.ti,ab. (2657)
4 climacter$.ti,ab. (119)
5 exp Hot Flush/ (90)
6 hot flush$.ti,ab. (98)
7 hot flash$.ti,ab. (336)
8 (vagina$ adj3 atroph$).ti,ab,sh. (25)
9 (vagina$ adj3 dry$).ti,ab,sh. (75)
10 endometri$.ti,ab. (1157)
11 or/1-10 (7143)
12 exp PHYTOESTROGEN/ (419)
13 phytoestrogen$.ti,ab. (166)
14 plant estrogen$.ti,ab. (7)
15 Daidzein/ or Isoflavone Derivative/ or Genistein/ or Soybean Oil/ or Soybean/ or Isoflavone/ or Soybean Protein/ or soy$.mp. (1274)
16 COUMESTROL DERIVATIVE/ or COUMESTROL/ (92)
17 coumestrol.ti,ab. (4)

18 pterocarpan$.ti,ab,sh. (2)
19 rotenone$.ti,ab,sh. (4)
20 linseed.ti,ab,sh. (10)
21 red clover.ti,ab,sh. (49)
22 daidzein.ti,ab,sh. (60)
23 promensil.ti,ab,sh. (2)
24 or/12-23 (1548)
25 11 and 24 (325)
26 Controlled study/ or randomized controlled trial/ (32099)
27 placebo/ (3396)
28 random$.ti,ab,hw,tn,mf. (55135)
29 latin square.ti,ab,hw,tn,mf. (90)
30 crossover.ti,ab,hw,tn,mf. (3780)
31 cross-over.ti,ab,hw,tn,mf. (14308)
32 placebo$.ti,ab,hw,tn,mf. (9780)
33 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask $)).ti,ab,hw,tn,mf. (12030)
34 (comparative adj5 trial$).ti,ab,hw,tn,mf. (2421)
35 (clinical adj5 trial$).ti,ab,hw,tn,mf. (38003)
36 (2006$ or 2007$).em. (204951)
37 or/26-35 (92291)
38 25 and 37 (140)
39 36 and 38 (23)
40 from 39 keep 1-23 (23)

(5) CENTRAL: Cochrane Central Register of Controlled Trials (March 2007)
1 exp perimenopause/ or exp postmenopause/ (3709)
2 postmenopaus$.ti,ab,sh. (5609)
3 menopaus$.ti,ab,sh. (3270)
4 exp Climacteric/ or exp Hot Flashes/ or exp Menopause/ (3755)
5 hot flash$.ti,ab. (179)
6 hot flush$.ti,ab. (426)
7 climacteric.ti,ab. (434)
8 (vagina$ adj3 atroph$).ti,ab,sh. (80)
9 (vagina$ adj3 dry$).ti,ab. (74)
10 endometri$.ti,ab. (2397)
11 or/1-10 (9772)
12 Phytoestrogens/ (85)
13 phytoestrogen$.ti,ab. (125)
14 Soy Foods/ (22)
15 soy$.ti,ab. (918)
16 exp isoflavones/ or coumestrol/ or genistein/ or pterocarpans/ or rotenone/ (287)
17 linseed.mp. or Flax/ (63)
18 isoflavon$.ti,ab. (299)
19 red clover.ti,ab. (21)
20 daidzein.ti,ab. (80)
21 promensil.ti,ab. (6)
22 or/12-21 (1139)
23 11 and 22 (298)
24 limit 23 to yr="2006" (22)
25 from 24 keep 1-22 (22)

The Trials Search Coordinator also searched the pecialised register of the Menstrual Disorders and Subfertility Group (MDSG).

Citation lists of included trials, conference abstracts and relevant review articles were searched by the first author. Novogen, a manufacturer of a standardised extract of phytoestrogens (Promensil) was contacted for details of unpublished trials.

Data collection and analysis

Selection

The selection of trials for inclusion in the review was performed at different times by two review authors (AL and either FK, JM or JB) after employing the search strategy described previously.

Data extraction and quality assessment

All assessments of the quality of trials and data extraction were performed independently by at least two review authors (AL and either FK, JM or JB) using forms designed according to Cochrane guidelines. Two of the review authors (HR and JE) are experts on clinical issues. The other four review authors (AL, FK, JM and JB) have statistical and methodological expertise. Where necessary, additional information on trial methodology or original trial data were sought from the principal or corresponding author of any trials which appeared to meet the eligibility criteria (see Acknowledgements for details of the authors who provided additional clarification of data beyond what was reported in the publications).

Included trials were analysed for the following quality criteria and methodological details.

Trial characteristics:
1. method of randomization;
2. presence or absence of blinding to treatment allocation (participants, investigators, assessors);
3. quality of allocation concealment;
4. number of patients randomised, excluded or lost to follow up;
5. whether an intention-to-treat analysis was done;
6. whether a power calculation was done;
6. duration, timing and location of the study.

Characteristics of the study participants:
1. age and any other recorded characteristics of women in the study;
2. other inclusion criteria;
3. exclusion criteria.

Interventions used:
1. types of phytoestrogen enriched food products or tablets used;
2. amount of phytoestrogen compounds within the food products or tablets used;
3. dose, duration and timing of administration of phytoestrogen food products or tablets.

Outcomes:
1. methods used to measure frequency and severity of vasomotor symptoms;
2. methods used to measure adverse events.

Analysis

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Menstrual Disorders and Subfertility Group and the Cochrane Handbook.

A priori, it was decided that results from the included studies would be combined in meta-analysis only if there were similarities in the baseline experience of hot flushes in the participants; the composition, type and dosage of the phytoestrogen interventions;

the duration of the studies and the outcomes measured. There was significant heterogeneity in the isoflavone concentration in the foods and extracts that were considered to contain high levels of phytoestrogens in the trials. 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 Additional tables).

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. Statistical heterogeneity between the results of these five different studies was examined by inspecting the scatter in the data points and the overlap in their confidence intervals and, more formally, by checking the results of the chi-squared test and the I-squared quantity. A priori, it was planned to look at the possible contribution of differences in trial design to any heterogeneity identified in this manner. Where substantial heterogeneity was indicated which couldn't be explained, a random-effects model was used as a more appropriate method for estimating an average treatment effect.

For the dichotomous data (for example, incidence of adverse events), results for each study were expressed as an odds ratio (OR) with 95% confidence intervals (CI) and combined for meta-analysis with RevMan software using the default odds ratio method.

For the continuous data (for example, percentage change in frequency of hot flushes), results for the pooled estimate were expressed as a weighted mean difference (WMD) with 95% confidence intervals (CI).

For the majority of trials, where the results were reported in tabular form, subgroup analysis was undertaken because of the variation in the phytoestrogen interventions. The trials were grouped a priori according to the type of phytoestrogen given in the experimental arms of the trials. The subgroups were:
1) trials where the phytoestrogen given was in the form of dietary soy, such as flour, beverage or powder containing isoflavones;
2) trials where the phytoestrogen given was in the form of a soy isoflavone extract;
3) trials where the phytoestrogen given was in the form of a red clover extract;
4) all other trials.

Sensitivity analysis was planned to compare the differences in participants, interventions, outcomes and methodological quality of included studies.
1) Comparison of trial results of all included studies with those studies with at least double blinding.
2) Comparison of trial results of all included studies with those studies where allocation concealment was reported as adequate.
3) Comparison of trial results of all included studies with those studies where a power calculation was performed for sample size.
4) Comparison of trial results of all included studies with those studies where intention-to-treat analysis was performed.
5) Comparison of trial results of all included studies with those studies where women were required to have at least five moderate to severe hot flushes per day before being eligible to participate.
6) Comparison of trial results of all included studies with those studies using more than 50 mg/day of isoflavones in the treatment group.

RESULTS

Description of studies

Studies

Thirty randomised controlled trials with a total of 2730 participants met the inclusion criteria. The outcomes varied and different numbers of participants contributed data to each of the outcomes. Full descriptive details of the studies are found in the Characteristics of included studies table.

Thirty-two trials were excluded. Reasons for exclusion were as follows: the participants were completely asymptomatic (in terms of vasomotor symptoms) at baseline, participants were not confirmed as peri or postmenopausal, treatment with phytoestrogens was for less than 12 weeks, participants had previous breast cancer, the phytoestrogen intervention was part of a composite treatment where effects due solely to phytoestrogens could not be determined, the amount of phytoestrogens in the experimental intervention could not be determined and if there was no assessment of the effects of phytoestrogens on hot flushes and night sweats or safety outcomes (on the endometrium and vagina). Details of the reasons for exclusion are found in the Characteristics of excluded studies table.

Participants

Participants were recruited solely from menopause clinics (11 trials) or from a mixture of advertisements and flyers in medical practices; the source of recruitment was not specified in seven trials. Participants in most trials were required to be experiencing vasomotor symptoms (either hot flushes or night sweats), ranging from at least one flush per day to more than seven flushes per day. Six other trials were also included where vasomotor symptoms were measured at baseline, although a specification of the level of these symptoms was not a requirement for inclusion in the trial. Two of these six trials measured the effects of treatment in subgroups (only those women with symptoms at baseline) of the randomised participants; in the other four trials all women had mild symptoms at baseline and the effects of treatment were assessed in all participants. Menopausal status was mostly confirmed by follicle stimulating hormone (FSH), luteinising hormone (LH) and plasma oestradiol measurements or amenorrhoea ranging from two months to greater than two years but elderly women were not included (participants mostly ranged in age from 40 to 65 years, although one trial included women up to age 75 years). Because the minimum threshold of the last menstrual period ranged from two to 12 months or more, many trials included a mix of peri and postmenopausal women. Two trials explicitly recruited perimenopausal women; women were required to have missed three or more periods in the last 12 months but must have menstruated at least once during this time (ages ranged from 45 to 55 years) in one trial and, in the other, women were required to have had at least one period in the last 12 months (average time since last menstrual period was 16 weeks). Women in five trials were from Australia, five trials were performed in Italy, six trials in the USA and the remainder in Israel, the UK, Canada, Brazil, France, Ecuador, Peru, Canada, the Netherlands, Austria and Hong Kong. In most

of the trials women using HRT, either currently or recently, were excluded. Other exclusion criteria were women on a vegetarian diet or on a soy-rich diet, malignancy, with other diseases and on 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 four trials specifically excluded women with a surgical menopause.

Interventions

The interventions used in the trials varied greatly.

Type and method of delivery of phytoestrogen
The trials were grouped into broad categories according to the method of delivery and type of phytoestrogen. Nine 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. Nine trials assessed the effects of varying types of soy isoflavone extracts, usually in tablet form. Seven trials assessed the effects of red clover extracts (five of the seven used a standardised extract manufactured by Novogen under the brand name Promensil™). The remaining trials (n = 5) assessed other types of phytoestrogen supplements: two assessed the effects of pure genistein extracts (a type of isoflavone), one looked at an extract of pueraria lobata (a Chinese herb containing isoflavones), another looked at two doses of a hop extract (Humulus luputus L.) and three looked at a flaxseed dietary supplement (two of which were had soy dietary supplement arms and were included in the first category).

Duration
Duration of the interventions was three months in most of the trials (or three months for the first phase of crossover trials). Four trials had a duration of 16 weeks, five trials had a duration of 24 weeks, two trials had a duration of one year and one trial had a duration of two years.

Comparison groups
The phytoestrogen interventions were mostly compared with placebo. Three open studies compared phytoestrogens with no treatment. Four placebo-controlled studies compared different doses of the phytoestrogen intervention and three other placebo-controlled studies compared different types of phytoestrogens (two compared soy with flaxseed and another trial compared different types of red clover extract: Promensil™ and Rimostil™). One study compared phytoestrogens with HRT and no treatment and another compared phytoestrogens solely with HRT.

Outcomes

A majority of the trials were pilot studies without power calculations. The effect of the interventions in the included studies on total menopausal scores from general menopausal symptom questionnaires (such as Kupperman and Greene) was not an outcome of this review. The Kupperman Index, in particular, has been criticised as inadequate as an outcome measure (Alder 1998) and the purpose of this review was to assess effects specifically on flushes and night sweats. Most of the 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 who reported any reduction in frequency). A few studies separately reported on the frequency and severity of night sweats. Five studies assessed the safety of the intervention (as measured by effects on endometrial stimulation) as the primary outcome and five others assessed these measures as secondary outcomes. A few studies also assessed the effects of the intervention on the vaginal epithelium or pH, surrogate outcomes which are biological indicators of oestrogenic activity. Adverse events were reported in a few trials but generally were collected as spontaneous reports. Most trials gave details of withdrawals before completion of the study and a few indicated whether these were because of adverse effects or problems with acceptability of the intervention.

Risk of bias in included studies

The methodological quality of the included studies is summarised in Table 1 of the Additional tables.Table 1

Design

Twenty-five studies had parallel-group design and the remaining five had crossover design. Two of the crossover studies had a one month washout period between treatments, two studies had a one week washout period and the remaining study had no washout period. For the crossover studies, statistical analyses assessing effects at the end of the study were reported in Table 1 of the Additional tables but for one study (Baber 1999) the data were pooled with other parallel-group studies and data were used from the first phase of the crossover study only.

Randomisation method and allocation concealment
Eighteen of the studies gave full descriptions of an adequate randomisation procedure; the remaining trials claimed that randomisation was the method of allocation but the method was not described. Fewer than half of the studies (n=12) indicated that allocation had been concealed from the trial investigators; the remaining trials provided no details.

Blinding
Nearly all of the trials reported that the treatments were blind to the participants and investigators but the procedures to ensure that this occurred were not always described. In one trial only the assessors were blinded and another trial reported triple blinding with participants, investigators and assessors all blinded. It is possible that outcomes were assessed by either the investigators or participants in some of the double-blinded trials, thereby ensuring complete blinding but this was not clearly reported. Two open studies were unblinded.

Power calculations for sample size
Power calculations for sample size were undertaken prospectively in 11 studies and retrospectively in one other study. In two of these studies, the numbers recruited did not reach the recommended totals so they were underpowered. The remaining 18 trials did not report power calculations and the majority of these were small and likely to be underpowered.

Intention-to-treat (ITT) analysis and attrition
In spite of the short duration of most of the trials (12 weeks), attrition varied widely. Eight trials had a withdrawal rate of less than 10%; in the remainder dropouts ranged from 10% to 31%. The reasons for withdrawal were mostly adequately described. Strict intention-to-treat analysis (analysis according to randomisation

and with the use of various methods to include the dropouts) took place in only two trials.

Baseline comparability
Fourteen studies included tables of initial demographic and other characteristics of the participants according to randomised group in order to demonstrate the success of the randomisation procedure. The remaining 16 studies either did not include a table or reported on these data only for the number of participants who completed the study.

Funding
Nineteen of the included studies were funded either wholly or in part by pharmaceutical companies or manufacturing companies of the supplements used in the active treatment arms. Five studies were supported by academic or other institutional grants and six studies provided no details of their funding support.

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 in the other included studies (dose, composition, type), these data could not be pooled and are displayed in separate tables for efficacy, safety and acceptability outcomes (*see* Additional tables).

Dietary soy

Efficacy
Of the nine included studies that used some type of substance containing dietary soy and had efficacy analyses of any kind, seven studies indicated that there were no significant differences between the soy intervention and the control group. The Albertazzi study of 104 women compared soy powder containing 76 mg/day of isoflavones with casein powder, over 12 weeks (Albertazzi 1998). It 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. The other positive study compared a phytoestrogen-enriched diet that was individualised for each participant by a dietician (exceeding the cutoff point of > 30 mg/day of isoflavones) with a control group that consumed a regular diet with avoidance of phytoestrogen-containing foods (Brzezinski 1997). In this study, the participants rated the severity of their hot flushes separately in a menopause symptoms questionnaire (MSQ). Hot flushes were reduced in severity in both arms of the study but significantly more in the phytoestrogen diet group. The study was one of the few that was not blinded and knowledge of treatment could have affected the participants' assessments.Table 2

Safety
Of the four studies that assessed adverse events, three were negative (no significant difference 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 to 17% of the placebo group. The side effects included bloating, nausea, weight gain and concerns about bowel function. One trial found no evidence of an oestrogenic effect on the endometrium (Balk 2002). Of two studies that assessed the effects of a soy diet on the vaginal maturation index, one found no evidence of a significant effect (Knight 2001) but the other reported that this index increased 103% from baseline with a soy diet compared to a 6% increase with linseed and an 11% increase with placebo (Dalais 1998).Table 3

Acceptability
Of the three studies that assessed the acceptability of the phytoestrogen intervention compared to control, one study reported a difference in the rate of withdrawal because of adverse events (Knight 2001) (P value not reported). This small study reported that 25% of participants consuming a beverage containing soy powder withdrew from the study because of a dislike of the taste compared to 8% in the placebo group.Table 4

Soy extracts

Efficacy
Of the nine studies comparing various types of soy extract in capsule or tablet form (eight versus placebo and one versus HRT), five studies (all versus placebo) reported significant differences in efficacy outcomes (either frequency or severity). Three trials (Bicca 2004; Faure 2002; Khaodhiar 2007) found a reduction in the frequency of flushes (one also found a reduction in the frequency of night sweats) and two trials found a reduction in severity of flushes as measured by the Kupperman vasomotor symptom score (Han 2002) and 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 according to group at the end of the study. The trial comparing soy extract with oestrogen therapy (Kaari 2006) reported no difference between ERT and soy extract in the percentage of participants reporting any reduction in their hot flushes (at six months, P = 0.74, students t test).

Safety
Of the eight studies that assessed safety outcomes, one assessed effects on endometrial stimulation, three on vaginal pH, four on endometrial thickness, four on vaginal maturation index and four on adverse events. The trial comparing soy extract with ERT (unopposed oestrogen therapy) (Kaari 2006) reported a significant improvement in vaginal pH and maturation index in the ERT group. The soy extract group had significantly thinner endometrium, less endometrial stimulation and fewer adverse events (all of which were genital bleeding in the ERT group). Of the trials that compared soy extract with placebo, one of the two trials found a significantly greater improvement in vaginal pH in the soy group (Bicca 2004). There were no differences in endometrial thickness, vaginal maturation index and incidence of adverse events.

Acceptability
No studies assessed the acceptability of the interventions.

Red clover extracts

Seven 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. We used data from the first phase of the Baber crossover trial.

Efficacy
Five studies reported on the frequency of daily hot flushes after treatment with two different doses of Promensil™ (40 mg/day and 80 mg/day) (Baber 1999; Jeri 2002; Knight 1999; Tice 2003; van De Weijer 2002). There was no significant difference between groups, overall (WMD -0.57, 95% CI -1.76 to 0.62) or in the dosage subgroups

(see meta-analysis). One large trial and one small trial assessed the percentage reduction in the number of hot flushes from baseline, resulting in a very imprecise pooled estimate (WMD 20.15, 95% CI -12.08 to 52.38) (Jeri 2002; Tice 2003). One small trial (Jeri 2002) reported that there was a significantly greater proportion of women with improvement in hot flush severity (from moderate to severe to none or light) in the Promensil group (OR 47.7, 95% CI 2.4 to 967.4). One trial found no difference in the change in vasomotor score from baseline to the end of the study (WMD 0.1, 95% CI -1.5 to 1.7) (Tice 2003).

One study that assessed an unspecified red clover extract (that was not included in the meta-analyses) reported a benefit for hot flush and night sweat severity (as assessed by the Kupperman Index) (Hidalgo 2005). After treatment, 15% of women taking 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 value not reported). The authors claimed that these values represented severity "as expressed as a percentage" but it is not clear what they meant.

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 difference in the proportion of women who experienced any adverse event (OR 0.92, 95% CI 0.5 to 1.7). There were also no differences in the rate of specific adverse events between groups. Two trials assessed the effects of treatment on endometrial thickness (Baber 1999; Imhof 2006). One trial (included in the meta-analysis) found no difference in endometrial thickness after 12 weeks of treatment. The other trial could not be included in the meta-analysis because of insufficient data. It reported a significant decrease of 15% in endometrial thickness in women treated with red clover compared with a zero change in women treated with placebo (SD of change not given, P < 0.001).

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). The other study assessed the effects of a red clover extract, MF11RCE, on the endometrium of women with vasomotor symptoms (Imhof 2006). The authors reported that this extract significantly decreased endometrial thickness in comparison with placebo (mean change from baseline of -0.55 mm with red clover versus -0.18 with placebo, P value for comparison between groups not given).

Acceptability
No trials assessed the acceptability of treatment.

Other phytoestrogens

One trial compared genistein extract with continuous HRT and placebo (Crisafulli 2004), one compared genistein extract solely with placebo (Sammartino 2003), three compared flaxseed dietary supplement with placebo (Dalais 1998; Dodin 2005; Lewis 2006), one compared two strengths of hop extract with placebo (Heyerick 2006) and one compared pueraria lobata (a Chinese medicinal herb) with sequential HRT and no treatment (Woo 2003).

Efficacy
Six trials assessed efficacy outcomes. Four trials with placebo arms found no significant differences in hot flush (Dodin 2005; Heyerick 2006; Lewis 2006) and night sweat severity scores (Dodin 2005) or in a vasomotor symptom score (Lewis 2006). Two trials found no evidence of a difference between groups in frequency of hot flushes after treatment (Dalais 1998; Lewis 2006).

One trial comparing a genistein extract with HRT and placebo found a 24% reduction in daily hot flushes with genistein compared to placebo (P < 0.05) and a 30% reduction in daily hot flushes with HRT compared to genistein (P < 0.05) (Crisafulli 2004). One trial reported no significant difference between a Chinese medicinal herb containing high doses of isoflavones, sequential HRT and no treatment in vasomotor symptom scores (Woo 2003).

Safety
Two trials assessed endometrial thickness after one year and reported no significant difference between groups (Crisafulli 2004; Sammartino 2003). There was also no evidence of a change in vaginal maturation index with flaxseed compared to placebo (Dalais 1998).

Acceptability
No trials assessed the acceptability of treatment.

DISCUSSION

This review has assessed the effectiveness, safety and acceptability of foods, supplements or extracts containing phytoestrogens when compared with placebo, no treatment and HRT in randomised studies completed by the end of 2006. It has been able to pool only the studies that used Promensil™ in meta-analyses because of the heterogeneity of the other phytoestrogen interventions.

Efficacy
(1) Dietary soy
The dietary food supplements in the trials varied enormously in the type of product used, the formulation and the isoflavone content (42 mg per day to 134 mg per day). Sensitivity analysis was undertaken to attempt to explain the differences between the two positive studies and 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 the trial results could have been caused by other factors that could not be controlled for. Intestinal flora 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). Another possibility that could explain differences is the severity of hot flushes at baseline. Of the two positive studies, Albertazzi but not Brzezinski required that women have at least five to seven moderate to severe flushes per day. In the other trials women were eligible for participation with less severe symptomatology. This needs to be investigated further but was not apparent in the other subgroups of phytoestrogens.

Quality of the trials in this subgroup was variable. In particular, there was a very high dropout rate in the two positive trials (24% and 21% respectively) and the Brzezinski study was not placebo controlled. Thus, the findings of these trials must be considered only tentative as significant bias cannot be excluded.

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

(2) Soy extracts

Of the nine trials that compared soy extracts with placebo, five had some positive results and four were negative. Sensitivity analyses exploring the effects of quality issues, levels of isoflavones in the active arm (ranging from 33 mg per day to 120 mg per day) or severity of flushes at baseline did not explain the differences in results. The three placebo-controlled trials that found a difference in flush frequency (Bicca 2004; Faure 2002; Khaodhiar 2007) out of the six that measured this outcome reported a reduction of 74%, 61% and 50% with soy extract compared with 43% and 21% and 38% with placebo, respectively. Two trials had a longer duration than the more usual 12 weeks, 25 and 16 weeks respectively. The trial comparing soy extract with oestrogen therapy (ERT) (Kaari 2006) found no difference in the percentage of participants reporting a reduction in hot flush frequency but participants only had mild symptoms at baseline (55% and 72% had hot flushes at baseline in the soy and ERT groups, respectively). Although there was no placebo group, the authors concluded that their results suggested the soy isoflavone extract at 120 mg/day was effective in relieving the frequency of hot flushes.

Severity scores were significantly different in two of the five trials that measured this outcome; one trial used the Kupperman vasomotor scale (rating severity from 0 to 3) (Han 2002) and the other was a simple severity scale (1 to 3 representing mild, moderate and severe symptoms) scored daily by the participants (Upmalis 2000). The variability in the results of the included trials was not explained by sensitivity analyses of the quality and other aspects of the studies.

Overall, there was no conclusive evidence that soy extracts had a positive effect on hot flush frequency or severity.

(3) Red clover extracts

Overall, there was no evidence that Promensil™ was effective at reducing either the frequency or severity of hot flushes. One small Peruvian study (n = 30) of poor quality (Jeri 2002) reported highly significant effects for both frequency and severity but gave no details of the randomisation method, allocation concealment or baseline comparability. The inclusion of this study in the meta-analyses caused highly significant heterogeneity, combined with other larger trials of better quality, and a random-effects model was chosen for presentation of results. Another study (van De Weijer 2002) reported a significant benefit of Promensil (with 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 good quality large trial (n = 252) (Tice 2003) that compared two types of red clover extract, Promensil (two tablets per day) and Rimostil, with 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 the studies also compared a higher dose of Promensil (160 mg/day) with placebo but substitution of these values in the meta-analysis did not alter the results. None of the sensitivity analyses had any effect on the direction or precision of the results.

Two studies compared other types of red clover extract (Hidalgo 2005; Imhof 2006) but only the first assessed efficacy. It reported highly significant differences in the severity of hot flushes and night sweats as separate scores (expressed as percentages) but with no reported P value or measure of variation. Results from these smaller poor quality studies are in conflict with those of the much larger and better powered trial comparing Promensil and Rimostil (Tice 2003).

Overall, there was no evidence that red clover extracts had a positive effect on hot flush frequency or severity.

(4) Other phytoestrogens

Of the six trials assessing the effects of other types of phytoestrogens, two studies included women with very mild symptoms at baseline and reported no significant differences in outcomes. One other study in women who had two to five daily flushes also found no evidence of significant differences between groups after 12 weeks of treatment with a phytoestrogen preparation derived from hops (Heyerick 2006). Two other studies (also containing soy diet arms) found no evidence of significant differences between flaxseed or linseed diets and placebo (Dalais 1998; Lewis 2006). One trial of moderate quality (Crisafulli 2004) reported that a genistein extract (54 mg/day) reduced the frequency of daily hot flushes over a year by 24% when compared with placebo; however, continuous HRT was more effective than the genistein extract. The inconsistency in the results of the studies is reflected in their variable quality and the heterogeneity in both the interventions and measurement of outcomes.

Overall, there were insufficient data to determine whether any other type of phytoestrogen product had significant effects on vasomotor symptoms.

Safety

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

Only one of eight trials found a significant difference in adverse event rates (Knight 2001). The phytoestrogen supplement in this small trial was in the form of a powder and the authors included data on the dislike of taste of the 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. In a trial comparing soy extract with combined HRT (Kaari 2006), women in the latter arm were more likely to experience genital bleeding which is a common symptom of HRT in perimenopausal women. This symptom was not experienced by women who took phytoestrogen supplements.

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. There was no evidence from two studies in the review that phytoestrogens promote a proliferative endometrium (Balk 2002; Kaari 2006). Most of the studies also found no difference in endometrial thickness between phytoestrogens and placebo. One study actually found a significant reduction of endometrial thickness from baseline (Imhof 2006). The lack of an oestrogenic effect on the endometrium was further supported by a study comparing phytoestrogens with ERT; endometrial thickness significantly changed from baseline with ERT but there was no change with phytoestrogens (Kaari 2006). Other studies have been performed in women without hot flushes

at baseline (not eligible for inclusion in this review). One of these studies (Unfer 2004) reported that long-term treatment (up to five years) with soy (150 mg/day isoflavones) was associated with an increased occurrence of endometrial hyperplasia compared to placebo. This has not been confirmed by other studies but the long-term endometrial safety of high doses of phytoestrogen supplements has not been fully established.

Evidence of the effects of phytoestrogens on the vaginal maturation index and pH is mixed. Four placebo-controlled trials did not find evidence of a stimulatory effect but two other studies found a positive oestrogenic effect increasing cellular mitotic activity as evidenced by improvements in maturation indices, one with a soy diet compared to a wheat diet and the other with a red clover extract (Dalais 1998; Hidalgo 2005). In the study with an ERT comparator, vaginal cytology values with ERT were significantly different from those with soy (Kaari 2006). Other studies not included in this review, where participants were either asymptomatic or had breast cancer, have also produced conflicting data. Three studies have found evidence of an 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 found an 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 with ERT, vaginal pH improved significantly more with ERT than 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.

Acceptability

Few trials specifically assessed this outcome in spite of the high dropout rate in many of the studies. There was no evidence of a difference in the acceptability of any of the phytoestrogen products used when compared with placebo.

Summary

In summary, there was no conclusive evidence of a benefit of phytoestrogen-enriched or derived products for menopausal vasomotor symptoms. Data are inconclusive regarding the oestrogenicity of phytoestrogens on the endometrium and the vagina in women with vasomotor symptoms. There was no evidence of an increase in adverse events and limited data suggested the phytoestrogen supplements were well tolerated.

Although some trials reported a significant beneficial effect of phytoestrogen treatment on symptoms, there was strong evidence of a placebo effect in the trials 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). Where 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.

A recent review has suggested that phytoestrogen products might be more effective in women with more severe flushes at baseline (Huntley 2004). Another systematic review and meta-analysis (Howes 2006) also came to the conclusion that women more severely affected with vasomotor symptoms had a small benefit with 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 the 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. Where there is such huge variation in included trials in the characteristics of the participants, types of intervention and outcomes measured, it is important to take into consideration the quality of the trials. The largest trial, (Tice 2003) was a good quality study with high compliance, 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 did not find any evidence of a benefit for Promensil™ or Rimostil™.

In addition to variable quality, the studies varied according to the total amount or 'dose' of isoflavone in the active treatment arm. The rationale for a role for isoflavones is supported by epidemiologic evidence from a community-based study which found that the incidence of hot flushes was inversely related to the amount 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). A majority of the studies in this review had treatments with at least 50 mg per day of isoflavones and 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 the different supplements and extracts differ considerably. The broad groupings in this review into 'types' of phytoestrogen did not give any clues as to the best way to deliver phytoestrogens for therapeutic effect.

In addition to the heterogeneity of the interventions used in the included studies, there is good evidence of variability 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 30% to 40% of the general population in the United States possess gut microflora that convert the isoflavone daidzein to the more oestrogenic dihydroxy isoflavan equol (Setchell 2002). It has been suggested that 'equol producers' comprise a distinct subpopulation that may gain the most benefit from soy isoflavones for relief of hot flushes and which may explain anecdotal reports by many women of phytoestrogen effectiveness in relieving their hot flushes. The studies included in this review did not control or stratify for this added potential source of variation in response to treatment with phytoestrogens.

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 their 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 un validated 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 headaches. A second weakness of the review is the potential for publication bias. The search for relevant studies was very comprehensive and attempted to access the grey literature. However, a number 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.

The findings of this review are broadly in accord with other recently published systematic reviews assessing the effects of phytoestrogens on menopausal symptoms (Geller 2005; Glazier 2001; Haimov-Kochman 2005; Howes 2006; Huntley 2004; Krebs 2004; Low Dog 2005; Nedrow 2006; Williamson-H 2006) and this review has included a number of more recently published studies. However, Williamson-H 2006 focused more specifically on soy isoflavone extracts and stratified the studies according to the amount of genistein in the extract. Their findings suggest that supplements that provide at least 15 mg of genistein per day are effective whereas those providing less genistein are not. 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 3198 women (Gold 2006). They reported that genistein intake in their sample was not related to vasomotor symptoms and 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.

AUTHORS' CONCLUSIONS

Implications for practice

There is no conclusive evidence that phytoestrogen supplements effectively reduce the frequency or severity of hot flushes and night sweats in postmenopausal women. Many of the included studies were of poor quality and results were inconsistent, providing no guidance on which type of product was likely to be more beneficial. Women need to be reassured that these symptoms will usually abate over time without any treatment. Where therapy is desired or required, the use of phytoestrogen supplements is not based on good quality evidence of benefit. There is no evidence of harmful side effects from the use of these supplements.

Implications for research

More research is required to test the following hypotheses.
(1) Supplements containing at least 15 mg of genistein are more effective than supplements containing less than 15 mg of genistein.
(2) Phytoestrogen supplements are more effective in women with more than five moderate to severe hot flushes per day compared to those with mild symptoms.
(3) Phytoestrogen supplements are as effective as low dose HRT and have a better endometrial safety profile.

In addition, future trials should be based on phytoestrogen products that are well characterised, to increase comparability; should provide strict monitoring of participants throughout the trial; should be well powered; 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	Randomisation method: Not stated Blinding: Double blinded Allocation concealment: Not stated Design: Parallel group No randomised: 92 initially plus a further 12 from reserve randomisation list = 104 No dropped out: 21 (9 in active group: 7 for gastro-intestinal symptoms, 1 for lack of efficacy, 1 non-compliant; 7 in placebo group for gastro-intestinal symptoms, 3 for lack of efficacy, 1 non-compliant; 1 for other reasons) No lost to follow up: 4 (2 in each group)

Albertazzi 1998 *(Continued)*

	No analysed: 79 Intention-to-treat analysis: No Power calculation: 90% power to detect a difference of 3 hot flushes per 24 hours (P = 0.05) Duration: 12 weeks Timing: Not stated Location: 2 Italian university hospitals Funding: Partial industry funding from Protein Technologies, Missouri
Participants	Inclusion criteria: Postmenopausal women requesting treatment for severe hot flushes, 6 months since last menstruation or 6 weeks since bilateral oophorectomy, minimum of 7 moderate to severe hot flushes or night sweats per 24 hours during 2 out of 4 weeks prior to 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 HRT within 6 weeks of study or other drug used for climacteric symptoms during study period Age: Active arm 53 (48-61), placebo 52 (45-62)
Interventions	1. Phytoestrogen: Isolated soy protein Formulation: 76 mg isoflavones (genistein 40 mg, daidzein 28 mg) per 60 mag sachet of powder VERSUS 2. Placebo: 60 gm 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

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Baber 1999

Methods	Randomisation method: Not stated Blinding: double Allocation concealment: Not stated Design: Crossover No screened for inclusion: Not stated No randomised: 51 No dropped out: 8 (7 for personal reasons, 1 for medical reasons not related to study) No lost to follow up: None stated Intention-to-treat analysis: No Power calculation: Not stated Duration: 3 months X 2 Timing:Not stated Location: Tertiary menopause clinic, Australia Funding: Industry (Novogen Ltd, Australia)
Participants	Inclusion criteria: Minimum of mean of 3 hot flushes per day in week preceding trial

Baber 1999 *(Continued)*

	Exclusion criteria: Intercurrent medical problems, HRT or antibiotics in previous 3 months, FSH <30mIU/ml, menstruation in previous 6 months, hysterectomy, vegetarian (>10 gm legumes per day) Age: 54 (+/- 4.1) Recruitment method: volunteers. Not further specified
Interventions	1. Phytoestrogen: Promensil (red clover extract) Formulation: 40 mg of standardised isoflavones (genistein, daidzein, Fourmentin and Biochemic) per tablet VERSUS 2. Placebo tablet Dose, duration and timing of administration: One tablet daily in morning for 3 months, one month washout period then crossover to opposite arm for 3 months and 2 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
Allocation concealment?	Unclear risk	B - Unclear

Balk 2002

Methods	Randomisation method: Computer generated in blocks of 6 Blinding: double Allocation concealment: Sequentially numbered opaque sealed envelopes Design: Parallel group No of women screened: "Hundreds" (most not amenorrhoeic for one year) No randomised: 27 No dropped out: 7 (5 in active arm: 2 for family reasons, 3 for adverse effects, 2 in placebo arm: 1 for lack of efficacy , 1 disliked taste) No lost to follow up: 1 (active arm) No analysed: 19 Intention-to-treat analysis: No Power calculation: Powered to detect endometrial changes but baseline proliferation rate under-estimated and study thus underpowered for primary outcome Duration: 6 months Timing: January 1998 - June 2000 Location: University hospital clinic Funding: Academic research grants
Participants	Inclusion criteria: Postmenopausal women, aged .40 with no vaginal bleeding for 1 year or aged over 30 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 replacement therapy on past year, using phytoestrogen supplements (diet logged for 2 weeks before study) Age: Active arm 56.8 +/- 5.9; P;placebo arm 57.9 +/- 8.2 Recruitment method: Primary and tertiary clinics, newspaper and radio advertisements, research institute web site
Interventions	1. 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

Balk 2002 *(Continued)*

	VERSUS 2. Placebo: Wheat cereal (Grapenuts) Dose, duration and timing of administration: 100 mg daily (1/2 cup cereal) for 3 months Given list of soy and phytoestrogen-containing foods to avoid
Outcomes	Menopausal symptoms : Weekly log monitoring 9 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 & gastrointestinal effects
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. The 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
Allocation concealment?	Low risk	A - Adequate

Bicca 2004

Methods	Randomisation method: table of random numbers kept by separate organisation. Allocation concealment: opaque envelopes. Design: parallel group. No of women screened: 90 No analysed: 75 No dropped out: 1 lost to follow up in soy group, 3 lost in placebo group (2 adverse events, 1 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 aged 42-61 years, symptomatic and no menses for 12 months. Exclusion criteria; oral HRT in previous 3 months, topical HRT in previous 30 days, use of medication that could influence the results, concomitant severe disease. Mean age: 54 years in soy group, 52 years in placebo group Recruitment method: advertisements
Interventions	1. Standardised soy extract (33 mg/d isoflavones VERSUS 2. Placebo capsule Dose, duration and timing of administration: 1 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

Bicca 2004 *(Continued)*

Allocation concealment?	Low risk	A - Adequate

Brzezinski 1997

Methods	Randomisation method: Random number sequence, non-computerised Blinding: Not mentioned Allocation concealment: Design: Parallel group No screened for inclusion: Not stated No randomised: 145 No dropped out: 31 (17 in active group: 2 for unbearable symptoms, 15 for personal reasons; 14 in control group: 7 for unbearable symptoms, 7 for personal reasons) No lost to follow up: None stated No 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: Peri and post-menopausal women aged 43-65, natural or surgical menopause with at least 3 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: 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	1. Phytoestrogens: Isoflavones and lignans Formulation: Daily consumption of 80 gm tofu (approx. 75 mg/gm daidzein, 200 mg/gm genistein), 2 X 200 ml glasses of soy drink (approx. 7 mg/gm daidzein, 35 mg/gm genistein, one teaspoon of miso (40 mg/gm daidzein, 35 mg/gm genistein), 2 teaspoons of ground flax seed (:approx. 4 mg/gm lignans): cooked if unpalatable uncooked VERSUS 2. 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
Allocation concealment?	Unclear risk	B - Unclear

Burke 2003

Methods	Randomisation method: Not stated Blinding: Double blinded

Burke 2003 *(Continued)*

	Allocation concealment: Not stated Design: Parallel group No screened for inclusion: 1571 (1230 ineligible: main reasons being lack of menopausal symptoms (293), refusal to stop HRT (241), cycle not perimenopausal (206) No randomised: 241 No dropped out: None stated No lost to follow up: None stated No analysed: 211 (30 had data missing from symptom diaries) Intention-to-treat analysis: No Power calculation: Duration: 2 years Timing: August 1996 - 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 3 months prior to randomisation), at least one vasomotor symptom per day, not using HRT for 3 months before recruitment, willingness to participate in one week run-in with isoflavone-free supplement Exclusion criteria: Acute MI or stroke within previous 6 months, history of breast or endometrial cancer, invasive cancer within previous 5 years, active thrombo-embolic disease, previous osteoporosis-related fractures being 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 unwilling to reduce consumption to once a week Age: mean 50.8 (SE 0.2) Recruitment method: "Recruited from the community"
Interventions	1. High dose phytoestrogens: isoflavones Formulation: 25 gm soy protein (58 mg isoflavones) in a drink VERSUS 2. Medium dose phytoestrogens: isoflavones Formulation:25 gm soy protein (42 mg isoflavones) in a drink AND VERSUS 3. Control: 25 mg soy protein, washed to remove isoflavones (maximum 4 mg isoflavones) in a drink Dose, duration and timing of administration: One 25 gm ready-to-drink beverage daily, chocolate or orange flavoured, for 2 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 weak per month Compliance: Compliance calendars
Notes	37 women (18%) took HRT during trial: 19=6 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
Allocation concealment?	Unclear risk	B - Unclear

Campagnoli 2005

Methods	Randomisation method: schedule prepared by the manufacturer of the product using computer generated randomisation list and distributed sequentially. Blinding: double Allocation concealment: adequate - blind to treatment allocation. Design: crossover

Campagnoli 2005 *(Continued)*

	No of women screened: not stated. No randomised: 36 No analysed: 29 No dropped out: 7 (not clear which group - 3 medical reason, 4 family reason) Intention-to-treat: No Power calculation: Yes - 95% power to detect at least a 20% greater reduction in hot flushes in active arm compared to 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 5 moderate to severe hot flushes/day, good general health, 45-58 years, BMI 18-28, surgical menopause (bilateral oophorectomy for at least 3 months or in spontaneous menopause with no menses for over 6 months, menopausal hormone profile (estradiol<30 pg/ml, FSH>40 UI/l) Exclusion criteria: use of drugs that influence vasomotor symptoms, hormone therapy or tibolone in previous 6 months, consumption of soy based food more than once per week, use of drugs that might reduce absorption of isoflavones Mean age in completers: 51 yrs. Recruitment method: menopause clinic.
Interventions	1. Standardised soy extract 200 mg (Soy select) capsules (60 mg/d isoflavones) VERSUS 2. Placebo capsules Dose, duration and timing of administration: 2 capsules per day in 2 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 1st phase of study)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Crisafulli 2004

Methods	Randomisation method: by computer software Blinding: double (participants/investigators) Allocation concealment: not stated Design: Parallel group No randomised: 90 No dropped out: 7 (no reasons given) No lost to follow up: 0 No analysed: 90 Intention-to-treat analysis: yes Power calculation: 90% power to detect a 2.5 mm difference in endometrial thickness among the 3 treatment groups (P=0.05) Duration: 12 months Timing: not stated Location: university clinic in Italy Funding: not stated

Crisafulli 2004 *(Continued)*

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-estradiol 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 estrogen, progestin, androgen or other steroids in the preceding year; smoking more than 10 cigarettes per day Age: mean in placebo group 51 years; mean in other 2 groups 52 years
Interventions	1. Phytoestrogen genistein (54 mg/day) 2. Continuous HRT (1mg/day 17B-estradiol plus norethisterone acetate 3. Placebo (identical tablets) All participants had a 4 week stabilisation diet (isocaloric, fat restriction) prior to treatment
Outcomes	Menopausal symptoms: Daily number of hot flushes at 3, 6 and 12 months Adverse effects: Endometrial thickness at 6 and 12 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dalais 1998

Methods	Randomisation method: Computerised Blinding: Double-blinding Allocation concealment: Not described Design: Cross-over No randomised: 52 No dropped out: 8 (7 for personal reasons, 1 due to lack of compliance) No lost to follow up: None stated Intention-to-treat analysis: No Power calculation: 80% chance of detecting a 40% decrease in hot flush rate Duration: 2 X 12 weeks with 4 week washout period Timing: Not stated Location: Australia Funding: Industry support (George Weston Foods)
Participants	Inclusion criteria: Postmenopausal women aged 45-65, FSH >40 IU/ml, >14 hot flushes per week, 12 months of amenorrhoea, non-smoking, non-vegetarian Exclusion criteria: Antibiotics or hormone replacement therapy during preceding 3 months Age: Mean 53.6 - 54.6 (SE 1.2-1.7) Recruitment method: Not stated
Interventions	1. High phytoestrogen diet: isoflavone Formulation: 45 g daily of soy grits, totaling 52.64 (SD 8.68) mg isoflavones daily (genistein and daidzein) OR 2. High phytoestrogen diet: mammalian lignan precursors Formulation: 45 g daily of linseed (secoisolariciresinol and matairesinol) VERSUS 3. Low phytoestrogen diet: Wheat Formulation: 45 g daily of kibbled wheat

Dalais 1998 *(Continued)*

	Dose, duration and timing of administration: Four slices of bread or 2 rolls (or equivalent combinations), substituted for daily bread intake for 2 X 12 week periods Participants completed a food diary for 2 weeks prior to randomisation and were asked repeat the same 2 weekly diet and 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
Allocation concealment?	Unclear risk	B - Unclear

Dodin 2005

Methods	Randomisation method: computer generated in blocks of 4 to 8. Blinding: double Allocation concealment: not stated Design: parallel group No of women screened: 1413 No randomised: 199 No dropouts: 20 (16 in flaxseed group: 7 medical, 3 non compliance, 4 personal, 1 symptomatic, 1 HRT; 4 in placebo group: 2 medical and 2 non compliant). 10 women in flaxseed group and 13 in placebo group discontinued during the trial but had an endpoint evaluation No analysed: 179 Intention-to-treat analysis: No Power calculation: Yes, based on changes in lipid profile and BMD Duration: 1 year Timing: January 2000 to May 2001 Location: Menopause clinic in Quebec, Canada Funding: Flax Council of Canada, Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada
Participants	Inclusion criteria: aged 45 to 65 years, FSH>/=40 mIU/ml, no menses for 6 months, normal mammogram in past year Exclusion criteria: early onset of menopause, personal history of neoplasm, osteoporosis, CVD, hepatic or renal disease, uncontrolled hyper- or hypothyroidism or diabetes, abnormal lipid profile, BP> 140/90 mmHg, malabsorption disease or gastrectomy, use of medication that interferes with lipid or calcium metabolism Mean age: 54 in flaxseed group and 55 in calcium group Recruitment method: from general population through newspaper, radio and TV advertising, flyers posted in clinics and clinicians
Interventions	1. Flaxseed (21,071ug total lignans) VERSUS 2. Placebo (wheat germ) (196ug total lignans) Dose, duration and timing of administration: given in 2 different ways: half given in bread and half given as ground grains to add to other foods over a period of 1 year
Outcomes	Flush and night sweat score (Menoquol questionnaire) in subgroup of women who were symptomatic at baseline.

Dodin 2005 *(Continued)*

Notes	64% of women in the flaxseed arm and 62% of women in the placebo arm were symptomatic at baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Duffy 2003

Methods	Randomisation method: not stated Blinding: double Allocation concealment: not stated Design: parallel group No of women screened: not stated No randomised: 36 No dropouts: 3, all from the placebo group because of concurrent Rx No analysed: 33 Intention-to-treat::No Power calculation: not reported Duration: 12 weeks Timing: Not stated Location: Kings College, London, UK Funding: Biotechnology and Biological Sciences Research Council, UK, Dunhill Medical Trust, Solbar Plant Extracts (manufacturer of the treatment in the active arm)
Participants	Inclusion criteria: non smokers, no menses in previous 12 months Mean age: 59 ys in soy group, 57 ys in placebo group Recruitment method: circular e-mail at Kings College or from a database of previous participants of study on bone mineral density Exclusion criteria: use of HRT in previous 12 months, use of antibiotics in previous 3 months, current illness, use of psychoactive medication
Interventions	1. Soy isoflavone supplement (Solgen 40) (60 mg/day isoflavone) VERSUS 2. Placebo capsules Dose, duration and timing of administration: 2 capsules per day for 12 weeks (1 in the morning and 1 in the evening)
Outcomes	Primary outcomes were measures of cognitive function. Secondary outcome: Greene vasomotor score
Notes	There was no requirement that women have vasomotor symptoms to participate in the trial, although these were measured at baseline. In general women had a low incidence of symptoms.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Faure 2002

Methods	Randomisation method: Not stated Blinding: Double-blinded (not further specified) Allocation concealment: Not described Design: Parallel group No randomised: 75 No dropped out: 17 for inefficacy (6 from active group, 11 from placebo group) No lost to follow up: 3 (placebo group) No 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 3 hot flushes per day, assuming a standard deviation of 3.8 hot flushes per day (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 6 months since last menstrual period, minimum of 7 moderate to severe hot flushes or night sweats during 2 weeks prior to study. Baseline FSH >40 IU/L and serum oestradiol < 35 pg/ml Exclusion criteria: Use any other drug for treatment of climacteric symptoms during study period, HRT within 6 weeks prior to study Age: Active group 53 (SD 5.6), placebo group 53.9 (SD 4.1)
Interventions	1. Phytoestrogen: Isoflavone Formulation: Phytosa - soy extract 325 mg capsules containing 17.5 mg total isoflavones (genistein, daidzein, biochanin and formononetin) VERSUS 2. Placebo (cellulose microcrystalline and sodium magnesium stearic) Dose, duration and timing of administration: 2 X 2 tablets daily for 16 weeks
Outcomes	Menopausal symptoms: Daily diary card recording number of mod/severe hot flushes and night sweats Adverse events recorded at each follow up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Han 2002

Methods	Randomisation method: Computerised random number generator Blinding: Double blinded (researchers and participants blinded) Allocation concealment: Numbered coded envelopes No screened for inclusion: Not stated No randomised: 82 No of dropouts: 2 (1 from each arm, 1 due to poor response, 1 due to nausea - not stated which arms they were on) No analysed: 80 Intention-to-treat analysis: No Power calculation: None stated Duration: 4 months Timing: August 1999 - Feb 2000

Han 2002 *(Continued)*

	Location: University clinic, Brazil Funding: Unclear. Investigators acknowledge the co-operation of a doctor employed by food supplement manufacturer Eugenbio
Participants	Inclusion criteria: Women aged 45-55, "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, anti-diabetic medications, soybean-derived products,or herbal supplements; uncontrolled hypertension, stroke or transient ischaemic attack, cancer diagnosed within past 5 years, previous myocardial infarction Age: mean active arm 48 (SE 1.1), placebo arm 49 (SE 1.3), Recruitment method: Not stated
Interventions	1. Phytoestrogen: Isoflavone capsules Formulation: Soy protein 50.3 mg & isoflavone 33.3 mg (genistein 23.3 mg, daizein 6.2 mg, glycitein in aglycone form 3.8 mg) per capsule VERSUS 2. Placebo Dose, duration and timing of administration: One capsule 8 hourly (= 100 mgs isoflavone daily), for 4 months
Outcomes	Menopausal symptoms: hot flashes (Kupperman index) Compliance: Examination of prescriptions/pills
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Heyerick 2006

Methods	Randomisation method: Online randomiser Blinding: double Allocation concealment: random codes kept separate Design: parallel group No of women screened: 84 No randomised: 67 No dropouts: 18% (12/67): 4 in high phytoE group (3 no efficacy, 1 other), 1 on low phytoE group (no efficacy), 7 in placebo group (all no efficacy) No 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, aged 45 to 60 years, intact uterus, no menses for past 12 months, at least 2-5 hot flushes per day, abstention of HRT for past 3 months Exclusion criteria: score of <2 on Kupperman hot flush index Mean age: 52 ys in placebo and low dose groups; 53 ys in high dose group Recruitment method: not stated
Interventions	1. Hop extract (100ug/d 8-prenylnaringenin)

Heyerick 2006 *(Continued)*

	VERSUS 2. Hop extract (250ug/d 8-prenylnaringenin) VERSUS 3. Placebo Dose, duration and timing of administration: 1 capsule a day for 12 weeks
Outcomes	Hot flush score on Kupperman index (severity)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Hidalgo 2005

Methods	Randomisation method: computerised random number generation Blinding: double Allocation concealment: opaque containers with investigators blinded to codes Design: crossover No women screened: not stated No randomised: 60 No dropouts: 12% (7/60): Not clear which group: 5 no reason, 2 adverse events Intention-to-treat analysis: No Power calculation: Yes, but insufficient Duration: 12 weeks, 7 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 HRT, moderate to severe menopausal symptoms (Kupperman index score >/=15, basal determination Exclusion criteria: no consent, indication of non compliance, conventional HRT, isoflavone supplements, thyroid medication or history of thyroid disease, medication that could interfere with vasomotor symptoms and/or lipid serum levels Mean age: 51 years Recruitment method: clinical database, private practice or from the general population through advertising and flyers
Interventions	1. Red clover extract (80 mg/d isoflavones) VERSUS 2. Placebo Dose, duration and timing of administration: participants acted as their own control - 2 capsules a day of the randomised treatment for 90 days, a 7 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

Hidalgo 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Imhof 2006

Methods	Randomisation method: not stated. Blinding: double Allocation concealment: not stated Design: crossover No of women screened: not stated No randomised: 113 No dropped out: 4 (3 in active arm and 1 in placebo arm - all started ERT). No analysed: 109 Intention-to-treat analysis: No 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 ERT, known isoflavone hypersensitivity Mean age: 55 yrs in active arm and 54 yrs in placebo arm Recruitment method: menopause clinic
Interventions	1. Red clover extract (MF11RCE) (80 mg/d isoflavones) VERSUS 2. Placebo capsules Dose, duration and timing of administration: 2 capsules per day for 12 weeks, 7 day washout period and crossed over to other treatment for next 12 weeks
Outcomes	Endometrial thickness
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jeri 2002

Methods	Randomisation method: Not stated Blinding: Double blind Allocation concealment: not stated No screened for inclusion: Not stated No randomised: 30 No dropped out: None stated No lost to follow up: None stated No analysed: 30

Jeri 2002 *(Continued)*

	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 over one year, aged under 60, FSH level >30 mIU/ml, having at least 5 hot flushes daily, averaged over one week, not using HRT, antidepressants or other medications, or soy or other oestrogen-active plant products for the past 16 weeks Exclusion criteria: Age: 51-2 Other characteristics of participants: All were Hispanic "with a middle class income and good education"
Interventions	1. Phytoestrogen: Promensil Formulation: 40 mg of standardised isoflavones (genistein, daidzein, formonetin and biochanin) per tablet VERSUS 2. 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	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kaari 2006

Methods	Randomisation method: computer software Blinding: double Allocation concealment: not stated Design: parallel group No women screened: 150 No randomised: 79 No dropouts: 14% (11/79): 7 from soy group (3 medical, 4 personal), 4 from ERT group (1 medical, 1 no reason, 1 scared of biopsy, 1 personal) No 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>/= 30mU/mL, intact uterus, endometrial thickness<5mm, 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 6 months,

Kaari 2006 *(Continued)*

	history of chronic disorders (incl benign breast disease), regular use of medication known to interfere with study endpoints, BMI>30 Mean age: 54yrs Recruitment method: menopause clinic
Interventions	1. Standardised soy extract 300 mg (120 mg/d isoflavones) VERSUS 2. Estrogen replacement therapy (CEE 0.625 mg + placebo) Dose, duration and timing of administration: 2 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	Patients were recruited from a menopause clinic but 18% in soy group and 26% of ERT group were asymptomatic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Khaodhiar 2007

Methods	Randomisation method: not stated Binding: double Allocation concealment: not stated Design: parallel group No women screened: 236 No dropouts: 20% (41/207) (not clear from which group - mostly because of inability to comply with the study protocol) No analysed: 166 Intention-to-treat analysis: No Power calculation: not stated Duration: 12 weeks Timing: not stated Location: Medical centre in Harvard Medical School, Boston, USA Funding: Nichimo Co Ltd, Japan
Participants	Inclusion criteria: postmenopausal, no menses for past 6 months, aged 38-60 years, between 5 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 HRT or any medication for hot flushes within past 6 weeks, BMI>/=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 illnesses Mean age: between 52 and 54 years in the 3 groups Recruitment method: referring physicians in the medical centre and newspaper advertisements
Interventions	1. Extract of isoflavones prepared from soy germ fermentation with Koji fungus, 40 mg/d VERSUS 2. Soy extract (see above) 60 mg/d VERSUS

Khaodhiar 2007 *(Continued)*

	3. Placebo (isoflavone quantity not known) Dose, duration and timing of administration: 1 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
Allocation concealment?	Unclear risk	B - Unclear

Knight 1999

Methods	Randomisation method:Computer random number generator Blinding: Double blinded (Participants and investigators) Allocation concealment: Remotely allocated Design: Parallel group No screened for inclusion: Not stated No randomised: 37 initially. When one woman dropped out after randomisation and before commencing treatment, another was recruited to the same treatment No dropped out: 2 in high dose group withdrawn on GP advice No lost to follow up: No 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 6 months with typical symptoms of menopause, FSH >40 IU/l), having at least 3 hot flushes daily, aged 40-65 Exclusion criteria: HRT use within previous 6 weeks, allergy to isoflavones, current bowel, liver or gallbladder disease, diabetes requiring medication, malignancy other than skin cancers, contra-indications to HRT use, vegetarians, regular soy product users, on liver- enzyme-inducing medications Age: High-dose 51.1 (+/- 8.8) ys, medium dose 54.5 (+/- 4.4) ys, placebo 53.1 (+/- 2.5) ys. Recruitment method: Through university department of obstetrics and gynaecology
Interventions	1. Phytoestrogen: Isoflavones: One Promensil tablet plus 3 placebo tablets VERSUS 2. Phytoestrogen: Isoflavones: Four Promensil tablets Formulation: Promensil tablets each 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) AND VERSUS 3. Placebo 4 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

Knight 1999 *(Continued)*

	Quality of life: Greene Menopause Scale Compliance: Pill counts
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Knight 2001

Methods	Randomisation method: Randomly permuted blocks of 6, using computerised random-number generator Blinding: Double-blinded (Participants and investigators) Allocation concealment: Remotely allocated Design: Parallel group No screened for inclusion: Not stated No randomised: 24 No dropped out: 3 (from active arm - all disliked taste) No lost to follow up: 1 (from placebo arm) No 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 6 months with typical symptoms of menopause, FSH >40 IU/l), having at least 3 hot flushes daily, aged 45-60 Exclusion criteria: HRT use within previous 6 weeks, allergy to isoflavones, current bowel, liver or gallbladder disease, diabetes requiring medication, malignancy other than skin cancers, contra-indications to HRT use, vegetarians, regular soy product users (>once a week), on liver- enzyme-inducing medications Age: Recruitment method: Two university hospital obstetrics and gynaecology clinics
Interventions	1. Phytoestrogen: Isoflavones Formulation: Take Care powder 4 scoops or 60 gm in each sachet, containing total isoflavones 134.4 mg (genistein, daidzein, glycetein) VERSUS 2. 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
Outcomes	Menopausal symptoms: Flush count Quality of life: Greene Menopause Scale Compliance: Sachet counts Adverse effects
Notes	

Risk of bias

Knight 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kotsopoulos 2000

Methods	Randomisation method: Not stated Blinding: Double blinded (not further specified) Allocation concealment: Not described Design: Parallel group No screened for inclusion: Not stated No randomised: 94 No dropped out: 19 (10 on active treatment, 9 on placebo, due to adverse effects) No lost to follow up: None No analysed: 73 (2 excluded from analysis as FSH in normal range) Intention-to-treat analysis: No Power calculation: Not stated Duration: 3 months Timing:Not stated Location: Australia Funding: Academic research grant
Participants	Inclusion criteria: Aged 50-75, postmenopausal (12 months of amenorrhoea and FSH>20U/l) Exclusion criteria: On antibiotics within 3 months prior to study, on HRT during 12 months prior to study, smoker, vegetarian, ingesting phytoestrogens or soy-based products Mean age: 59 years Recruitment method: Subgroup of a larger trial
Interventions	1. Phytoestrogen: Isoflavones Formulation: Soy dietary supplements containing 118 mg isoflavones daily (daidzein, genistein, glycitein and their respective glycosides: 2.11 mg total isoflavones per gm of protein or 1.72 mg aglycone per gram of protein). In powder form for mixing into a drink VERSUS 2. Placebo powder (casein) Dose, duration and timing of administration: 2 drinks daily for 3 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	There was no requirement for vasomotor symptoms 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
Allocation concealment?	Unclear risk	B - Unclear

Lewis 2006

Methods	Randomisation method: separate site prepared randomisation codes

Lewis 2006 *(Continued)*

	Blinding: double Allocation concealment: adequate Design: parallel group No women screened: 792 No randomised: 99 No dropouts: 12% (12/99): 2 in soy group (1 could not accept Rx, 1 adverse event), 5 in flaxseed group (2 could not accept Rx, 1 adverse event, 1 medical, 1 personal), 5 in placebo group (1 could not accept Rx, 1 adverse event, 2 medical, 1 protocol violation) No 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: 45-60 years old, natural menopause with last menses in previous 1 to 8 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 ERT in past 3 months, no phytoestrogens, steroids or antibiotics in past month Mean age: 53 ys Recruitment method: Mailings to family practice, previous participants of menopause workshops and to gynaecologists and family physicians
Interventions	1. Flaxseed muffins (50 mg/d lignans) 2. Soy muffins (42 mg/d isoflavones) 3. Placebo muffins (low levels of lignans and no isoflavones) Dose, duration and timing of administration: 1 muffin per day
Outcomes	Menoquol vasomotor score (0-6) No of flushes per day Severity of flushes (0-6)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Penotti 2003

Methods	Randomisation method: Random numbers list, balanced in blocks of 10 Design: Parallel group Blinding: Double blind (not further defined) Allocation concealment: Not described No randomised: 62 No dropped out: 13 did not complete 6 months of treatment (6 in active group, 1 due to diarrhoea and 5 due to persistent hot flushes; 7 in placebo group due to persistent hot flushes) No analysed: 49 at 6 months No lost to follow-up: Nil Intention-to-treat analysis: No Power calculation: Not stated

Penotti 2003 *(Continued)*

	Duration: 6 months Timing: Not stated Location: Outpatient menopause clinics, Italy Funding: Not stated
Participants	Inclusion criteria: Postmenopausal for at least 6 months, aged 45-60, FSH and 17-B E2 levels within postmenopausal range; experiencing at least 7 hot flushes daily (evaluated by patient diary completed over 15 days pre-randomisation, computerised bone mineralometry score of more than -2.5 at level of lumbar spine Exclusion criteria: Serious disease such as hypertension, heart disease, diabetes, renal disease, peripheral vascular disease Age: 52.5 (49-58)
Interventions	1. Phytoestrogen: Isoflavone tablets Formulation: 36 mg soy-derived isoflavones (5.5 mg genistein, 18 mg daidzein, 12.5 mg glyciteine)) & 48 mg soy saponine per tablet VERSUS 2. Placebo: 0.5 gm talc & 0.5 mg microcrystalline cellulose Dose, duration and timing of administration: 2 tablets daily, one before lunch and one before dinner for 6 months
Outcomes	Menopausal symptoms: Mean daily number of hot flushes per month (+ SD)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sammartino 2003

Methods	Randomisation method: computer generated randomisation list Blinding: none Allocation concealment: not stated Design: crossover (no washout) No of women screened: not stated No randomised: 70 No dropouts: 7 (3 in genistein grp: 2 no compliance, 1 personal; 4 in calcium grp: 3 no compliance, 1 personal) No analysed: 63 Intention-to-treat analysis: No Power calculation: not reported Duration: 1 year Timing: not stated Location: Menopause clinic at University Department in Naples, Italy Funding: not stated
Participants	Inclusion criteria: minimum no of 7 moderate to severe hot flushes (including night sweats)/day (defined), postmenopausal (hormones in the menopausal range: FSH>40IU/l; estradiol<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 >5mm or endometrial abnormalities Mean age: 52 ys in both groups

Sammartino 2003 *(Continued)*

	Recruitment method: menopause clinic
Interventions	1. Genistein VERSUS 2. Calcium supplements Dose, duration and timing of administration: 36 mg/day (2 tablets) genistein and 3.3g calcium phosphate + 8mg/day colecalciferol for 12 cycles of 28 days.
Outcomes	Endometrial thickness and adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

St Germain 2001

Methods	Randomisation method: Not stated Blinding: Double-blind Allocation concealment: Not described Design: Parallel group No screened for inclusion: 1000 (of whom 102 passes first screening. Subsequently 22 found to be ineligible, 6 could not tolerate treatment, 1 died, 1 had family member die, 2 had medical conditions preventing continuance, 1 was non-compliant) No randomised: 69 No dropped out: **CHECK No lost to follow up: No 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 lab tests
Participants	Inclusion criteria: Perimenopausal women, one or both ovaries remaining, FSH at least 30 IU/L BMI 20-31,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, chronic medication use, taking HRT at time of study or during the previous 12 months, Age: Median 50 (42-62)
Interventions	1. High phytoestrogen: Isoflavone Formulation: 40 gm daily of isoflavone-rich soy protein (80.4 mg/day aglycone components) plus daily vitamin/mineral supplement VERSUS 2. Low phytoestrogen: Isoflavone Formulation: 40 gm daily of isoflavone-poor soy protein (4.4 mg/day aglycone products)plus daily vitamin/mineral supplement AND VERSUS 3. Placebo (whey protein)plus daily vitamin/mineral supplement

St Germain 2001 *(Continued)*

	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 and 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
Allocation concealment?	Unclear risk	B - Unclear

Tice 2003

Methods	Randomisation method: Computer generated in random blocks of 6, stratified by centre Blinding: Double blinded (researchers at clinical centre and co-coordinating centre and participants blinded) Design: Parallel group, active arms versus placebo Allocation concealment: Allocation schedule maintained remotely, at pharmacy No screened: 1191 (Principal reasons for ineligibility were too few hot flushes [251], not interested [216], medical conditions/medications [192]) No randomised: 252 No dropped out: 6 (2 on Promensil [one too busy, 1 no improvement], 2 on Rimostil [1 nauseated, 1 on physician's advice], 2 on placebo [1 feared possible placebo, 1 too busy]) No lost to follow up: No 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 to placebo. 25% placebo effect anticipated. Duration: 12 weeks Timing: November 1999 - March 2001 Location: 3 US academic clinical research sites Funding: Industry (Novogen inc.)
Participants	Inclusion criteria: Women aged 45-60, experiencing at least 35 hot flushes per week, FSH level 30 mIU/ml, either documented bilateral oophorectomy or at least 2 consecutive months of amenorrhoea prior to enrolment with at least 6 months of amenorrhoea in the year prior to entry. Exclusion criteria: Vegetarian, Ate soy products >once a week, on medications affecting isoflavone absorption or hormonal preparations during previous 3 months, significant gastrointestinal disease, > 2 alcoholic beverages per day, allergic to red clover, consumed <80% of expected study tablets during the 2 week placebo run-in Age: 52.3 (SD 2.8 - 3.4 in different arms) Recruitment method: Newspaper and radio advertising, flyers, directed mailings
Interventions	1. Phytoestrogen: Isoflavones Formulation: Promensil tablets, containing average of 41 mg total isoflavones per tablet (range 37 - 43 mg), with a higher proportion of biochanin A and genistein than Rimostil OR 2. Phytoestrogen: Isoflavones

Tice 2003 *(Continued)*

	Formulation: Rimostil tablets, containing average of 28.6 mg of total isoflavones per tablet (range 25.6 - 31.4 mg) with a higher proportion of formononetin and daidzein than Promensil VERSUS 3. Placebo: Contained <0.04 mg total isoflavones per tablet Dose, duration and timing of administration: 2 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 ups, specific method unclear
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Upmalis 2000

Methods	Randomisation method: Not stated Blinding: Double-blind Allocation concealment: Not described Design: Parallel group No screened for inclusion: Not stated No randomised: 177 No dropped out: 40 (21 in active arm: 1 did not take supplement, 9 ineligible, 11 violated protocol, 1 had urinary tract infection; 18 in placebo arm: 1 did not take supplement, 4 ineligible, 13 violated protocol) No lost to follow up: 15 (9 in active group, 6 in placebo group) discontinued before week 12 No 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 5 hot flushes per day, aged over 50, 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 lest 6 months, discontinued HRT at least 60 days before study entry Exclusion criteria: History of breast cancer, hyperplasia, endometrial carcinoma or cervical neoplasia, positive pregnant 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: Mean 55 ys
Interventions	1. Phytoestrogen: Isoflavone Formulation: Soy isoflavone extract tablet (50 mg genistein and daidzein daily, approximately 25 gm of each) VERSUS 2. Placebo Dose, duration and timing of administration: 2 tablets at bedtime for 12 weeks

Upmalis 2000 *(Continued)*

	Intake of other soy products and dietary supplements was 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 6 and week 12 Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van De Weijer 2002

Methods	Randomisation method: Blank envelopes containing allocation shuffled, numbered consecutively then given consecutively to participants Blinding: Double blinded (Participants and researchers blinded)) Allocation concealment: Participants took envelope to pharmacy where number in envelope was matched with batch number of medication Design: Parallel group No screened for inclusion: 42(6 ineligible, 24 did not return to clinic, 2 recorded inadequate data in diary during screening phase) No randomised: 30 No dropped out: 6 (3 in each group, mainly due to lack of efficacy) No lost to follow up: 4 (all in placebo group: data sets not evaluated) No 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 aged 49-65 with at least 12 months' amenorrhoea, average of >5 hot flushes daily Exclusion criteria: HRT or antibiotics within 12 weeks of study entry, undiagnosed vaginal bleeding,active liver or renal disease, history of allergy for foodstuffs, cardiovascular disease or thrombo-embolism. Age: Active arm 52.5 (SD 5.2), placebo 54.2 (SD 7.4)
Interventions	1. Phytoestrogen: Isoflavones Formulation: Promensil 40 mg tablets (daidzein, genistein, biochanin, formononetin) VERSUS 2. Placebo tablets Dose, duration and timing of administration: 2 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 7 days from 4-week screening phase.

van De Weijer 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Woo 2003

Methods	Randomisation method: Not stated. Blinding: single (assessors only) Allocation concealment: B Design: parallel group No women screened: not stated No randomised: 136 No dropouts: 7 (5 in HRT group - adverse events and personal, 2 in phytoE group - 1 medical, 1 personal, 2 in control group - both personal) No analysed: 127 Intention-to-treat analysis: No Power calculation: Yes Duration: 12 weeks Timing: not stated Location: Chinese University of Hong Kong Funding: Chinese University of Hong Kong Strategic Research Grant; Pura Pharm Company Ltd (manufacturers of Pueraria lobata extracts)
Participants	Inclusion criteria: aged 50-65 years, no menses for past 12 months Exclusion criteria: hypertension, Ischaemic heart disease, stroke, dementia, diabetes, thyrotoxicosis, breast lump/malignancy, abnormal Pap smear, using lipid lowering drugs or HRT Mean age: 56yrs in HRT group and 57 years in other 2 groups
Interventions	1. HRT (CEE 0.625 mg/day + MPA 5mg for 14 days of cycle 2. Extract of Pueraria lobata (100 to 200 mg isoflavones/day) 3. No treatment Dose, duration and timing of administration: HRT once daily, Pueraria lobata once daily, control no treatment for 3 months
Outcomes	Vasomotor score and mean change in vasomotor score (calculated from menopause questionnaire)
Notes	Hot flushes in participant were measured at baseline but were not a requirement for inclusion. Average flush score at baseline was at the mild end of the scale.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Aglycone: unconjugated parent forms of isoflavones
Dropouts: did not complete treatment as per protocol, reason for dropping out and/or outcome reported
Intention to treat analysis: all women randomised 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, 7 somatic, 2 vasomotor, 1 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 compasints to severe
Per protocol analysis: analysis according to treatment actually received
Lost to follow up: women whose reason for withdrawing and/or outcome is unknown or not reported

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.
Atkinson 2003	About half of the women in each group had hot flushes but this was not a requirement for participation in the study.
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.
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
Chiechi 2003	Analyses effects of soy-rich diet on vaginal epithelium of asymptomatic postmenopausal women. Symptomatic women excluded.
Colacurci 2004	There is no evidence that the control group was randomised.
Duncan 1999	No outcomes of interest - outcomes were physiological rather than clinical
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.
Jou 2005	Treatment for only 6 weeks.
Kok 2005	Participants were asymptomatic and effects measured on quality of life, not vasomotor symptoms
Lamlertkittikul 2004	This was a dose finding study with no control group
Manonai 2006	No evidence that women had vasomotor symptoms at baseline.
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.
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
Quella 2000	Participants had breast cancer.
Russo 2003	The intervention was a composite of phytoestrogens and black cohosh. It was not possible to determine whether effects solely due to phytoestrogens.

Study	Reason for exclusion
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 HRT. First part of the trial, soy vs placebo, only for 6 weeks.
Secreto 2003	About 10% of the participants had breast cancer
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.
Washburn 1999	Treatment given for only 6 weeks.
Xue 2004	Outcome was a composite of menopausal symptoms. Effects on vasomotor symptoms could not be separated.

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

Agrawal 2005

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Amato 2005

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Brzezinski 1999

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Casserta 2005

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Cheng 2007

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

D'Anna 2007

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Jeri 1999

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Kolarov 2001

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Nachtigall 1999

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Paixao 2005

Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

Stanosz 2006	
Methods	not completed by review author
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

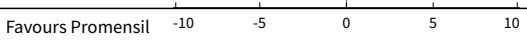
Comparison 1. Promensil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of hot flushes (number/day)	5	300	Mean Difference (IV, Random, 95% CI)	-0.57 [-1.76, 0.62]
1.1 40mg/day	3	105	Mean Difference (IV, Random, 95% CI)	-0.54 [-2.34, 1.27]
1.2 80mg/day	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 Proportion with improvement in hot flush severity	1	27	Odds Ratio (M-H, Fixed, 95% CI)	47.73 [2.35, 967.37]
4 Change in vasomotor score from baseline to end of study	1	165	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.54, 1.74]
5 Proportion with any adverse events	1	169	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.49, 1.72]
6 Incidence of specific adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Cold or upper respiratory tract infection (URTI)	1	169	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.25, 1.49]
6.2 Headache	1	169	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.14, 1.28]
6.3 Myalgia	1	169	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.54, 4.16]
6.4 Nausea	1	169	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.24, 4.19]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.5 Arthralgia	1	169	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.24, 2.84]
6.6 Diarrhea	1	169	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 4.09]
6.7 Vaginal spotting	1	169	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.25, 9.44]
7 Endometrial thickness after treatment	1	51	Mean Difference (IV, Fixed, 95% CI)	0.06 [-4.94, 5.06]

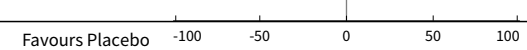
Analysis 1.1. Comparison 1 Promensil versus placebo, Outcome 1 Incidence of hot flushes (number/day).

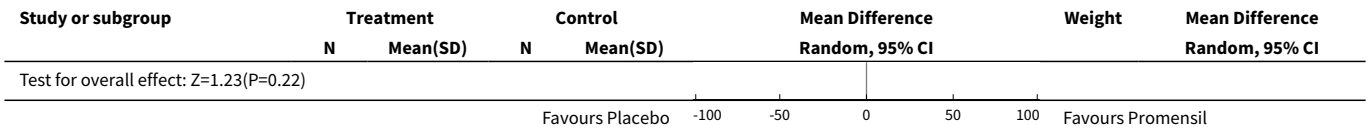
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 40mg/day							
Baber 1999	25	4.8 (3.4)	26	4 (2.6)		22.18%	0.88[-0.78,2.54]
Jeri 2002	15	3.6 (1.2)	15	5.1 (1.2)		32.85%	-1.5[-2.33,-0.67]
Knight 1999	12	4.9 (4.8)	12	5.8 (4.5)		8.08%	-0.9[-4.62,2.82]
Subtotal ***	**52**		**53**			**63.1%**	**-0.54[-2.34,1.27]**
Heterogeneity: Tau²=1.61; Chi²=6.32, df=2(P=0.04); I²=68.35%							
Test for overall effect: Z=0.58(P=0.56)							
1.1.2 80mg/day							
Tice 2003	84	5.1 (4.2)	85	5 (3.5)		28.33%	0.1[-1.07,1.27]
van De Weijer 2002	15	3.4 (3)	11	6 (5.5)		8.57%	-2.69[-6.28,0.9]
Subtotal ***	**99**		**96**			**36.9%**	**-0.76[-3.28,1.77]**
Heterogeneity: Tau²=2.04; Chi²=2.1, df=1(P=0.15); I²=52.37%							
Test for overall effect: Z=0.59(P=0.56)							
Total ***	**151**		**149**			**100%**	**-0.57[-1.76,0.62]**
Heterogeneity: Tau²=0.94; Chi²=9.99, df=4(P=0.04); I²=59.94%							
Test for overall effect: Z=0.94(P=0.35)							
Test for subgroup differences: Chi²=1.57, df=1 (P=0.21), I²=36.19%							



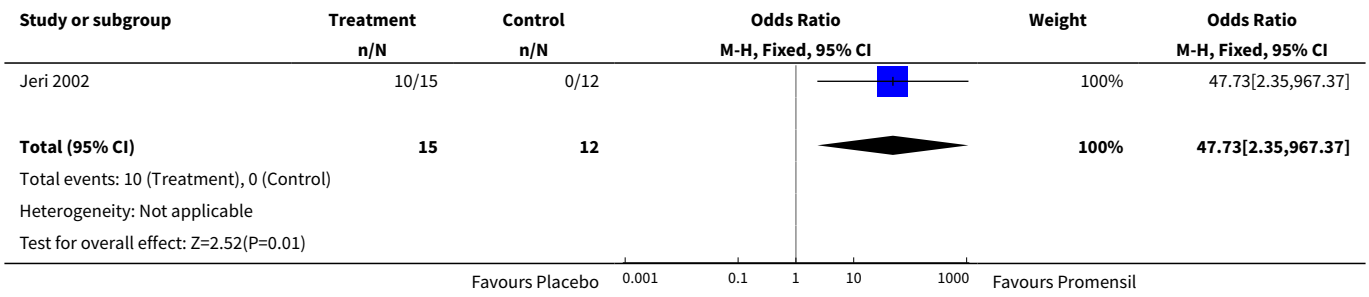
Analysis 1.2. Comparison 1 Promensil versus placebo, Outcome 2 Change in frequency of hot flushes (% reduction).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Jeri 2002	15	48.5 (27.9)	15	10.5 (37.2)		45.9%	38[14.47,61.53]
Tice 2003	84	41 (51.4)	85	36 (44.7)		54.1%	5[-9.53,19.53]
Total ***	**99**		**100**			**100%**	**20.15[-12.08,52.38]**
Heterogeneity: Tau²=444.95; Chi²=5.47, df=1(P=0.02); I²=81.72%							

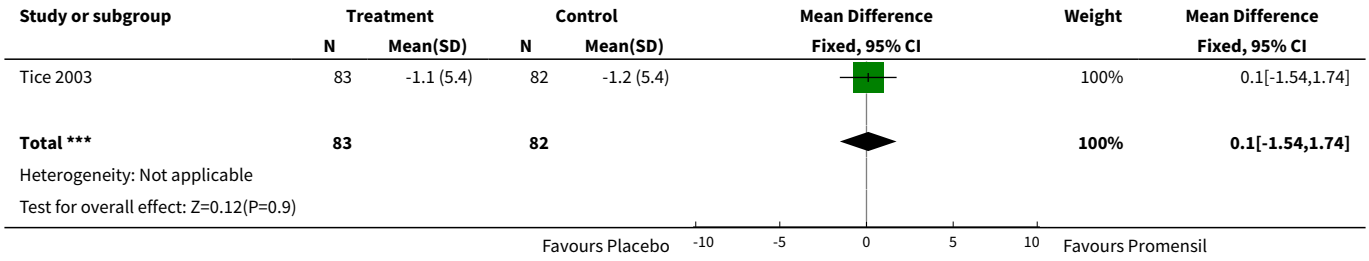




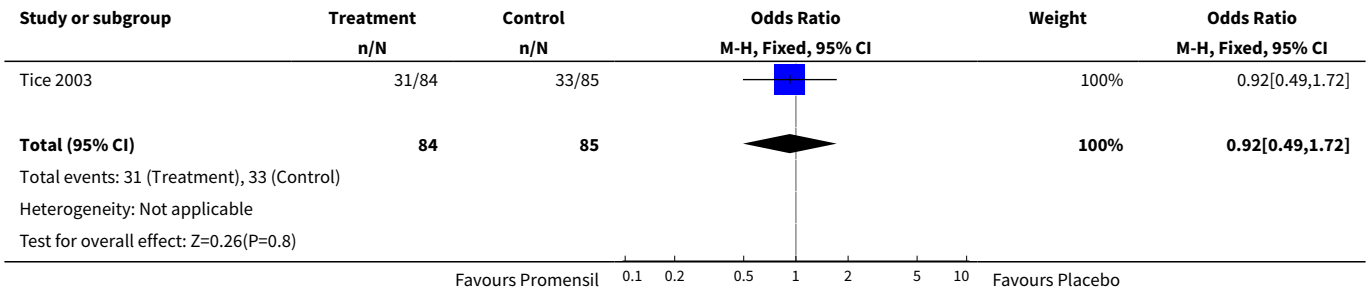
Analysis 1.3. Comparison 1 Promensil versus placebo, Outcome 3 Proportion with improvement in hot flush severity.



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

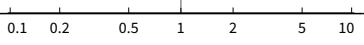


Analysis 1.5. Comparison 1 Promensil versus placebo, Outcome 5 Proportion with any adverse events.



Analysis 1.6. Comparison 1 Promensil versus placebo, Outcome 6 Incidence of specific adverse events.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Cold or upper respiratory tract infection (URTI)					
Tice 2003	9/84	14/85		100%	0.61[0.25,1.49]
Subtotal (95% CI)	**84**	**85**		**100%**	**0.61[0.25,1.49]**
Total events: 9 (Treatment), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.08(P=0.28)					
1.6.2 Headache					
Tice 2003	5/84	11/85		100%	0.43[0.14,1.28]
Subtotal (95% CI)	**84**	**85**		**100%**	**0.43[0.14,1.28]**
Total events: 5 (Treatment), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
1.6.3 Myalgia					
Tice 2003	10/84	7/85		100%	1.51[0.54,4.16]
Subtotal (95% CI)	**84**	**85**		**100%**	**1.51[0.54,4.16]**
Total events: 10 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					
1.6.4 Nausea					
Tice 2003	4/84	4/85		100%	1.01[0.24,4.19]
Subtotal (95% CI)	**84**	**85**		**100%**	**1.01[0.24,4.19]**
Total events: 4 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.99)					
1.6.5 Arthralgia					
Tice 2003	5/84	6/85		100%	0.83[0.24,2.84]
Subtotal (95% CI)	**84**	**85**		**100%**	**0.83[0.24,2.84]**
Total events: 5 (Treatment), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.29(P=0.77)					
1.6.6 Diarrhea					
Tice 2003	2/84	3/85		100%	0.67[0.11,4.09]
Subtotal (95% CI)	**84**	**85**		**100%**	**0.67[0.11,4.09]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					
1.6.7 Vaginal spotting					
Tice 2003	3/84	2/85		100%	1.54[0.25,9.44]
Subtotal (95% CI)	**84**	**85**		**100%**	**1.54[0.25,9.44]**
Total events: 3 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.64)					



Analysis 1.7. Comparison 1 Promensil versus placebo, Outcome 7 Endometrial thickness after treatment.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Baber 1999	25	3.3 (9)	26	3.2 (9.2)		100%	0.06[-4.94,5.06]
Total ***	**25**		**26**			**100%**	**0.06[-4.94,5.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.02(P=0.98)							

ADDITIONAL TABLES

Table 1. Quality assessment of included trials

Trial	Design	Randomisation proced	Allocation concealmt	Blinding	Power calc	ITT analysis	Dropouts	B'line comparability
Albertazzi 1998	Parallel	adequate	A	double	Yes	No	24% by end of 1st month	Yes
Baber 1999	Crossover	not reported	B	double	not reported	No	16% (8/51). 7 for personal reasons, 1 for medical reason not related to study	not reported
Balk 2002	Parallel	adequate	A	double	Yes, but insufficient	No	30% (8/27). 6 in soy grp (2 family, 2 medical, 1 ineffective, 1 lost to follow up); 2 in placebo grp (1 lack of efficacy, 1 bad taste of cereal)	Yes
Bica 2004	Parallel	adequate	A	triple	not reported	No	5% (4/75). 1 in soy grp (l follow up), 3 in placebo grp (2 adverse events, 1 other)	No
Brzezinski 1997	Parallel	not reported	B	none	Yes	No	21% (31/145). 17 in soy grp (4 taste, 2 symptoms, 11 personal), 14 control grp (7 symptoms, 7 personal)	Yes
Burke 2003	Parallel	not reported	B	double	not reported	No	12% (30/241). Not clear which grp - data were missing	No, did not include missing participants
Campagnoli 2005	Crossover	adequate	A	double	Yes	No	19% (7/36). Not clear which grp. 3 medical, 4 family	Yes
Crisafulli 2004	Parallel	adequate	B	double	Yes	Yes	8% (7/90). Reason or grp not given	Yes
Dalais 1998	Crossover	adequate	B	double	Yes	No	15% (8/52). Not clear which grp. 7 personal, 1 non compliant	Yes
Dodin 2005	Parallel	adequate	B	double	Yes	No	10% (20/199). 16 in flaxseed grp (7 medical, 3 non compliance, 4 personal, 1 symptomatic, 1 HRT); 4 in placebo grp (2 medical, 2 non compliant)	No, did not include dropouts
Duffy 2003	Parallel	not reported	B	double	not reported	No	8% (3/36). All from placebo grp - concurrent Rx.	No, did not include dropouts

Table 1. Quality assessment of included trials *(Continued)*

Faure 2002	Parallel	not reported	B	double	Yes	No	27% (20/75). 6 in soy grp (4 inefficacy, 1 l follow up, 1 other), 14 in placebo grp (11 inefficacy, 2 adverse events, 1 l follow up)	Yes
Han 2002	Parallel	adequate	B	double	not reported	No	2% (2/82). Not clear which grp. 1 inefficacy, 1 adverse event	No, did not include 2 dropouts
Heyerick 2006	Parallel	adequate	A	double	not reported	No	18% (12/67). 4 in hi phyto grp (3 no efficacy, 1 other), 1 in low phyto grp (no efficacy), 7 in placebo grp (all no efficacy)	No, did not include dropouts
Hidalgo 2005	Crossover	adequate	A	double	Yes, but insufficient	No	12% (7/60). Not clear which grp. 5 no reason, 2 adverse events	No, did not include dropouts
Imhof 2006	Crossover	not reported	B	double	not reported	No	4% (4/113) excluded post randomisation because they started ERT	not reported
Jeri 2002	Parallel	not reported	B	double	not reported	No	10% (3/30). All from placebo grp - no reasons.	Yes, but no table provided
Kaari 2006	Parallel	adequate	B	double	not reported	No	14% (11/79). 7 from soy grp (3 medical, 4 personal), 4 from E grp (1 medical, 1 no reason, 1 scared of biopsy, 1 personal)	No, did not include dropouts
Khaodhiar 2007	Parallel	not reported	B	double	not reported	No	20% (41/207) (not clear from which group, mostly for inability to follow protocol)	No, did not include dropouts
Knight 1999	Parallel	adequate	A	double	not reported	No	3% (1/37) for personal reason but replaced. 5% (2/37) withdrawn by GP.	Yes
Knight 2001	Parallel	adequate	A	double	not reported	No	17% (4/24). 3 from soy grp (taste), 1 from placebo grp (l follow up)	Yes
Kotsopoulos 2000	Parallel	not reported	B	double	not reported	No	20% (19/94). 10 in soy grp (7 could not accept Rx, 2 adverse events, 1 not known), 9 in placebo grp (6 could not accept Rx, 3 adverse events)	Yes
Lewis 2006	Parallel	adequate	A	double	not reported	No	12% (12/99). 2 in soy grp (1 could not accept Rx, 1 adverse event), 5 in flaxseed grp (2 could not accept Rx, 1 adverse event, 1 medical, 1 personal), 5 in placebo grp (1 could not	

Table 1. Quality assessment of included trials *(Continued)*

							accept Rx, 1 adverse event, 2 medical, 1 protocol violation).	
Penotti 2003	Parallel	adequate	B	double	done retrospectively	No	21% (13/62). 6 in soy grp (1 medical, 5 no efficacy), 7 in placebo grp (all no efficacy).	Yes
Sammartino 2003	Parallel	adequate	B	no	not reported	No	10% (7/70). 3 in genistin grp (2 no compliance, 1 personal), 4 in calcium grp (3 no compliance, 1 personal)	No, did not include dropouts
St Germain 2001	Parallel	not reported	B	double	Not reported	No	14% (11/80). Not clear which grp. 6 could not accept Rx, 1 died, 1 family member died, 2 medical, 1 non compliance.	No, did not include dropouts
Tice 2003	Parallel	adequate	A	double	Yes	Yes	2% (6/252). 2 in Promensil grp (1 no efficacy, 1 personal), 2 in Rimostil grp (1 adverse event, 1 physician advice), 2 in placebo grp (both personal)	Yes
Upmalis 2000	Parallel	not reported	B	double	not reported	No	31% (55/177). 31 in soy grp (9 did not meet inclusion, 11 protocol violation, 10 no reason, 1 adverse event), 24 in placebo grp (4 did not meet inclusion, 13 protocol violation, 7 no reason)	No, did not include dropouts
Van de Weijer 2002	Parallel	adequate	A	double	not reported	No	13% (4/30). All from lack of efficacy (1 in Promensil grp, 3 in placebo grp)	Yes
Woo 2003	Parallel	not reported	B	single (assessors)	Yes	No	7% (9/136). HRT 5 (adverse events, personal), 2 in phyto grp (1 medical, 1 personal), 2 in control grp (both personal)	No, did not include dropouts

Table 2. Summary of findings: efficacy outcomes

Trial	No	Intervention	Comparison	Duration	Efficacy outcomes	Results(btwn grp cp)
SOY DIETARY SUPPLEMENTS						
Albertazzi 1998	104	60 g soy powder (76 mg isoflavones)	Placebo (60 g casein)	12 weeks	No flushes/day after treatment; %age decrease in number of flushes	At end of study, a significant difference between placebo and soy: -1.59 (-1.95 to -1.2), p<0.01 representing a mean reduction of 1.6 flushes per day in soy group compared to placebo. 45% reduction in flushes with soy vs 30% reduction with placebo; p<0.01.
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 (1-4)	NS all outcomes
Brzezinski 1997	145	Phytoestrogen enriched diet (individualized by dietician) (isoflavone amount not given)	Control - regular diet (avoiding phytoestrogens)	12 weeks	MSQ hot flush severity reduction sub score (0-3)	Greater reduction with PE rich diet, p=0.004 (no CI given)

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

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	No and severity of flushes/sweats per day after Rx (symptom diary); also subgroup analysis in women with 4+ symptoms/d at baseline	NS all outcomes
Dalais 1998	52	(1) soy diet (53 mg/d isoflavones); (2) linseed diet (high in isoflavones - amount not given)	Placebo (wheat diet (low isoflavones))	12 weeks + 12 weeks	%age decrease in no of hot flushes	NS. 22% reduction with soy; 41% reduction with linseed; 51% reduction with wheat.
Knight 2001	24	Soy powder 60 g/d for beverage (134.4 mg/d isoflavones)	Placebo (casein powder for beverage)	12 weeks	No flushes/wk after Rx	NS. 29 flushes/wk in soy group; 46 flushes/wk in placebo group (reduction in 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) (0-3) after Rx	NS. 0.77 score with soy; 0.83 score with placebo
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; no flushes per day; severity of flushes (1-7 scale) after Rx	NS all outcomes
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	%age of participants perceiving a decrease in (1) frequency, (2) duration and (3) severity of flushes; no of flushes/wk after Rx; no of sweats/wk after Rx	NS

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

SOY EXTRACT						
Bica 2004	75	Standardized soy extract (33 mg/d isoflavones)	Placebo capsule	25 weeks	Greene vasomotor sub scale (intensity); %age who experienced a decrease in frequency of flushes and sweats from baseline	NS Greene vasomotor scale; 74% with soy vs 43% with placebo had decrease in no of hot flushes; p=0.007; 68% with soy vs 46% with placebo had decrease in no of night sweats; p=0.049. NS: severity of symptoms.
Campagnoli 2005	36	Standardized soy extract (Soy select) (60 mg/d isoflavones)	Placebo capsules	12 weeks + 12 weeks	No flushes/week after Rx	NS
Duffy 2003	36	Soy supplement capsules (Solgen) (60 mg/d isoflavones)	Placebo capsules	12 weeks	Greene vasomotor symptom score (severity)	NS
Faure 2002	75	Standardized soy extract capsules (70 mg/d isoflavones)	Placebo capsules	16 weeks	%age decrease in flushes/day; %age of 'responders' (participants who had reduction of at least 50%)	61% decrease with soy vs 21% reduction with placebo (p value not reported); 66% of soy group were responders vs 34% in placebo group; p<0.005.

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

						Repeated measures analysis confirmed the soy-placebo treatment effect.
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 vs 9.9 in placebo group; p<0.01
Kaari 2006	79	Soy extract capsules (S40/Ach-1) (120 mg/d isoflavones)	Estrogen + placebo capsules	24 weeks	%age of participants reporting reduction (subgroup)	NS
Khaodhiar 2007	207	Soy extract capsule (isoflavone quantity not known) (1) 40 mg/d, (2) 60 mg/d	Placebo	12 weeks	%age reduction in frequency of hot flushes (from daily diary), %age reduction in severity of hot flushes (daily diary)	50% reduction in hot flush frequency in both soy groups at 12 weeks compared to 38% reduction with placebo (NS). When both treatment groups were combined, there was an average reduction of 1.2 more flushes per day in

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

						women on soy compared to women on placebo (p=0.016). NS for hot flush severity score (p=0.07)
Penotti 2003	62	Soy tablets (72 mg/d isoflavones)	Placebo tablets	24 weeks	No flushes per day after Rx	NS
Upmalis 2000	177	Standardized soy extract tablets (50 mg/d of genistin and daidzin)	Placebo tablets	12 weeks	%age change in flush severity/wk; %age change in flush frequency/wk; %age change in sweat frequency/wk	34% change in severity with soy vs 21% change in severity with placebo: p=0.01); NS for %age change in frequency (p=0.078 repeated measures analysis); NS for change in reduction of night sweats.
RED CLOVER EXTRACTS						
Baber 1999	51	Promensil (standardised red clover extract) (40 mg/d isoflavones)	Placebo tablet	12 weeks + 12 weeks	No flushes per day after Rx; %age flush reduction	NS
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 vs 98%

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

						with placebo; night sweats: 30% with red clover vs 93% with placebo; p value not given
Jeri 2002	30	Promensil (standardized red clover extract) (40 mg/d isoflavones)	Placebo tablet	16 weeks	%age reduction in no flushes per day; severity of flushes per day (scale)	Frequency: 49% reduction with red clover vs 11% reduction with placebo: p<0.001); severity: reduction from 2.53 to 1.33 with red clover vs no reduction with placebo: p<0.001.
Knight 1999	37	Promensil (standardized red clover extract) (40 mg/d isoflavones)	Placebo tablet	12 weeks	No flushes per day	NS
Tice 2003	252	(1) Promensil (standardized red clover extract) (82 mg/d isoflavones - 2 tablets); (2) Rimostil (standardized red clover extract) (57 mg/d isoflavones - 2 tablets)	Placebo tablets	12 weeks	No flushes per day; %age reduction in flushes; rate of reduction over time	No flushes per day NS; %age reductions NS; Promensil had faster reduction over time vs placebo (p=0.03)

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

Van de Weijer 2002	30	Promensil (standardized red clover extract) (80 mg/d isoflavones - 2 tablets)	Placebo tablets	12 weeks	No flushes per day; median %age change in no of flushes	3.4 flushes per day with Promensil vs 6 flushes per day with placebo (p value not reported); 44% reduction with Promensil vs 0% reduction with placebo: p=0.01 (variation not reported)
OTHER PHYTOESTROGENS						
Crisafulli 2004	90	(1) Genistein extract (54 mg/d isoflavones); (2) continuous HRT (17B estradiol 1mg/d + norethisterone acetate)	Placebo tablets	1 year	%age change in no of flushes per day	24% reduction with genistein when compared with placebo: p<0.01; 30% reduction with HRT when compared with genistein: p<0.05
Dodin 2005	112	Flaxseed dietary supplement (in bread and ground grain) (21,071ug lignans)	Placebo (wheat germ) (196ug lignans)	1 year	Menoquol hot flush and sweat scores (severity)	NS
Heyerick 2006	67	(1) hop extract 1 (100ug 8-prenylnaringenin); (2) hop extract	Placebo capsule	12 weeks	Kupperman hot flush score (severity)	NS at the end

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

		2 (250ug 8-prenylnaringenin) (Menohop)				of the study period
Woo 2003	136	Sachets of Pueraria lobata (Chinese medicinal herb) (100 mg/d isoflavones)	(1) Sequential HRT (CEE 0.625 mg/d continuously + MPA 5mg/d for 14 days of cycle), (2) no treatment	12 weeks	Vasomotor symptom score; mean change in score (menopause questionnaire)	NS
Dalais 1998		see above for results in the flaxseed arm				
Lewis 2006		see above for results in the flaxseed arm				

Table 3. Summary of findings: safety outcomes

Trial	No	Intervention	Comparison	Duration	Safety outcomes	Results(btwn grp cp)
SOY DIETARY SUPPLEMENTS						
Albertazzi 1998	104	60g soy powder (76 mg isoflavones)	Placebo (60g casein)	12 wks	Adverse events	NS
Balk 2002	27	Soy and corn flour cereal (100 mg/d isoflavones)	Placebo (wheat cereal)	24 wks	Endometrial stimulation; adverse events	Endometrial stimulation: NS (all participants had atrophic endometrium). Adverse events: NS
Dalais 1998	52	(1) soy diet (53 mg/d isoflavones), (2) linseed diet (high in isoflavones - amount not given)	Placebo (wheat diet - low isoflavones)	12 wks + 12 weeks	Vaginal maturation index (%age increase from baseline)	Increase of 103% with soy diet (p=0.03), 6% increase with linseed (NS), 11% increase with placebo (NS)

Table 3. Summary of findings: safety outcomes *(Continued)*

Knight 2001	24	Soy powder 60g/d for beverage (134.4 mg/d isoflavones)	Placebo (casein powder for beverage)	12 wks	Adverse events; vaginal maturation index	Total adverse events: 75% with soy vs 17% with placebo, p<0.001; vaginal maturation index NS
Kotsopoulos 2000	94	Soy powder for beverage (118 mg/d isoflavones)	Placebo (casein powder for beverage)	12 wks	Adverse events	Total adverse events NS
SOY EXTRACTS						
Bica 2004	75	Standardized soy extract (33 mg/d isoflavones)	Placebo capsule	25 wks	Vaginal maturation index; vaginal pH (% with improvement)	Maturation: NS; pH: 21% with soy vs 11% with placebo had improvement in pH, p=0.008
Campagnoli 2005	36	Standardized soy extract (Soyselect) (60 mg/d isoflavones)	Placebo capsules	12 wks + 12 weeks	Vaginal maturation index	NS
Faure 2002	75	Standardized soy extract capsules (7mg/d isoflavones)	Placebo capsules	16 wks	Adverse events	NS
Han 2002	80	Soy capsules (100 mg/d isoflavones)	Placebo capsules	16 wks	Endometrial thickness	NS
Kaari 2006	79	Soy extract capsules (S40/Ach-1) (120 mg/d isoflavones)	Estrogen + placebo capsules	24 wks	Vaginal pH; vaginal maturation index; endometrial thickness; endometrial stimulation; adverse events	pH: 5.5 in soy grp vs 4.8 in ERT grp: p=0.0012; maturation index: significant difference in intermediate and superficial cells frequency in ERT grp when compared with soy grp (p value not given); endometrial thickness: 5.9 mm in ERT grp vs 3.0 mm in soy grp (significant, p value not given); non atrophic

Table 3. Summary of findings: safety outcomes *(Continued)*

						endometrium: 54% in ERT grp vs 88% in soy grp, p<0.01; adverse events: 17% genital bleeding in ERT grp vs 0% in soy grp.
Khaodhiar 2007	207	Soy extract capsules (isoflavone quantity not known) - 2 different doses: 40 mg/d and 60 mg/d	Placebo	12 wks	Adverse events	Very few events reported - no group comparisons reported
Penotti 2003	62	Soy tablets (72 mg/d isoflavones)	Placebo tablets	24 wks	Endometrial thickness	NS
Upmalis 2000	177	Standardized soy extract tablets (50 mg/d of genistin and daidzin)	Placebo tablets	12 wks	Adverse effects; vaginal pH; vaginal maturation index; endometrial thickness	Adverse events: 34% (30/89) of soy grp reported 70 events vs 45% (39/86) in placebo grp reported 79 events (no p value); pH: NS; maturation index NS; endometrial thickness: NS
RED CLOVER EXTRACTS						
Baber 1999	51	Promensil	Placebo	12 wks + 12 weeks	Endometrial thickness	NS
Hidalgo 2005	60	Red clover supplement capsules (80 mg/d isoflavones)	Placebo	12 wks + 12 weeks	Vaginal cytology (karyopyknotic index, cornification index, maturation index)	Significant changes (p<0.05) in all indexes when compared with placebo.
Imhof 2006	113	Red clover extract capsules (80 mg/d isoflavones)	Placebo	12 wks + 12 weeks	Endometrial thickness	Significant decrease in thickness with red clover (15%) but not with placebo (placebo values not given), p<0.001

Table 3. Summary of findings: safety outcomes *(Continued)*

Tice 2003	252	(1) Promensil (standardized red clover extract) (82 mg/d isoflavones - 2 tablets); (2) Rimostil (standardized red clover extract) (57 mg/d isoflavones - 2 tablets)	Placebo	12 wks	Adverse events	NS
OTHER PHYTOESTROGENS						
Crisafulli 2004	90	(1) Genistein extract (54 mg/d isoflavones); (2) continuous HRT (17B estradiol 1mg/d + norethisterone acetate)	Placebo	1 year	Endometrial thickness	NS
Sammartino 2003	70	Genistin extract tablets (amount of isoflavones not given)	Placebo tablets	1 year	Endometrial thickness	NS
Dalais 1998		see above for results in the flaxseed arm				

Table 4. Summary of findings: acceptability outcomes

Trial	No	Intervention	Comparison	Duration	Outcomes	Results(btwn grp cp)
Albertazzi 1998	104	60g soy powder (76 mg/d isoflavones)	Placebo	12 wks	Withdrawal because of adverse events	20% in soy grp vs 23% in placebo grp (p value not reported
Knight 2001	24	Soy powder 60g/d for beverage (134.4 mg/d isoflavones)	Placebo	12 wks	Withdrawal because of adverse events	25% in soy grp vs 8% in placebo grp (p value not reported)
Kotsopoulos 2000	94	Soy powder for beverage (118 mg/d isoflavones)	Placebo	12 wks	Withdrawal because of adverse events or inability to tolerate the treatment	20% in soy grp vs 18% in placebo grp (p value not given)

WHAT'S NEW

Date	Event	Description
20 September 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 1999
Review first published: Issue 4, 2007

Date	Event	Description
6 November 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, data entry and wrote the review.
Julie Brown undertook searches, selection of studies, data extraction, contact with authors, quality assessment and commented on the final version of the review.
Jane Marjoribanks undertook data extraction, quality assessment, preparation of tables and commented on the final version of the review.
Fredi Kronenberg undertook selection of studies, data extraction, quality assessment and commented both on 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 has 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

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Female; Humans