



Menopause: a review of botanical dietary supplements

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Since the release of the Women's Health Initiative (WHI) findings, an increasing number of dietary supplement products specifically targeting women in menopause have appeared in the American marketplace. This growth highlights the need for a critical evaluation of the tolerability and effectiveness of these products. The purpose of this article is to assess the evidence for safety and benefit of botanical monoprparations used for relief of menopause-related symptoms. The Cochrane Library and Medline databases were searched from January 1966 to October 2004, using a detailed list of terms related to botanicals and menopausal symptoms. Studies were considered eligible (1) if they were controlled trials of a botanical monoprparation administered orally for a minimum of 6 weeks to perimenopausal or postmenopausal women with hot flashes and (2) if they included a placebo or comparative treatment arm. Topical preparations, botanical combinations, and dietary interventions, such as soy food or protein, were not included. No language restrictions were imposed on the search. A total of 19 studies met the inclusion criteria. The majority of studies indicate that extract of black cohosh (*Actaea racemosa* L.) improves menopause-related symptoms; however, methodologic shortcomings in the trials were identified. To date, 4 case reports of possible hepatotoxicity have been published, although previous safety reviews suggest that black cohosh is well tolerated and that adverse events are rare when it is used appropriately. The results of 6 clinical studies on soy (*Glycine max* L.) isoflavone extracts are mixed. Moreover, the composition and dose of soy supplements varies widely across studies, making comparisons and definitive conclusions difficult. One study challenged the long-term safety of high-dose soy isoflavone extract (150 mg/day for 5 years) on the uterine endometrium. Clinical data from 5 controlled trials assessing the efficacy of semipurified isoflavone red clover (*Trifolium pratense* L.) leaf extracts to reduce hot flash frequency and severity or to relieve symptoms associated with the domains of the Greene Menopausal Symptom Scale are contradictory. The largest study showed no benefit for reducing symptoms associated with menopause for 2 different red clover isoflavone products compared with placebo. No significant adverse events have been reported in the literature. Single clinical trials do not support the use of dong quai (*Angelica sinensis* L.), ginseng (*Panax ginseng* C.A. Mey), or evening primrose seed oil (*Oenothera biennis* L.) for improving menopausal symptoms. We conclude that black cohosh extracts appear to ease menopausal symptoms; ongoing studies funded by the National Institutes of Health (NIH) will provide more definitive safety and efficacy data. Soy isoflavone extracts appear to have minimal to no effect, although definitive conclusions are difficult given the wide variation in product composition and dose. Long-term safety of higher dosage (150 mg/day) soy isoflavone extracts is uncertain. Semipurified isoflavone red clover leaf extracts have minimal to no effect in reducing menopausal symptoms. Dong quai, ginseng extract, and evening primrose seed oil appear to be ineffective in ameliorating menopausal symptoms at the dosages and in the preparations used in these studies.

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When the Women's Health Initiative (WHI) was discontinued owing to unanticipated increases in risk for breast cancer, stroke, heart attack, and blood clots among women taking estrogen plus progestin, the search for alternative treatments that were perceived to offer beneficial effects with less risk intensified. Some women turned to botanical dietary supplements with the presumption that these "natural substances" are relatively safe and effective. Whether these presumptions are correct remains to be seen.

Although botanical remedies have been used for centuries, many products in the American marketplace bear little resemblance to the simple preparations of the past. Potent, concentrated products extracted via a range of solvents may be consumed for prolonged periods, often in combination with over-the-counter and prescription drugs—unique circumstances when compared with use of the apothecary of yesteryear. Thus, a "long history" of use cannot be presupposed, and questions of safety and efficacy must continue to be entertained.

The purpose of this article is to systematically assess the evidence for safety and benefit of single constituent botanical products (often referred to as *monopreparations*) for the treatment of menopause-related symptoms. This review is based on the most rigorous scientific studies published in peer-reviewed literature.

Methods

The Cochrane Library and Medline databases were searched from January 1966 to October 2004, using a detailed list of terms related to botanicals and menopausal symptoms. Terms used in the search included the following: menopause, hot flashes, climacteric, herb, botanical, phyto-, phytoestrogen, isoflavone, soy, black cohosh, *Cimicifuga*, *Actaea*, red clover, *Trifolium*, dong quai, *Angelica*, licorice, wild yam, *Dioscorea*, ginseng, *Panax*, evening primrose oil, γ -linolenic acid, hops, kava, *Piper methysticum*, St. John's wort, *Hypericum*, chastetree, *Vitex*, valerian, and motherwort. References were then reviewed to identify additional studies.

Study selection

Studies were considered eligible (1) if they were controlled trials of a botanical monopreparation administered orally for a minimum of 6 weeks to perimenopausal or postmenopausal women with hot flashes and (2) if they included a placebo or comparative treatment arm. Topical preparations, botanical combinations, and dietary interventions, such as soy food or protein, were not included. No language restrictions were imposed. A total of 19 studies met the inclusion criteria.

Results

Black cohosh (*Actaea racemosa* L.; *Cimicifuga racemosa* [L.] Nutt.)

The root and rhizome of black cohosh, an indigenous North American herb, have been researched for >30 years for the relief of menopause-related symptoms. German health authorities endorse the use of black cohosh extract for premenstrual discomfort, dysmenorrhea, and menopause.¹ Similarly, the World Health Organization (WHO)² recognizes its use for "treatment of climacteric symptoms such as hot flashes, profuse sweating, sleeping disorders and nervous irritability." The North American Menopause Society³ recommends black cohosh, in conjunction with lifestyle approaches, as a treatment option for women with mild menopause-related symptoms.

Of 13 published trials identified for black cohosh, 5 met criteria for inclusion in this review (Table 1).⁴⁻⁸

Efficacy

Most studies indicate that black cohosh extract reduces some symptoms associated with menopause; however, methodologic shortcomings and variations in product and dosage limit definitive conclusions. The randomized, double-blind study by Stoll⁵ reported a statistically significant ($P < 0.001$) reduction in Kupperman Index (KI) and Hamilton Anxiety Rating Scale (HAM-A) scores among women assigned to black cohosh compared with those given conjugated estrogens or placebo. Daily hot flash incidence decreased from 4.9 to 0.7 in the black cohosh group, from 5.2 to 3.2 in the estrogen group, and from 5.1 to 3.1 in the placebo group. Attrition bias may have occurred; 12 of 30 women dropped out of the estrogen group between weeks 5 and 8 due to "perceived lack of efficacy," a finding that, in itself, raises questions about the study. Lehmann-Willenbrock and Riedel⁶ found black cohosh reduced KI scores as effectively as hormone therapy (HT). However, their study suffered from small sample size, lack of a placebo arm, lack of blinding, and no description of the randomization process. The trial by Warnecke⁴ reported "highly significant reduction" in all outcome measures, but it did not report calculations or provide analytical details. The study lacked a placebo arm and included diazepam—a drug not typically used for relief of menopausal symptoms—in 1 treatment arm. Wuttke and coworkers⁸ found a statistically significant reduction in the Menopause Rating Scale (MRS) score among women taking black cohosh compared with those assigned to placebo; however, reduction in hot flashes (item 1 on the MRS) did not differ significantly between the black cohosh and placebo groups. Jacobson and colleagues⁷ failed to detect any reduction in hot flash frequency or severity among breast cancer survivors taking black cohosh. This study included a large number of participants (69%) taking tamoxifen, a drug

Table 1 Controlled trials of black cohosh

Study	N	Sample	Control	Treatment	Primary Outcome Measures	Results
Warnecke ⁴	60	Peri- and postmenopausal women	CEs (0.6 mg/day) or diazepam (2 mg/day) for 12 wk	40 drops Remifemin* liquid extract bid (4 mg/day 27-deoxyactein) for 12 wk	KI, HAM-A score, Global Impressions, and Self-Assessment Depression Scale	All 3 groups showed significant decrease in neurovegetative and psychological symptoms. Black cohosh and estrogen groups experienced proliferation of vaginal epithelium. No significant adverse effects noted.
Stoll ⁵	80	Postmenopausal women	CEs (0.625 mg/day) or placebo for 12 wk	Remifemin 4 mg (27-deoxyactein) bid for 12 wk (equivalent to 80 mg bid extract)	KI, HAM-A score	Remifemin group had most pronounced reduction in KI and HAM-A scores compared with estrogen and placebo groups ($P < 0.001$). Remifemin group had most significant change in proliferation of vaginal epithelium ($P < 0.01$).
Lehmann-Willenbrock and Riedel ⁶	60	Surgically menopausal women	Estriol (1 mg/day) or CEs (1.25 mg/day) or estrogen + progestin therapy (2 mg/day estradiol + 1 mg/day norethisterone acetate) for 6 mo	Remifemin 4 mg bid (27-deoxyactein) for 6 mo (equivalent to 80 mg bid extract)	KI	Authors concluded that all 3 groups had decreased KI; no significant difference. Remifemin group had no change in LH or FSH level.
Jacobson et al ⁷	85	Women with vasomotor symptoms and history of breast cancer	Placebo for 60 days	20 mg bid of an unspecified black cohosh product for 60 days	4-day hot flash diary; menopausal symptom questionnaire	Black cohosh was not significantly more efficacious than placebo for hot flash number or intensity; sweating was the only symptom with significantly greater improvement over placebo. No change in FSH or LH level in either group.
Wuttke et al ⁸	62	Postmenopausal women	CE (0.6 mg/day); or placebo for 12 wk	CR BNO 1055/ Menofem [†] (40 mg/day) for 12 wk	MRS	Statistically significant reduction in MRS score; however, reduction in hot flashes (item 1 on MRS) did not differ significantly between groups. Beneficial effect on bone metabolism and vaginal cytology reported in both CE and CR BNO groups. CR BNO had no effect on endometrial thickness, which was increased by CE.

CE = conjugated estrogen; FSH = follicle-stimulating hormone; HAM-A = Hamilton Anxiety Rating Scale; KI = Kupperman Index; LH = luteinizing hormone; MRS = Menopause Rating Scale.

*Remifemin (black cohosh; Schaper & Brummer GmbH & Co. KG, Salzgitter, Germany). Remifemin preparations are standardized to contain 1 mg triterpene glycosides (expressed as 27-deoxyactein (23-epi-26-deoxyactein) in each dose, equivalent to 20 mg root/rhizome.

[†]Menofem (CR BNO aqueous ethanolic extract of black cohosh; Bionorica AG, Neumarkt, Germany).

Table 2 Placebo-controlled trial of dong quai

Study	N	Sample	Control	Treatment	Primary Outcome Measures	Results
Hirata et al ²⁵	71	Postmenopausal women	Placebo for 24 wk	Dong quai, 3 capsules tid (4.5 g/day) for 24 wk	KI, hot flash frequency	No difference between groups in serum hormone levels, vaginal cytology, hot flashes, KI scores

KI = Kupperman Index.

known to induce hot flashes, and thus limited the generalization of the results to women going through natural menopause and not taking tamoxifen.

Safety

Our understanding of the mechanism of action of black cohosh is a work in progress, but recent research suggests a nonhormonal effect.⁹ An abstract reporting increased metastases from breast to lung in mice given black cohosh has raised questions concerning safety for women with breast cancer¹⁰; however, other studies in animals have not found an effect on mammary tumors.^{11,12} Four case reports^{13–16} purportedly link black cohosh use with acute liver disease in 5 patients. Evaluation of these reports is difficult, however, because 2 of the 5 cases involved combination herbal products, 3 cases failed to analyze suspected products for purity and identification, and 1 case did not report the brand or dose of black cohosh consumed. No serious adverse events have been reported in published clinical trials, and 2 safety reviews have found black cohosh extract to be well tolerated and adverse events to be rare when it is taken for up to 6 months.^{17,18}

Dose and preparation

There is a wide variety of black cohosh products and formulations available in the American marketplace, including combination preparations. Clinical trials have been conducted on 2 proprietary preparations. The majority of studies used Remifemin (Schaper & Brummer GmbH & Co. KG, Salzgitter, Germany), although the method of extraction in this preparation has changed over time from hydroethanolic (60% ethanol by volume) to isopropyl alcohol (40% by volume) and the dosage form has changed from liquid to tablets, thus complicating any comparison of research trials. In 2 recent studies, investigators used CR BNO 1055, an aqueous ethanolic extract (58% vol/vol), sold as Klimadynon and Menofem (Bionorica AG, Neumarkt, Germany). It is unclear whether pharmacologic equivalence can be assumed between products. The dose of extract used in clinical trials is 40 to 160 mg/day.

Conclusion

Most published reviews^{19–24} lend support for the contention that black cohosh extract is beneficial for the relief of

menopause-related symptoms; however, clinical trials published to date suffer from methodologic shortcomings that necessarily temper endorsement of this botanical. It is hoped that ongoing National Institutes of Health (NIH)–funded clinical studies will provide more definitive information regarding safety and efficacy of black cohosh for the alleviation of menopausal symptoms.

Dong quai (*Angelica sinensis* [Oliv.] Diels)

Dong quai root has been used to treat a variety of disorders in traditional Chinese medicine (TCM) for ≥ 20 centuries and is now quite popular in the US marketplace. Our search revealed 1 published clinical trial on dong quai that met the inclusion criteria (**Table 2**).²⁵

Efficacy

A double-blind study by Hirata and coworkers²⁵ failed to find any benefit for women receiving 4.5 g/day dong quai (aqueous extract standardized to 0.5 mg/kg of ferulic acid) when compared with placebo with respect to relief of hot flashes or other menopausal symptoms captured by the KI over a 24-week period.

Dong quai is not typically used in TCM to treat menopausal symptoms, nor is it typically administered as a single agent. However, since the majority of dong quai products sold in the United States are not prepared in accordance with TCM principles, the findings of Hirata and coworkers²⁵ may be relevant to over-the-counter use of the botanical.

Safety

There is little information available on the hormonal effects of dong quai. Hirata and coworkers²⁵ did not detect any change in serum hormone levels or vaginal cytology. One case report of male gynecomastia was purportedly caused by dong quai ingestion.²⁶ No significant adverse effects are reported in the literature; however, a case report²⁷ and results of animal research²⁸ suggest a possible herb-drug interaction between dong quai and warfarin.

Table 3 Placebo-controlled trial of evening primrose seed oil

Study	N	Sample	Control	Treatment	Primary Outcome Measures	Results
Chenoy et al ³⁰	56	Postmenopausal women	Placebo for 24 wk	4 capsules evening primrose oil capsules bid (4,000 mg/day) for 24 wk	KI, hot flash and sweating episode frequency	No significant difference in any outcome measure between active and placebo groups

KI = Kupperman Index.

Dose and preparation

There are numerous dong quai products in the American marketplace, the majority of which are combination preparations. No particular product dominates the marketplace, and most are not standardized to any constituent. The recommended "serving size" varies across manufacturers, but most recommend 3 to 6 g/day, usually taken in 3 divided doses.²⁹

Conclusion

Based on the data from Hirata and coworkers,²⁵ dong quai as a single therapeutic intervention does not appear to be an effective treatment for relieving the vasomotor symptoms of menopause. However, the paucity of data limits definitive conclusions.

Evening primrose seed oil (*Oenothera biennis* L.)

Evening primrose oil is extracted from the seeds of the evening primrose plant, a wildflower native to North America. The seed oil is a rich source of linoleic acid and γ -linolenic acid. Our search identified 1 clinical trial evaluating the efficacy of evening primrose oil for the relief of menopausal symptoms (**Table 3**).³⁰

Efficacy

The study by Chenoy and colleagues³⁰ randomized 56 women reporting >3 hot flashes per day to 2,000 mg evening primrose oil plus 20 mg vitamin E or placebo twice daily for 24 weeks. The investigators did not find any significant benefit for evening primrose oil over placebo in relieving the vasomotor symptoms of menopause. However, the trial was small and suffered from attrition; only 35 participants completed the study.

Safety

Evening primrose oil is generally well tolerated. Mild nausea, diarrhea, flatulence, and bloating have been reported in some individuals.³¹ Limited data suggest a possible aggravation of temporal lobe epilepsy.³²

Dose and preparation

Evening primrose oil products generally are standardized to contain 320 to 360 mg linoleic acid and 40 mg γ -linolenic acid per capsule, although levels vary between manufacturers. Vitamin E may be added to prevent rancidity. The recommended dosage ranges from 3 to 6 g/day.

Conclusion

There was no demonstrated benefit for evening primrose oil over placebo in relieving menopause-related symptoms. However, the paucity of data limits any definitive conclusions.

Ginseng (*Panax ginseng* C.A. Mey)

Ginseng root has held a place of importance in Asian medicine for millennia, and it is among the most popular herbal supplements sold in the American market. The common name, *ginseng*, is used to describe a number of chemically different species of *Panax*. Thus, caution must be exercised when interpreting data between species. The German Commission E¹ and the WHO³³ endorse the use of *Panax ginseng* as a tonic or restorative agent for invigoration and fortification in times of fatigue, debility, or physical or mental exhaustion. We found 1 clinical trial that met our criteria (**Table 4**).³⁴

Efficacy

Wiklund and colleagues³⁴ conducted a randomized, double-blind, placebo-controlled study of ginseng in 384 women reporting ≥ 6 hot flashes on ≥ 3 days per week. Subjects received either 200 mg/day ginseng extract or placebo for 16 weeks. With regard to the primary end point, the Psychological General Well-Being (PGWB) index, ginseng showed a tendency only for better overall symptomatic relief ($P < 0.1$). Exploratory analysis of PGWB subsets, however, reported favorable results for ginseng compared with placebo ($P < 0.05$) on the depression, well-being, and health subscales.

Table 4 Placebo-controlled trial of ginseng

Study	N	Sample	Control	Treatment	Primary Outcome Measures	Results
Wiklund et al ³⁴	384	Symptomatic postmenopausal women	Placebo for 16 wk	4 capsules evening primrose oil bid (4,000 mg/day) for 24 wk	Hot flash and sweating episode frequency, PGWB, WHQ, VAS	No significant difference in any outcome measure between active and placebo groups

PGWB = Psychological General Well-Being index; WHQ = Women's Health Questionnaire; VAS = Visual Analogue scale.

Safety

A systematic review³⁵ found that *Panax ginseng* mono-preparations are rarely associated with adverse events or drug interactions, and the few effects reported were mild and transient. Data from clinical trials suggest that the incidence of adverse events is similar for ginseng and placebo, with subjects reporting headache as well as sleep and gastrointestinal disturbances.

Dose and preparation

There are numerous products and formulations of ginseng available in the United States. Doses of standardized extract range from 100 to 600 mg per day. Ginsana (standardized to 4% ginsenosides; Pharmaton S.A., Lugano, Switzerland, distributed by Pharmaton Natural Health Products) was the product used in the study by Wiklund and colleagues.³⁴

Conclusion

Panax ginseng may be helpful with respect to quality-of-life outcomes, such as well-being, mood, and sleep. However, based on the results of 1 large clinical trial, it does not appear to be beneficial for vasomotor symptoms.

Red clover (*Trifolium pratense* L.)

Although red clover blossoms have been used in traditional herbal medicine for centuries, it is the semipurified isoflavone leaf extracts for relief of menopause-related symptoms that interest researchers. Red clover contains isoflavones, which are sometimes referred to as phytoestrogens because of their estrogen-like effects. Isoflavones may act as an estrogen agonist or antagonist depending on the individual compound and level present in the body. We found 5 clinical trials that met our inclusion criteria (Table 5).^{36–40}

Efficacy

The largest study of semipurified isoflavone red clover leaf extracts by Tice and colleagues³⁶ randomized 252 postmenopausal women reporting ≥ 35 hot flashes per week to Promensil (red clover isoflavones; Novogen Ltd., North

Ryde, New South Wales, Australia) 82 mg/day, Rimostil (red clover isoflavones; Novogen Ltd.) 57 mg/day, or placebo for 12 weeks. There was no significant benefit for either red clover product over placebo in improving hot flash frequency or Greene Menopause Symptom score. Women receiving Promensil initially had a more rapid decline in hot flash frequency compared with women in the other 2 groups. However, at 12 weeks, the reduction in mean number of daily hot flashes was similar for women receiving Promensil (41%), Rimostil (34%), and placebo (36%).

The crossover study by Baber and colleagues⁴⁰ administered Promensil 40 mg/day isoflavones or placebo to 51 menopausal women for 12 weeks, followed by all participants receiving 1 month of placebo, and then 12 weeks of the alternate arm. There were no significant differences in hot flashes, flushing, or other physiologic parameters between the Promensil and placebo groups. Limitations of the study include small sample size, single-blind design, and the finding that some women in the placebo groups had higher urinary isoflavone levels at the end of the trial compared with baseline, raising questions about possible dietary confounders. Knight and coworkers³⁹ reported no statistically significant difference in alleviation of symptoms between groups receiving isoflavones 40 mg/day, isoflavones 160 mg/day, or placebo (reduction in hot flashes of 29%, 34%, and 29%, respectively). The study was small; only 37 postmenopausal women were enrolled.

In contrast to these negative findings, 2 smaller studies^{37,38} found a statistically significant reduction in hot flash frequency among women taking Promensil compared with placebo. van de Weijer and Barentsen³⁷ randomized 30 women reporting ≥ 5 hot flashes per day to either Promensil (80 mg/day isoflavones) or placebo for 12 weeks. Hot flash frequency was significantly ($P < 0.01$) lower in women receiving red clover, although no significant difference was seen in the Greene score across groups. The study was limited by its small sample size, lack of detailed description of methodology or calculations, and lack of intention-to-treat analysis. Jeri³⁸ compared Promensil (40 mg/day isoflavones) with placebo for 16 weeks in a small sample ($N = 30$) of women in Peru. A significant ($P < 0.001$) reduction in hot flash frequency (48.5%) and severity was reported in the active group compared with the

Table 5 Placebo-controlled trials of red clover

Study	N	Sample	Control	Treatment	Primary Outcome Measures	Results
Tice et al ³⁶	252	Postmenopausal women	Placebo for 12 wk	Promensil* (82 mg/day isoflavones) or Rimostil† (57 mg/day isoflavones) for 12 wk	Hot flash frequency, changes in QOL	No significant difference between groups in hot flash frequency. Greene scale or adverse events
van de Weijer and Barentsen ³⁷	30	Postmenopausal women	Placebo for 12 wk	Promensil (80 mg/day isoflavones) for 12 wk	Hot flash frequency, Greene Menopause Symptom score	Reduction in hot flash frequency per day in active treatment (5.4 to 3.4) compared with placebo (5.8 to 6.0; $P < 0.01$). No significant difference in Greene score
Jeri ³⁸	30	Postmenopausal women	Placebo for 16 wk	Promensil (40 mg/day isoflavones) for 16 wk	Hot flash frequency and severity	Reduction in hot flash frequency (48.5%) and severity (47%) significantly greater with active treatment than placebo (10.5% reduced frequency and no change in severity; $P < 0.001$)
Knight et al ³⁹	37	Postmenopausal women	Placebo for 12 wk	Promensil (160 mg/day isoflavones) or Promensil (40 mg/day isoflavones) for 12 wk	Hot flash frequency and Greene Menopause Symptom score	No statistically significant difference between 2 red clover arms and placebo
Baber et al ⁴⁰	51	Postmenopausal women	Placebo or active for 3 mo followed by 1 mo placebo, then 3 mo alternate arm	Promensil (40 mg/day isoflavones)	Hot flash frequency and Greene Menopause Symptom score	No statistically significant difference between active treatment and placebo groups

QOL = quality of life.

*Promensil (red clover isoflavones; Novogen Ltd., North Ryde, New South Wales, Australia).

†Rimostil (red clover isoflavones; Novogen Ltd.).

placebo group, who experienced a small reduction in frequency (10.5%) and no change in hot flash severity.

Safety

No serious adverse effect has been reported in clinical trials or in the medical literature, but because red clover leaf extracts contain semipurified isoflavones, the question of safety in hormone-sensitive tissue is important, especially when considering high doses over prolonged periods. Atkinson and coworkers⁴¹ found no significant difference in mammographic breast density after 12 months' administration of Promensil (43.5 mg/day isoflavones) compared with placebo in a study in 177 women (aged 49 to 65 years) with increased breast density, nor

was there any statistically significant effect on estradiol, follicle-stimulating hormone (FSH), or luteinizing hormone levels. Clifton-Bligh and colleagues⁴² found that Rimostil dosages up to 85.5 mg/day taken for 6 months did not increase endometrial thickness. Baber and coworkers⁴⁰ found no significant differences in serum estradiol, FSH, sex hormone-binding globulin, vaginal cytology, or endometrial thickness after 3 months' administration of Promensil 40 mg/day. At this time, the safety of red clover leaf extracts in women with a history of breast cancer is unknown. Although not an adverse effect per se, red clover isoflavones can inhibit the drug-metabolizing cytochrome P-450 system enzymes CYP1A1, CYP1B1, and CYP2C9⁴³; however, no herb-drug interaction has been reported.

Dose and preparation

Clinical trials for menopause-related symptoms have been conducted primarily on the proprietary semipurified isoflavone leaf extracts marketed as Promensil and as Rimostil. The ratio of genistein plus biochanin A to daidzein plus formononetin is 1.9:1.0, with 40.0 to 43.5 mg total isoflavones per Promensil tablet. Rimostil purportedly contains a ratio of genistein plus biochanin A to daidzein plus formononetin of 0.15:1.0, with <29.5 mg total isoflavones per tablet. It is important to avoid simply comparing the difference in total isoflavones between these products because the isoflavone profiles differ considerably.

Conclusion

The majority of clinical data do not support the efficacy of semipurified isoflavone red clover leaf extracts in reducing hot flash frequency and severity or in relieving symptoms associated with the domains of the Greene Menopausal Symptom Scale.

Soy (*Glycine max* L.)

It has been postulated that dietary intake of soy may explain, in part, the lower reporting of hot flashes by Asian women,⁴⁴ compared with women in the United States.⁴⁵ This has led to a surge in interest in soy in the research community and among consumers. The present review considers soy extracts only in dietary supplement form. We identified 6 controlled studies of soy extract dietary supplements that met our inclusion criteria (Table 6).^{46–51}

Efficacy

In aggregate, the 6 studies presented in Table 6 produced equivocal results. The largest study, by Upmalis and coworkers,⁵¹ found a statistically significant reduction in hot flash severity, but no reduction in incidence, in the active treatment group (50 mg/day soy isoflavones; genistein and daidzein) compared with placebo ($P = 0.01$). However, the use of the glycoside form of isoflavones, as opposed to the biologically active aglycones, at the dose administered may have influenced the findings.

The crossover study by Nikander and coworkers⁴⁹ failed to find any significant difference between the active treatment (114 mg/day soy isoflavone tablets containing glycitein 58%, daidzein 6%, and genistein 6%) and placebo groups with respect to KI or other outcome measures. Penotti and colleagues⁴⁶ did not detect any significant difference in hot flash frequency or severity between postmenopausal women receiving soy isoflavones 72 mg/day (genistein 11 mg, daidzein 36 mg, and glycitein 25 mg) and those receiving placebo. Both groups had a 40% reduction in the number of hot flashes.

In contrast to the negative results from other trials, Scambia and colleagues⁵⁰ reported that after 6 weeks, women

receiving soy extract 400 mg/day (corresponding to isoflavones 50 mg/day) had a significant reduction in mean number of hot flashes ($P < 0.01$) and mean point values 19 (hot flashes) and 20 (night sweats) on the Greene scale ($P < 0.001$) when compared with those taking placebo. The study was of short duration and was small; only 39 women were enrolled.

Faure and coworkers⁴⁷ randomized 75 women reporting ≥ 7 hot flashes per day to placebo or soy extract (total isoflavones 70 mg/day [genistein, daidzein, biochanin, and formononetin]). Women experiencing a $\geq 50\%$ reduction in hot flashes were significantly ($P < 0.005$) more likely to be in the soy treatment group (65.8%) than in the placebo group (34.2%). However, the trial suffered from attrition; 39% of the placebo group failed to complete the study.

Han and associates⁴⁸ found a significant ($P < 0.01$) reduction in KI score among women taking isoflavones 100 mg/day (genistein 70 mg, daidzein 18 mg, and glycitein 12 mg) compared with placebo. The mean KI score decreased from 44.6 to 24.9 in the active treatment group, whereas there was a small increase (from 40.3 to 41.6) in the placebo group. Lack of placebo response is highly unusual in a menopause study.

Safety

Soy extracts appear to be well tolerated, with few if any serious adverse effects noted in clinical studies. A review by Munro and colleagues⁵² concluded that the literature, when viewed in its entirety, supports the notion that soy isoflavones consumed in foods or dietary supplements are safe. The report by Unfer and associates,⁵³ however, has raised questions of safety with regard to long-term use of higher doses of soy isoflavones. After 5 years, 6 cases (3.8%) of endometrial hyperplasia were detected by endometrial biopsy in women receiving soy extract 1,800 mg/day (soy isoflavones 150 mg/day); no case was found in the placebo group. Investigators reported that the difference in rates of endometrial hyperplasia between the 2 groups was statistically significant ($P < 0.05$), although 41 biopsy specimens from the placebo group were considered unassessable at the final 5-year point.

Dose and preparations

There are numerous soy extracts in the marketplace that provide widely varying levels of isoflavones in a range of mixtures and ratios. The isoflavone dosages used in the majority of clinical trials are in the 50- to 100-mg/day range.

Conclusion

The results from clinical studies are contradictory and difficult to evaluate owing to variation in soy preparations, dosages, and durations of treatment. Many products fail to adequately declare the composition of isoflavones (e.g.,

Table 6 Placebo-controlled trials of soy extracts

Study	N	Sample	Control	Treatment	Primary Outcome Measures	Results
Penotti et al ⁴⁶	62	Postmenopausal women	Placebo for 6 mo	1-g tablet bid (72 mg/day soy isoflavones) for 6 mo	Self-reported hot flash frequency (diary)	No significant difference between groups: both had 40% reduction in hot flash incidence
Faure et al ⁴⁷	75	Menopausal women	Placebo for 16 wk	2 Phytosoya* capsules bid (70 mg/day soy isoflavones) for 16 wk	Self-reported hot flashes and night sweats (symptom card)	The percentage of "responders" (hot flashes reduced by $\geq 50\%$ at end of treatment) was 65.8% in the soy extract group and 34.2% in the placebo group ($P < 0.005$)
Han et al ⁴⁸	80	Postmenopausal women with breast cancer	Soy protein without isoflavones (50.3 mg) for 16 wk	1 soy extract capsule tid (100 mg/day soy isoflavone) for 16 wk	KI	Greater decrease in KI score with soy extract (44.6 to 24.9) than with placebo (40.3 to 41.6) ($P < 0.01$)
Nikander et al ⁴⁹	62	Women with vasomotor symptoms and history of breast cancer	Placebo for 3 mo, followed by 2-mo washout, then 3 mo alternate arm	3 phytoestrogen tablets bid (114 mg/day isoflavones)	KI, VAS, mood	No significant difference between groups in KI, VAS, or other outcome measures
Scambia et al ⁵⁰	39	Menopausal women	Placebo for 12 wk	SoySelect [†] (50 mg/day isoflavones) qd for 12 wk	Hot flash frequency and severity, Greene Menopause Scale	At 6 wk, compared with placebo, soy decreased frequency ($P < 0.01$) and severity ($P < 0.001$) of hot flashes; no change in other outcome measures
Upmalis et al ⁵¹	177	Postmenopausal women	Placebo for 12 wk	Soy extract (50 mg/day isoflavones) qd for 12 wk	Hot flash and night sweat frequency and severity	At 12 wk significant reduction in severity of hot flashes and night sweats ($P < 0.01$) but not frequency

KI = Kupperman Index; VAS = Visual Analogue Scale.

*Phytosoya; Arkopharma, Carros, France.

[†]Soy Select; Indera SpA, Milan, Italy.

percentage of individual isoflavone, glycoside or aglycone form), further complicating comparison between trials. Substantial interindividual differences in isoflavone metabolism exist in the general population,⁵⁴ which may also affect study outcomes. At this time, the scientific evidence cannot support the recommendation of soy isoflavone extracts for the relief of menopausal symptoms.

Summary and discussion

Whereas studies indicate that black cohosh extracts ease menopausal symptoms, most investigations are limited by methodologic shortcomings; additionally, comparison between trials is complicated by variations in dosing and in use of products with different extraction systems. A total of

4 case reports of acute hepatitis involving 5 women using black cohosh have been reported in the literature, although previously published safety reviews suggest that the herb generally is well tolerated. Soy isoflavone extracts appear to exert minimal effects, but dose differences and marked variation in product composition limits definitive conclusions. Long-term safety of higher-dose (150 mg/day) soy isoflavones is uncertain. Most clinical data do not support the efficacy of semipurified isoflavone red clover leaf extracts to reduce hot flash frequency and severity or to relieve symptoms associated within the domains of the Greene Menopausal Symptom Scale. Limited data suggest that dong quai, ginseng extract, and evening primrose seed oil are ineffective in ameliorating menopausal symptoms at the doses and in the preparations used in these studies; no significant adverse effect has been associated with their use.

Reports in the literature on botanicals used to treat menopausal symptoms reveal equivocal findings, with some studies reporting efficacy for specific products and others reaching opposite conclusions. Differences in findings across studies of the same botanical may be a function of less than optimal trial design, variation in products used, duration of treatment, inadequate dosing, and/or use of small or non-comparable population samples. When comparing products that differ in extraction technique, delivery system, ratio of ingredients, and dose, the question of equivalency must be considered. It also makes the "pooling" of trial data problematic. For example, reaching a definitive conclusion on the efficacy of soy isoflavone extracts is difficult when the products vary so markedly in composition. Many of the trials failed to provide adequate definitions for "postmenopausal" or "menopausal," which also may contribute to varied findings. Some treatments may be more effective in the perimenopausal woman than in the postmenopausal woman, or vice versa.

Future research should include long-term safety assessments of botanical preparations used for menopause-related symptoms because women may use these products for prolonged periods. Dose-escalation studies should be conducted before conducting expensive clinical studies on botanical extracts. The development of analytical methods for identifying and verifying the quantity of active ingredients, or marker compounds, in botanical products must be a priority, as is improving quality-control measures from seed to shelf. In addition to implementing rigorous clinical trial designs, researchers must clearly describe the botanical product being studied (i.e., plant part, method of botanical identification, solvent extraction method, etc.) to enable replication and critical analyses of the research.

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