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A systematic review of herbal medicinal products for the treatment of menopausal symptoms

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Abstract

Objective: Many women have turned to complementary and alternative medicines for relief from their menopausal symptoms. The prevalence of herbal medicinal product use among menopausal women highlights the need for investigation into these interventions. The aim of this study was to evaluate the benefit of herbal medicinal products for the treatment of menopausal symptoms by performing a systematic review of randomized clinical trials.

Design: Literature searches of four computerized databases were done to identify randomized clinical trials of herbal medicinal products for the treatment of menopausal symptoms. Manufacturers of herbal products were contacted, and our own files were also searched. There were no restrictions on the language of publication. Trials were considered if the outcome measures related to the physical or psychological impact of menopause, whether by compendium scores, questionnaires, or women's symptom diaries, excluding studies describing artificially induced menopause. This review was not concerned with biochemical or pathological data.

Results: Eighteen randomized clinical trials that fit our criteria were identified. These studies investigated black cohosh (n = 4), red clover (n = 4), kava (n = 3), dong quai (n = 1), evening primrose oil (n = 1), ginseng (n = 1), and combination products (n = 4). Trial quality was generally good, with 16 of 18 studies scoring 3 or more (maximum 5) on the Jadad Scale.

Conclusions: There is no convincing evidence for any herbal medical product in the treatment of menopausal symptoms. However, the evidence for black cohosh is promising, albeit limited by the poor methodology of the trials. The studies involving red clover suggest it may be of benefit for more severe menopausal symptoms. There is some evidence for the use of kava, but safety concerns mean this herbal product is not a therapeutic option at present. The evidence is inconclusive for the other herbal medicinal products reviewed.

Key words: Herbal medicine – Menopause – Black cohosh – Red clover – Kava.

The most common conventional medical treatment for menopausal symptoms is hormone replacement therapy (HRT). The primary reason women use HRT is for the relief of vasomotor symptoms attributed to menopause, although there is evidence for other benefits, such as protection against bone loss and ischemic heart disease.[1] However, there is also recent evidence to suggest that HRT may increase breast cancer, heart attacks, coronary attacks, and strokes.[2]

It seems that because of a fear and dislike of adverse effects as well as these possible long-term risks of HRT, many women have turned to complementary and alternative medicines, hoping that these might relieve menopausal symptoms.[3,4,5]

In a study of 500 women by the Women's Nutritional Advisory Service, the most common reason cited for not taking HRT was concern over risks.[5] In a survey of 100 menopausal women carried out in the US, 29% were taking HRT, 16% used HRT plus dietary supplements, 32% used dietary supplements alone, and 13% were on no medication.[6]

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It has been estimated that over one third of North American adults use herbal medicinal products (HMPs) at an annual cost of $13.7 billion.[7] A Swedish study suggests that approximately 4% of women treat their menopausal symptoms this way.[8] HMPs have been promoted for both the physical and psychological symptoms of menopause. Some are thought to have estrogenic effects, eg, red clover. In general, the actual mechanisms involved are still to be elucidated. Other herbal medicines, such as kava, are used to relieve anxiety in menopause. In addition, it is well documented that there is a marked placebo and time effect on menopausal symptoms during trials.[9]

The aim of this systematic review is to summarize and critically analyze all relevant randomized clinical trials (RCTs) on this topic.

METHODS

Identification of clinical trials

Computerized literature searches were performed to identify RCTs of HMPs for the treatment of menopausal symptoms. The databases used were Medline, Embase, Phytodoc and The Cochrane Library (all from their inception to December 2002). The search terms used were menopaus*, climacteric, hot flushes/flashes, herb*, phyto*, plant, diet, supplement, isoflavones, coumestans, lignans, nutrition, naturopathy, black cohosh, blue cohosh, burdock, dong quai, evening primrose oil, feverfew, ginseng, hops, kava, liquorice, linseed, motherwort, red clover, St John wort, traditional Chinese medicine, vitex agnus castus, valerian, wild yam, and wheat.

In addition, 43 manufacturers of herbal products marketed for menopause were asked to contribute published and unpublished material, and our own extensive files were searched. The bibliographies of the studies thus retrieved were scanned for further trials. There were no restrictions on the language of publication.

Inclusion and exclusion criteria

RCTs of HMPs for menopausal symptoms were considered if the outcome measures related to the physical or psychological impact of menopause, whether by compendium scores, questionnaires, or participant's symptom diaries. This review was not concerned with outcome measures of blood hormonal level data, vaginal cytology, or other nonclinical endpoints. This review also did not include studies describing artificially induced menopause. This review did not include soy, as it was felt by the authors to be a topic in itself and this review would not be able to discuss the issues involved in sufficient depth.

Data extraction and evaluation

The data were extracted according to predefined criteria by the first author. The trials were assessed for methodological quality using the Jadad score.[10] It measures the likelihood of bias based on description of randomization, blinding, and withdrawals on a scale of 0 (minimum) to 5 (maximum). Due to the diverse nature of the interventions and outcome measures, no quantitative analysis took place; thus, the information was evaluated in a qualitative manner. Descriptions and safety aspects of the HMPs included in this review are detailed in Table 1 and in the discussion (excluding Chinese medicine mixture).

RESULTS

Our systematic searches revealed 18 RCTs of HMPs for the treatment of menopausal symptoms. These RCTs describe black cohosh ($n = 4$), red clover ($n = 4$), kava ($n = 3$), dong quai ($n = 1$), evening primrose oil ($n = 1$), ginseng ($n = 1$), and combination products ($n = 4$). The quality of these trials was generally good, with 16 of 18 scoring 3 points or more on the Jadad score (Tables 2, 3, and 4). One trial was only available in abstract form so the Jadad score could not be calculated.

Black cohosh: *Actaea racemosa (Cimicifuga racemosa)*

Most of the information about black cohosh in the literature (Table 2) relates to the product Remifemin (Schaper & Brümmer, Salzgitter, Germany).

Warnecke randomized 60 menopausal women to receive either 40 drops of Remifemin, conjugated estrogen, or diazepam daily for 12 weeks.[11] Outcome measures were the Kupperman Index, Hamilton Anxiety Scale (HAMA), Self-Assessment Depression Scale Index (SDS) and Clinical Global Impression (CGI) Scale. Although the authors stated that Remifemin resulted in the greatest improvement in all outcome measures, neither actual data nor statistical analysis was reported.

Stoll et al reported a 12-week study involving 80 menopausal women who received Remifemin, low-dose estrogen, or placebo daily.[12] Outcome measures were the Kupperman Index and the HAMA Scale. All groups improved, but the greatest improvement was in the Remifemin group, with a statistically significant ($P < 0.001$) and clinically relevant reduction in Kupperman Index compared with baseline.[13] Similarly, the HAMA Scale was significantly reduced for Remifemin compared with baseline ($P < 0.001$). No intergroup differences were reported.

TABLE 1. *Descriptions of the plant-based medicines reviewed*

Herbal medicine	Active ingredient & mode of action	Possible adverse effects & interactions
Black cohosh (*Actaea racemosa,* also known as *Cimicifuga racemosa*)	Putative active ingredient: triterpene glycosides (Remifemin standardized to 27-deoxyacetein content). Originally thought that action was through a direct estrogenic/endocrine effect. New research suggests otherwise.	Gastrointestinal complaints, hypotension, headache, dizziness, nausea, allergic reactions.[31] May interact with antihypertensive agents.[33]
St. John's wort (*Hypericum perforatum*)	Active ingredient may be hypericin and hyperforin. Use for mild to moderate depression, possibly acting through inhibiting the reuptake of serotonin, norepinephrine, and dopamine.	Most common reports are of gastrointestinal symptoms, allergic reactions, fatigue, and anxiety. Several cases of mania and one subacute toxic neuropathy have been reported. Photosensitivity is possible, particularly in fair-skinned individuals. Interactions: serotonin reuptake inhibitors, oral contraceptives, cyclosporins, warfarins, anticonvulsants, digoxin, theophylline, HIV protease inhibitors.[36]
Red clover (*trifolium pratense*)	Putative active ingredient: isoflavones. It is postulated that substances with natural estrogenic-like activity alleviate climacteric symptoms.	Breast tenderness, menstruation changes, weight gain. Theoretically may interfere with anticoagulants and hormonal therapies.[36]
Kava (*Piper methysticum*)	Follicle-stimulating hormone surges in menopausal women. Active ingredients: kavapyrones, acting through the γ-aminobutyric acid-A receptors in nerve endings. Demonstrated anxiolytic effects.	Stomach complaints, restlessness, mydriasis, allergic skin reactions, dermatomyositis, hepatitis. Potentiation of central nervous system drugs such as alcohol, bezodiazepines, and barbiturates.[32]
Dong quai (*Angelica sinensis*)	Reputed to have estrogenic properties.	Bleeding, photosensitivity. Interaction with anticoagulants.[36]
Burdock (*Arctium lappa*)	Reputed to have estrogenic properties.	Potential to interact with antidiabetic medications.[36]
Licorice (*Glycyrrhiza glabra*)	Contains isoflavones & glycyrrhetinic acid. β sitosterol is reputed to influence estrogen activity.	Adverse effects consistent with adrenocorticotrophic actions.[36]
Motherwort (*Leonorus cardiaca*)	Contains alkaloid leonurine that is thought to stimulate uterine activity.	Potential to interact with cardiac glycosides, antihypertensives.[36]
Wild yam (*Dioscorea barbasco/Dioscorea villosa*)	Steroidal glycosides based on the sapogenin diosgenin. Mode of action has not been determined.	No adverse reactions or known drug interactions except some cases of hormonal effects with one commercial product.[37]
Evening primrose oil (*Oenothera biennis*)	Rich in gamma-linolenic acid (GLA). GLA production may be compromised in some conditions, including aging. Part of the pathway to prostaglandin E_1 production.	Gastrointestinal symptoms, headache. Theoretical interactions with antiinflammatory drugs, corticoidsteroids, beta-blockers, antipsychotics, anticoagulants, and epileptogenic agents.[36]
Ginseng (*Panax ginseng*)	Ginsenosides (triterpene saponins) are thought to have estrogenic properties.	Insomnia, diarrhea, vaginal bleeding, mastalgia, swollen tender breasts, increased libido, manic episodes, a possible cause of Stevens-Johnson syndrome. Interactions with monoamine oxidase (MAO) inhibitors such as phenelzine, increased effects of hypoglycemics.[36]
Flax seed (*Linum usitatissimum*)	Reputed to have estrogenic, antiestrogenic, and steroid-like activity.	No known side effects. The absorption of other drugs may be negatively affected.[37]
Geranium (*Pelargonium graveolens*)	Reputed to have hormonal effects.	No information found.
Sage (*Salvia officinalis*)	Traditionally thought to have antihydrotic properties.	Potential to interact with antihypertensives and antidiabetics.[36]

All citations correspond to the References list at the end of this article.

In a 24-week study involving 60 hysterectomized women with one intact ovary and climacteric symptoms, participants were randomized to receive Remifemin, estriol, conjugated estrogens, or estrogen-progesterone therapy.[14] The outcome measure was a modified Kupperman Index. All groups improved significantly ($P = 0.01$), and there was no difference among groups. None of the treatments resulted in a decrease in the Kupperman Index to below 15 points.

The most recent study by Jacobson et al involved 85 breast cancer patients experiencing menopausal symptoms.[15] Of this group, 42 women were assigned to

TABLE 2. *Randomized clinical trials of black cohosh and red clover for menopausal symptoms*

First author (yr)	Trial setting, duration of therapy, and trial design	Study participants (age)	Experimental treatment (*N*)	Control treatments (*N*)	Outcome measures	Results	Adverse events	Jadad score
Warnecke (1985)	Not described, 2 w, open	60 women with no or irregular menses & climacteric complaints (54 ± 4 y)	40 drops of Remifemin twice daily (4 mg of 27-deoxyacetin) (20)	• 0.6 mg conjugated estrogen daily (20) • 2 mg diazepam daily (20)	• KI • HAMA • SDS Index • CGI Index	Remifemin produced "greatest improvement" in all measures, but no actual data given.	None stated	2
Stoll (1987)	Not described, 12 w, double-blind	80 women with ≥3 hot flushes daily & 1 more symptom (51.2 ± 3.1 y)	4 tablets daily of Remifemin (4 mg of 27-deoxyacetin) (26)	• Low-dose estrogen (0.625 mg) daily (29) • Placebo (20)	• KI • HAMA	Remifemin produced greatest improvement in KI (<15) & HAMA, ($P < 0.01$) compared with baseline	Increase in weight, headaches, heavy legs, & aching breasts in all 3 groups	3
Lehmann-Willenbrock (1988)	University clinical department, 24 w, open	60 hysterectomized women with 1 intact ovary & climacteric symptoms (<40 y)	4 tablets of Remifemin daily (4 mg of 27-deoxyacetin) (15)	• Estriol 1-mg tablet daily (15) • Conjugated estrogens 1.25-mg tablet daily (15) • Estrogen-progestogen sequential therapy, 1 tablet daily (15)	• Modified KI	Improvement in all groups ($P < 0.01$) for most treatments at most times. No difference between groups	None stated	2
Jacobson (2001)	Medical center 60 d, double-blind	85 former breast cancer patients with menopausal symptoms (≤50 ≥60 y)	1 black cohosh tablet twice daily with food (42)	Placebo (43)	• 4-day hot flash diary at 0, 30 & 60 days • Menopausal symptoms questionnaire	Both groups improved; NS difference between groups	3 serious (1 placebo, 2 treatment), 10 minor (2 placebo, 8 treatment)	5
Baber (1999)	Menopause clinic, 30 w, double-blind crossover	51 women with >3 flushes daily and no menses for 6 months (54 ± 4.1 y)	1 tablet of Promensil (40 mg isoflavone) daily in morning (51)	Placebo (51)	• Greene menopause symptom score • Daily symptom diary	NS difference between groups	None observed	3

TABLE 2. *Continued*

First author (yr)	Trial setting, duration of therapy, and trial design	Study participants (age)	Experimental treatment (*N*)	Control treatments (*N*)	Outcome measures	Results	Adverse events	Jadad score
Knight (1999)	University clinical department, 12 w, double-blind	37 women with ≥3 flushes daily, no menses for 3 mon & elevated FSH levels (53-56 y)	• 1 tablet of Promensil (40 mg isoflavone) daily (12) • 4 tablets of Promensil daily (160 mg isoflavone) (13)	Placebo (12)	• Greene menopause symptom score • Number of flushes	NS difference between verum and placebo group	None stated	5
Van de Weijer (2002)	Hospital department, 4-w placebo washin & 12 w of trial, double-blind	30 women with >12 months amenorrhoea & >5 hot flushes daily (49-65 y)	2 tablets of Promensil daily (80 mg isoflavones) (16)	Placebo (14)	• Number of flushes daily • Greene Menopause Scale	Hot flushes decreased (44%) with verum $P < 0.01$ compared with placebo Greene score decreased with verum by 13%, NS		5
Jeri (2002)	Climacteric unit at medical institute, 16 wk, double-blind	30 healthy, nonvegetarian women, postmenopausal for 1 y, elevated FSH levels, & ≥5 hot flushes daily (<60 y)	1 tablet of Promensil (40 mg isoflavones) (15)	Placebo (15)	• Number & severity of hot flushes	Number (48.5%) & severity (47%) of hot flushes significantly reduced in the verum group v placebo $P < 0.001$		3

KI, Kupperman Index; HAMA, Hamilton Anxiety Score; SDS, Self-Assessment Depression Scale; CGI, Clinical Global Impressions; FSH, Follicle-stimulating hormone; NS, not significant.

TABLE 3. *Kava, dong quai, evening primrose oil and gingseng products for menopausal symptoms*

First author (yr)	Trial setting, duration of therapy, trial design	Study participants	Experimental treatment (*N*)	Control treatments (*N*)	Outcome measures	Results	Adverse events	Jadad score
Warnecke (1990)	Gynecology practice, 12-w, double-blind	40 women with climacteric syndrome (anxiety & vegetative symptoms dominate) (~52 y)	Kavosporal 150 mg × 2 (60 mg kavapyrones) daily (20)	Placebo (20)	• KI • ASI Index • Patient daily diary	Reduction in KI, ASI Index & diaries from week 4 onwards in kava group v baseline ($P = 0.001$); no reduction with placebo	Gastrointestinal effects in 15% of placebo & 10% of verum patients	5
Warnecke (1991)	Gynecology practice, 8 w, double-blind	40 women with climacteric-related symptoms (45-60 y)	Kava WS 1490 extract 100 mg × 3 daily (210 mg kavapyrones) (20)	Placebo (20)	• KI • Schneider scale • HAMA score for anxiety • DSI score • Patient diary • CGI scale	Significant improvements with kava v placebo in KI ($P < 0.01$), HAMA ($P < 0.001$), & DSI ($P < 0.01$); Schneider scale, NS; diary & CGI, descriptive	4 in verum group, 6 in control group, restlessness, stomach complaints, drowsiness, tremor	5
De Leo (2000)	University-based obstetrics and gynecology department, 6 mon, open	24 women in physiological menopause (mean ~59 y), 16 women in surgical menopause (mean ~51 y)	HRT & 100 mg kava (55% kavaina) daily for physiological menopause (HRT + K) (13) ERT & 100 mg kava daily for surgical menopause (ERT + K) (11)	HRT & placebo daily for physiological menopause (HRT + P) (9) ERT & placebo daily for surgical menopause (ERT + P) (7)	• HAMA	Significant reduction in all groups at 3 & 6 months; the two groups with kava (HRT + K & ERT + K) showed the greatest reduction compared with HRT or ERT alone when compared with baseline	"All participants completed the study"	3
Hirata (1997)	Department of obstetrics & gynecology, 24 w, double-blind	71 women with no menses for 6 months, >14 hot flushes/night sweats weekly & elevated FSH (52 ± 6 y)	Dong quai granular powder, 3 capsules daily (4.5 g dong quai) (35)	Placebo (36)	• KI • Diary of hot flushes	No difference between groups	Similar occurrence of burping, gas, & headache for both verum & placebo	3
Chenoy (1994)	District general & teaching hospital, 24 w, multicenter double-blind	56 women with no menses for 6 mon, ≥3 hot flushes daily & raised gonadotrophin levels (45-57 y)	4 capsules of 500 mg EPO with 10 mg of natural vitamin E daily (28)	4 capsules of 500 mg liquid paraffin daily (28)	• Patient diary of flushing & sweating	NS difference between groups	Slight nausea with verum (3); dyspepsia & diarrhea with placebo (2)	3
Wiklund (1994)	Hospital departments, 16 w, multicenter double-blind	384 women with no menses for 6 mon & 6 episodes of hot flushes for ≥3 days in 7 (53.5 ± 4 y)	Ginseng extract (Ginsana), two capsules of 100 mg before breakfast (193)	Placebo (191)	• WHQ, PG WB, & VAS • Physiological parameters, including hot flushes	PGWB index better with verum vs. placebo ($P < 0.01$) plus subsets for depression, well being & health ($P < 0.05$)	Severe (7 verum, 9 placebo); other (1 verum, 4 placebo); possible (36 verum, 42 placebo)	3

KI, Kupperman Index; ASI, Anxiety State Index; HAMA, Hamilton Anxiety Score; DSI, Depression Status Inventory; CGI, Clinical Global Impressions; QOL, quality of life; PGWB, Psychological General Well-Being Index; VAS, Visual Analogue Scale; NS, not significant; HRT, 50 mg natural estrogens with progestin; ERT, 50 mg natural estrogens without progestin.

TABLE 4. *Herbal combinations for menopausal symptoms*

First author (yr)	Trial setting, duration of therapy, trial design	Study participants	Experimental treatment (*N*)	Control treatments (*N*)	Outcome measures	Results	Adverse events	Jadad score
Boblitz[a] (1999)	Clinical research center, 6 w, double-blind	179 patients, no details or ages available	2 tablets of Remifemin Plus daily (87)	Placebo (92)	• KI	Improvement with verum v control ($P < 0.001$) but not clinically relevant	6 similar nonserious events in 5 participants in each group	Not known
Hudson (1999)	Naturopathic college 12 w, double-blind	13 women with no menses for 3 mon & hot flushes plus 1 additional symptom (no ages given)	Two 500-mg capsules botanical herbal formula × 3 daily (7)	Placebo (6)	• Patient symptom diary • Physician symptom record	71% verum group v 17% placebo group reported fewer total symptoms; 100% verum group v 67% placebo group reported a reduction in symptom severity	None stated	3
Davis (2001)	Clinical university department, 12 w, double-blind	55 women with no menses (>12 mon) with ≥14 hot flushes/night sweats weekly (45-70 y)	CHM granules twice daily (42)	Corn starch & bitter enhancer twice daily (36)	• Frequency of vasomotor symptoms • MenQol questionnaire • Menopause symptoms, blood pressure	NS differences between groups	Frequency and type equal in both groups: bloating, lower abdominal pain, loose stools, headache, joint pain, & dizziness	4
Komersaroff (2001)	Menopause clinic, 6 mon, double-blind crossover	Menopause symptoms, last menses >12 mon ago, & elevated FSH (average age 53.3 y)	Biogest cream, 1 tsp twice daily rubbed onto arms, legs, & abdomen	Placebo cream	• Symptom diary	NS differences between groups	No adverse events	3

KI, Kupperman Index; CHM, Chinese herbal medicine; NS, not statistically significant; MenQol, menopausal quality of life.
[a]Study available as abstract only.

Remifemin and 43 to placebo for 60 days, and 69% of the women were on tamoxifen. Patients completed a questionnaire about menopausal symptoms at enrollment and at the end of the trial. They also completed a four-day hot flash diary at the start of the trial, at 30 days, and at 60 days, with 69 women completing all three hot-flash diaries. Both treatment and placebo groups improved, but there were generally no differences between the groups.

Red clover: *Trifolium pratense*

Four RCTs were found for red clover isoflavone extract and menopausal symptoms[16-19] (Table 2). All four of these involved the use of the proprietary brand Promensil (Novogen Ltd, North Ryde, Australia).

In a crossover study, 51 postmenopausal women were randomized to receive either one placebo or one Promensil tablet daily for 12 weeks, followed by a 1-month washout period and the other treatment for an additional 14 weeks.[16] The outcome measures were the Greene menopause symptom score and a daily symptom diary, including hot flushes. There were no significant differences between the placebo and the active treatments. Analysis performed on the interim data time-points revealed a numerically greater reduction in flushing in the active compared with the placebo group at 4 and 8 weeks, but the difference was not statistically significant.

Knight et al conducted a study involving 37 postmenopausal women who received either one or four Promensil tablets or identical placebo daily for 12 weeks.[17] Outcome measures were the Greene menopause symptom score and number of hot flushes. No difference was seen between the experimental and placebo groups.

The study by van de Weijer involved 30 women taking single blind placebo tablets for 4 weeks, followed by subsequent randomization to either two tablets of Promensil or identical placebo for an additional 12 weeks.[18] Outcome measures were the number of hot flushes daily and the Greene Climacteric Menopause Scale score. During the first 4 weeks of placebo treatment, the frequency of hot flushes decreased by 16%. During the subsequent double-blind stage, a further statistically significant decrease of 44% was seen in the Promensil group ($P < 0.01$) compared with the placebo group. The Greene score decreased in the active group by 13% but was not statistically significant compared with the placebo treatment.

In the study by Jeri, 30 healthy nonvegetarian women were given a single daily tablet of Promensil or an identical placebo for 16 weeks.[19] All participants were asked to record incidence and severity of hot flushes at the beginning and end of the treatment period. At the end of the 16-week study, a significant reduction was seen in both the frequency (48.5%) and the severity (47%) of hot flushes in the Promensil group. These changes were statistically significant compared with the placebo group ($P < 0.001$).

Kava: *Piper methysticum*

Kava is prepared from the rhizome of *Piper methysticum*. In the South Pacific, kava extracts have been traditionally used for recreational and medicinal purposes. It is known for its anxiolytic effects.[20] There are three RCTs (Table 3) investigating its value for menopausal symptoms.[21-23]

In the first study, 40 women with climacteric symptoms were randomized to receive either kava extract, Kavosporal (Müller, Göppingen, Germany NB), or placebo tablets daily for 12 weeks.[21] The outcome measures were the Kupperman Index, Anxiety-State Index (ASI) and a daily symptom diary. There was a statistically and clinically significant improvement in all three measures (Kupperman < 15 points) compared with baseline by week 4 ($P < 0.001$ for all). There were no significant changes in any of the measures in the placebo group compared with baseline. There were no intergroup comparisons. No statistical analysis could be performed at 12 weeks as only 6 patients remained in the placebo group (18 remained in the verum group).

In the second study, 40 menopausal women were randomized to receive either Kava WS 1490 (Schwabe, Karlsruhe, Germany) or placebo daily for 8 weeks.[22] The outcome measures were the Kupperman Index, HAMA Score, Depression Status Index (DSI), CGI scale, patient daily diary and Schneider Scale. Scores of the Kupperman Index (<15 points) and the HAMA Scale were significantly improved with kava, when compared with placebo, at weeks 1, 4, and 8. In addition, the DSI was significantly reduced with kava treatment, when compared with placebo, at weeks 4 and 8. Both the CGI scale and patient diary were described as showing improvement with kava over placebo, but no statistics were provided. There were no significant changes in the Schneider Scale.

In a more recent study by De Leo and colleagues, kava was evaluated for its efficacy for the treatment of anxiety in menopause in combination with and without HRT.[23] Forty women in physiological or surgical menopause were randomly assigned to the appropriate HRT plus either 100 mg of kava or placebo for 6 months. The outcome of the study was to evaluate changes in the HAMA score. All groups improved in

terms of the HAMA score over the 6 months, but the women treated with HRT plus kava showed the greatest reduction in the HAMA score ($P < 0.05$) when compared with baseline. No intergroup comparisons were made.

Dong quai: *Angelica sinensis*

The use of dong quai for postmenopausal symptoms was investigated by Hirata and colleagues[3] (Table 3). Seventy-one women were randomized to receive either three capsules of dong quai powder or placebo (maltodextrin) for 24 weeks. The outcome measures were the Kupperman Index and a daily flush diary. These measures improved in both groups, and there were no statistically significant differences between verum and placebo.

Evening primrose: *Oenothera biennis*

Fifty-six menopausal women were randomized to receive either four 500-mg capsules of evening primrose oil (EPO) or placebo (liquid paraffin) daily for 24 weeks[24] (Table 3). One of the outcome measures was a patient symptom diary of flushing and sweating. In the group of women taking EPO, the only significant improvement was a reduction in the maximum number of nighttime flushes ($P < 0.05$) over baseline, but EPO offered no benefit in any of the measures over placebo.

Ginseng: *Panax ginseng*

Wiklund and colleagues investigated the effects of a standardized ginseng extract, Ginsana, on the quality of life and physiological parameters in postmenopausal women[25] (Table 3). For this study, 384 menopausal women were randomized to receive either two capsules of Ginsana or placebo for 16 weeks. The outcome measures were quality-of-life questionnaires—the Women's Health Questionnaire (WHQ), Psychological General Well-Being Index (PGWB), and Visual Analogue Scales (VAS)—as well as measurement of physiological parameters, including hot flushes. Only the PGWB index ($P < 0.01$) and its subscales for depression, well-being, and health ($P < 0.05$) showed a statistically significant improvement with ginseng when compared with placebo. There were no significant changes in any of the other parameters measured.

Herbal combinations

Boblitz and colleagues investigated the effect of Remifemin Plus (*A. racemosa* and St. John's wort) on patients with climacteric complaints[26] (Table 4). For this study, 179 participants were randomized to receive Remifemin Plus or placebo for 6 weeks. The outcome measure was the Kupperman Index. A greater reduction was found in the verum (31.39 to 18.7) compared with the placebo group (30.22 to 22.29). However, this reduction in the Kupperman Index was not clinically relevant, ie, below 15 points.

In a study by Hudson et al, an herbal mixture was assessed for its effects on menopausal symptoms[27] (Table 4). The mixture contained burdock *(Arctium lappa)*, licorice root *(Glycyrrhiza glabra)*, motherwort *(Leonorus cardiaca)*, dong quai *(Angelica sinensis)*, and Mexican wild yam *(Dioscorea barbasco)*. Thirteen menopausal women were randomized to receive either this mixture or placebo three times daily for 12 weeks. The outcome measures were patient symptom diaries and physician symptom records. Of the women in the herbal group, 71% reported fewer total symptoms, as did 17% in the placebo group. All (100%) of the women in the herbal group experienced a reduction in symptom severity versus 67% in the placebo group. No test statistics were reported.

The effects of a defined Chinese herbal formula (*Rehmannia glutinosa, Cornus officinalis, Dioscorea opposita, Alisma orientalis, Paeonia suffruticosa, Poria cocos, Citrus reticulata, Lycium chinensis, Albizzia julibrissin, Zizyphus jujuba, Eclipta prostrata, Ligustrum lucidum*) on postmenopausal women was investigated in a trial by Davis et al[28] (Table 4). For this study, 55 Australian women completed 12 weeks of intervention with either a defined formula of CMH or placebo taken twice daily as a beverage. The primary endpoint was frequency of vasomotor events, and the secondary endpoint was the Menopause Specific Quality of Life (MENQOL) Questionnaire score. There was a reduction in the average frequency of vasomotor events in both the CMH and placebo groups with a nonsignificant advantage to the placebo. There was significant reduction in the MENQOL score in both groups but with no intergroup differences. Interestingly, there was evidence of effect modification by previous use of natural therapies, with women with no prior use of natural therapies responding to therapy, whereas prior users did not.

A recent trial by Komersaroff and coworkers examined the effect of a BioGest cream on menopausal symptoms[29] (Table 4). In this crossover study, after a 4-week baseline period, 50 women were randomized to the active cream *(Dioscorea villosa, Linum usitatissimum, Pelargonium graveolens, Salvia officinalis*) or placebo cream for 3 months in a random order. The cream was applied to arms, legs, or abdomen. Meno-

pausal symptoms, recorded in a daily diary, were used to assess its effect, but no differences were found between the active and placebo cream. This study suffered from a small number of women to start and a high number of dropouts[27] caused by unrelieved symptoms in the majority of cases.

DISCUSSION

Critical analysis of RCTs of HMPs for menopausal symptoms suggests that there is some evidence for black cohosh. Trial data suggests that red clover maybe beneficial for women with more severe vasomotor symptoms. There is reasonable evidence for the use of kava to alleviate menopausal symptoms. However, the serious safety concerns over this herbal product make it difficult to recommend at the present time. The evidence is inconclusive for dong quai, EPO, ginseng, and for the four combination products reviewed.

Eighteen RCTs fulfilled our inclusion criteria. The design of these studies was variable, with the majority of them placebo-controlled, but some were comparative studies with conventional menopause drugs or different diets. Two of the RCTs had a crossover design.[16,29] The quality of the trials was generally good, with 16 of the 18 studies scoring 3 or more on the Jadad Scale (Tables 2, 3, and 4). Low scores were generally due to insufficient description of the randomization and blinding procedure. Of the 18 RCTs, 15 reported dropouts or withdrawals in an acceptable way. One of the remaining trials was only available in abstract form, and thus a Jadad score could not be calculated nor could the detail on dropouts be extracted.[26] Three RCTs had an open design.[11,14,23] Many of the trials described statistical improvement with respect to baseline and not intergroup differences. This is an important issue because of the known significant placebo effect with menopause treatments.[9] The possibility of publication bias must be also be considered as there is a tendency for trials with negative results to remain unpublished.[30]

Several RCTs of black cohosh (Remifemin) for menopausal symptoms exist.[11,12,14,15] Unfortunately, the overall quality of this research is poor, and the collective evidence is therefore weak. There are three RCTs of black cohosh that used the same dosage and suggested improvements with Remifemin, yet two of them were open studies and did not have a placebo control.[11,12,14] The Kupperman score was not reduced to values below 15 in either of these trials.[11,14] A score of 15 or below is considered to be a favorable therapeutic result as it is indicative of mild or no symptoms.[13] The best quality (placebo-controlled) study showed a reduction in the Kupperman Index to below 15 but yielded nonsignificant differences in the intergroup comparisons.[12] The most recent study by Jacobson is negative but used half the dosage of the three previous trials.[15] This study primarily demonstrated that black cohosh does not reduce hot flushes in breast cancer survivors on tamoxifen. Subset analysis is too small for the women not on tamoxifen. The adverse events in this trial were almost all thought to be related to the cancerous status of the women or their treatment with tamoxifen. However, black cohosh occasionally causes gastrointestinal disturbances and rashes.[31] Drug interactions are not known, and the tolerance is generally good in the short-term.[31] Thus, the evidence for black cohosh looks interesting, but there is not convincing data at present to prove its efficacy above that of placebo. Better-designed, placebo-controlled trials are required.

The authors of one of the two negative studies of red clover extract (Promensil) suggest that participants of the trial may have increased their dietary isoflavone intake, thus masking the effect of the Promensil tablets.[16] A strong correlation between the level of urinary isoflavone excretion and the incidence of hot flushes provides some evidence for this. The authors of the other negative red clover trial suggest, because menopausal symptoms improved in all groups, that the control diet (wheat) may provide a class of estrogenic substance.[17] There were two major differences between these latter trials and the trials performed in 2002. In the van der Weijer study, Dutch women were used as a study group because of the traditionally low legume content in the Dutch diet.[18] These women were also given a list of phytoestrogen-containing foods to avoid during the trial. In the Jeri trial, nonvegetarian women were recruited.[19] In addition, the women in both the 2002 studies had a greater frequency of vasomotor symptoms than did women in the previous two trials. These data suggest that red clover may be beneficial for women with more severe hot flushes.

There were three RCTs on the use of kava for menopausal symptoms; all three were high quality, with two of them scoring 5 on the Jadad Scale.[21-23] Unfortunately, two of the trials only performed statistical tests compared with baseline, not placebo.[21,23]

One of these trials had a significant dropout rate in the placebo group, rendering analysis impossible.[21] However, both physical and psychological symptoms seemed to be alleviated with kava. In addition, other trials have examined the effect of kava on anxiety with different conditions, and with positive outcomes.[20] The optimum dosage of kava is unclear, with about a four-

fold difference in kavapyrones between the Warnecke (1991) study[22] and the two others.[21,23]

Allergic skin reactions, dermatological problems and neurological symptoms have been described with kava.[32] Interactions may occur with other anxiolytics,[33] with one case report suggesting a possible interaction of kava with alprezolam.[34] More recently, kava has been associated with liver damage and has consequently been removed from the market in Canada and several countries in Europe.[35]

Because there is only one RCT of ginseng for menopause, no conclusions can be drawn.[25] The active ingredients of ginseng (*Panax ginseng*) are the ginsenosides. Prolonged use of ginseng may result in hypertension, edema, diarrhea, skin eruptions, insomnia, depression, and amenorrhea.[36] There are three case reports of likely interaction of ginseng with phenelzine associated with mania, headaches, hallucinations, and insomnia.[34] The incidence of related adverse reactions is low in the above-named study.

With one study on dong quai, evening primrose oil, and each of the herbal combination products for menopausal symptoms, it is impossible to say anything definitive on their therapeutic value. There has been one case report of suspected interaction of dong quai with warfarin and one possible interaction of EPO with phenytoin, with a loss of seizure control in an epileptic patient.[34]

CONCLUSIONS

Many herbal medicinal products are recommended for menopause. Evidence from randomized clinical trials suggests that black cohosh and red clover may be of benefit in alleviating menopausal symptoms. Kava also appears to be useful, but safety concerns mean that it is not a therapeutic option at present. Further work into the efficacy and safety of herbal medicinal products for menopausal symptoms is warranted.

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