

Treatment of Vasomotor Symptoms of Menopause with Black Cohosh, Multibotanicals, Soy, Hormone Therapy, or Placebo

A Randomized Trial

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Background: Herbal supplements are widely used for vasomotor symptoms.

Objective: To test the efficacy of 3 herbal regimens and hormone therapy for relief of vasomotor symptoms compared with placebo.

Design: 1-year randomized, double-blind, placebo-controlled trial conducted from May 2001 to September 2004.

Setting: Group Health, Washington State.

Participants: 351 women age 45 to 55 years with 2 or more vasomotor symptoms per day; 52% of the women were in menopausal transition and 48% were postmenopausal.

Measurements: Rate and intensity of vasomotor symptoms (1 = mild to 3 = severe), and Wiklund Vasomotor Symptom Subscale.

Interventions: 1) Black cohosh, 160 mg daily; 2) multibotanical with black cohosh, 200 mg daily, and 9 other ingredients; 3) multibotanical plus dietary soy counseling; 4) conjugated equine estrogen, 0.625 mg daily, with or without medroxyprogesterone acetate, 2.5 mg daily; or 5) placebo.

Results: Vasomotor symptoms per day, symptom intensity, Wiklund Vasomotor Symptom Subscale score did not differ between

the herbal interventions and placebo at 3, 6, or 12 months or for the average over all the follow-up time points ($P > 0.05$ for all comparisons) with 1 exception: At 12 months, symptom intensity was significantly worse with the multibotanical plus soy intervention than with placebo ($P = 0.016$). The difference in vasomotor symptoms per day between placebo and any of the herbal treatments at any time point was less than 1 symptom per day; for the average over all the follow-up time points, the difference was less than 0.55 symptom per day. The difference for hormone therapy versus placebo was -4.06 vasomotor symptoms per day for the average over all the follow-up time points (95% CI, -5.93 to -2.19 symptoms per day; $P < 0.001$).

Limitations: The trial did not simulate the whole-person approach used by naturopathic physicians. Differences between treatment groups smaller than 1.5 Vasomotor symptoms per day cannot be ruled out.

Conclusion: Black cohosh used in isolation, or as part of a multibotanical regimen, shows little potential as an important therapy for relief of vasomotor symptoms.

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Hormone therapy remains the recommended treatment for vasomotor symptoms, but trials have shown serious risks with even short-term use (1, 2). The use of herbs, particularly black cohosh, multibotanical supplements, and dietary soy for menopausal symptoms has grown dramatically (3–6). Few of these approaches have been scientifically evaluated. Women and providers are seeking safe, effective alternatives to hormone therapy. We designed the Herbal Alternatives for Menopause Trial (HALT) to provide rigorous evidence on the efficacy and short-term safety of commonly used naturopathic approaches for management of vasomotor symptoms.

METHODS

Design Overview and Setting

HALT was a 1-year double-blind, randomized, controlled trial designed to investigate the effects of 3 naturopathic approaches for vasomotor symptom relief and hormone therapy compared with placebo. Study methods have been described elsewhere (7). The Group Health Institutional Review Board approved this study, and a data and safety monitoring committee monitored it. The study was conducted at Group Health, an integrated health plan in Washington State.

Participants

Eligibility criteria were as follows: age 45 to 55 years; late menopausal transition (≥ 1 skipped menses within the preceding 12 months) or postmenopausal (no bleeding within 12 months, or follicle-stimulating hormone level > 20 IU/mL if patient had undergone hysterectomy without bilateral oophorectomy); and 2 or more vasomotor symptoms per day over 2 weeks (≥ 6 moderate to severe symptoms). Women in menopausal transition were included because many are highly symptomatic and trial data are lacking for this group. Exclusion criteria were the following: contraindications to hormone therapy; use of hor-

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Context

Caution about taking estrogen for treating postmenopausal vasomotor symptoms has led to increasing substitution of herbal regimens despite few tests of their effectiveness.

Contribution

The authors randomly assigned 351 perimenopausal or postmenopausal women to herbal treatments (black cohosh, multibotanicals, or multibotanicals plus counseling about dietary soy), estrogen with or without progesterone, or placebo. At 3, 6, and 12 months, patients receiving the herbal interventions had the same change in vasomotor symptoms as those receiving placebo (except for more severe symptoms at 12 months for patients taking multibotanicals plus dietary soy). Estrogen substantially decreased vasomotor symptoms.

Cautions

Most participants were white and were well-educated.

Implications

Herbal regimens did not reduce postmenopausal vasomotor symptoms in this sample of women.

—The Editors

mone therapy or oral contraceptives within 3 months before the trial; use of herbal medicines for menopausal symptoms within 1 month before the trial; soy allergy; bilateral oophorectomy; history of breast cancer; and non-adherence during the run-in period (<80% of capsules taken).

From May 2001 through August 2003, women were recruited by using direct mail. Screening calls determined initial eligibility. Women attended an orientation visit at which eligibility was confirmed, physical measurements were collected, and placebo medication and questionnaires for the 2-week run-in period were provided.

Randomization and Interventions

Participants were randomly assigned by using SAS software (SAS Institute, Inc., Cary, North Carolina), stratified by previous hormone therapy and hysterectomy; block sizes within strata ranged from 5 to 25. Treatment assignments were sent to the University of Washington Research Pharmacy, where medications were bottled and labeled with a sequential identification number without treatment group indication. At the randomization visit, vasomotor symptom diaries and medication counts were examined to confirm eligibility and adherence. The study nurse determined the appropriate stratum, assigned the participant the next study number in that stratum without knowledge of group assignment, and distributed study medications.

The publication of results from the Women's Health Initiative (WHI) estrogen-progestin trial (2) raised new

concerns about the safety of estrogen therapy. New study participants were given the choice of 5-arm (including hormone therapy) versus 4-arm (no hormone therapy) randomization. Current participants gave consent again, incorporating risk estimates from the WHI, and were given the option of finding out whether they had been assigned to hormone therapy; 16 were unblinded, 1 discontinued use of the study drug, and all remained enrolled. Following publication of the WHI Memory Study (8, 9), we informed participants of those findings and restricted randomization to herbs and placebo. No further women were unblinded or discontinued use of the study drug.

Naturopathic medicine provided the model for study interventions. The herbal products, doses, and soy diet were based on approaches used by naturopaths when the study was designed (7). The study groups were as follows: 1) black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*), 160 mg daily; 2.5% triterpene glycosides; 70% ethanol extract); 2) multibotanical; 3) multibotanical plus soy diet counseling; 4) conjugated equine estrogen, 0.625 mg daily, with (for women with a uterus) or without (for women without a uterus) medroxyprogesterone acetate, 2.5 mg; and 5) placebo. The multibotanical delivered daily doses of the following: black cohosh, 200 mg; alfalfa (*Medicago sativa*), 400 mg; boron, 4 mg; chaste tree (*Vitex agnus-castus*), 200 mg; dong quai (*Angelica sinensis*), 400 mg; false unicorn (*Chamaelirium luteum*), 200 mg; licorice (*Glycyrrhiza glabra*), 200 mg; oats (*Avena sativa*), 400 mg; pomegranate (*Punica granatum*), 400 mg; Siberian ginseng (*Eleutherococcus senticosus*, standardized constituents 0.8% eleutherosides E and B), 400 mg.

Black cohosh was provided by Pure World, Inc., (Hackensack, New Jersey). The multibotanical, ProGyne, was purchased from Progena Professional Formulations (Albuquerque, New Mexico) and encapsulated to study specifications. Both companies follow current good manufacturing practices, and single batches were used. Consumer Lab.com (White Plains, New York) tested the products after the study commenced. Dong quai, false unicorn, and pomegranate were not detected, suggesting that they were of poor quality or did not contain the tested marker compounds. Other marker compounds were detected in the approximate doses as labeled (7). The **Appendix Table** (available at www.annals.org) describes the herbal products in detail.

To facilitate blinding, medications and lactose placebo were encapsulated to provide 2 white and 2 blue capsules to each woman, and medication boxes were labeled with a unique identification number that did not indicate study group.

The soy food intervention was modeled after a successful 5-a-day intervention (10). We chose soy foods because of uncertainty about the efficacy of isoflavone supplements and because naturopaths commonly recommend whole soy foods. Participants received 5 telephone calls from a clinical dietitian and a 34-page booklet recommending 2 soy

food servings per day (12 to 20 g of soy protein) (7). Other participants received 1 telephone call and a similar booklet reinforcing fruit and vegetable intake. Participants were instructed not to discuss dietitian calls with study nurses and were unaware that soy counseling was linked to the multi-botanical.

Outcomes and Measurements

The primary outcomes were change from baseline (measured over 2-week run-in period) to 3, 6, and 12 months (each measured for 4 weeks) and change from baseline to the average for all follow-ups with regard to the mean frequency and intensity of vasomotor symptoms (daytime hot flashes plus night sweats) and the mean Wiklund Vasomotor Symptom Subscale score (11, 12). We also evaluated change from baseline to follow-up (months 3, 6, and 12 and average change) for daytime hot flash rate, night sweat rate, and the total Wiklund Menopause Symptom Scale score. Symptom diaries and global ratings of menopause symptoms are almost universally used in studies of vasomotor symptoms. Participants used a vasomotor symptom diary to record daytime hot flashes and night sweats, rating intensity as mild, moderate, or severe (scale, 1 to 3), as recommended by the U.S. Food and Drug Administration (13). Women completed the Wiklund Menopause Symptom Scale, rating the severity of 13 menopausal symptoms (sweats, hot flashes, sleep disturbance, fatigue, vaginal dryness, depression, headache, irritability, muscle/joint pain, breast tenderness, nervousness, palpitations, and dizziness/fainting on a scale of 0 (none) to 10 (severe) (11). Soy food intake was monitored by using a self-reported, validated soy food questionnaire (14).

Follow-up Procedures

Participants returned to the research clinic at 3, 6, and 12 months. Questionnaires were collected, and study medication was dispensed. Medication adherence counts were conducted by staff without participant contact and without knowledge of treatment assignment. Study nurses encouraged adherence and monitored adverse events during monthly telephone calls and at visits. Adverse events were identified through participants' responses to the question, "Have you had any medical problems or been hospitalized?" Responses were recorded and adverse events were followed until they were resolved. The study nurse determined intensity (mild, moderate, or severe) and whether the event was serious (yes or no). Events were reviewed by the study physician, who determined whether the event was study related, without knowledge of group assignment. Adverse events were coded by using the *Coding Symbols for Thesaurus of Adverse Reaction Terms* (15).

The Data and Safety Monitoring Committee reviewed study progress and unblinded outcome and safety data 5 times.

Statistical Analysis

The study was powered to detect an effect of herbs halfway between the expected effects of hormone therapy

and placebo, an outcome that we hypothesized would be meaningful.

Treatment effects, the difference between each treatment group and the placebo group with regard to the mean change from baseline, and the associated 95% CIs and *P* values were estimated by using a multivariate mixed model (PROC MIXED in SAS). We used an unstructured covariance matrix for the repeated measures, with separate parameter estimates for women in the hormone therapy group, since this structure best fit the data. Mixed models increase statistical power because of their ability to use all follow-up data and to better handle missing data. Although retention rates were very high, mixed-model analysis allowed us to use a true intention-to-treat approach, including data from all 351 randomly assigned women ($n = 349$ in adjusted analyses because of missing covariate data). The two Wiklund measures were analyzed after square-root transformation to normalize their distributions.

Mixed models were evaluated with and without adjustment for covariates. All models included a term for randomization protocol (4-arm vs. 5-arm). The adjusted models also controlled for age, body mass index (BMI), hysterectomy, menopausal status (menopausal transition vs. postmenopausal), and previous hormone therapy. All covariates except for BMI were selected a priori because of their hypothesized correlations with study outcomes and exposures. Results from the adjusted and unadjusted models were identical; we present only the adjusted results.

We also tested whether treatment effects differed by 4-arm versus 5-arm randomization (arm by-treatment interaction). Since they did not differ, we present the results based on all randomly assigned women. An "as-treated" sensitivity analysis, restricted to women who took at least 80% of their study medications, was conducted, but results were similar and are not presented. Finally, we used mixed models to test whether the effect of each treatment varied in a statistically significant manner with BMI (nonobese [$BMI < 30 \text{ kg/m}^2$] vs. obese), hysterectomy, menopausal status, previous use of hormone therapy, and baseline symptom rate (<7 symptoms per day vs. ≥ 7 symptoms per day).

Adverse events rates were compared between each group and placebo by using chi-square tests or Fisher exact test (if expected count was <5). The study biostatistician conducted all analyses.

Role of the Funding Sources

This study was funded by the National Institute on Aging and National Center for Complementary and Alternative Medicine. These agencies did not participate in the design, conduct, or analysis of the study or in decisions to submit the manuscript for publication. The National Institute on Aging did participate in decisions related to recruitment redesign in response to the release of the WHI findings and had a representative who attended all Data and Safety Monitoring Committee meetings.

RESULTS

Participants and Follow-up

We mailed 157 493 informational brochures and received 3443 responses (Figure 1). The baseline visit was attended by 509 women; of the 398 eligible women, 351 consented and were randomly assigned as follows: black cohosh ($n = 80$); multibotanical ($n = 76$); multibotanical plus soy counseling ($n = 79$); conjugated equine estrogen with medroxyprogesterone acetate ($n = 29$ women with a uterus) or without medroxyprogesterone acetate ($n = 3$ women without a uterus, all receiving unopposed estrogen); or placebo ($n = 84$). We enrolled 159 women under the 5-arm randomization scheme and 192 under the 4-arm randomization scheme; 147 of 183 women who were given a choice selected the 4-arm protocol. Ninety-two percent of women completed the study (327 of 351), and 87% (306 of 351) were taking study medication at 12 months.

Baseline characteristics were similar across treatment groups, with the exception of BMI (Table 1). On average, BMI was lower in the black cohosh group than in the placebo group and was higher in the hormone therapy group than in the placebo group. Average age was 52.2 years; 93% of participants were white, and all had at least a high school education. Women averaged 6.5 vasomotor symptoms per day (SD, 3.7; range, 1.4 to 24), and 34% averaged at least 7 symptoms per day at baseline. Average symptom intensity was 1.8 (on a scale of 1 to 3); 29% of participants reported symptom intensity averaging at least 2.0. The average Wiklund Menopause Symptom Scale score was 2.3 (SD, 1.2; range, 0.2 to 6.5) and the average Wiklund Vasomotor Symptom Subscale score was 4.5 (SD, 2.0; range, 0.8 to 10). Of 183 women (52%) who were in menopausal transition at baseline, 79 (46.6%) achieved 12 months of amenorrhea during the study.

Among women assigned to the soy food intervention, 77% completed 3 or more telephone calls (mean, 3.6). At baseline, women reported an average of 0.6 serving of soy per day. On average, women in the multibotanical plus soy intervention increased dietary soy by 1.1 servings per day between baseline and 3 months, compared with 0.1 serving per day in the other 4 groups.

Primary Outcomes

The average adjusted number of vasomotor symptoms per day (Figure 2) and the Wiklund Vasomotor Symptom Subscale score (Figure 3) decreased between baseline and 3 months in all groups. There were no statistically significant differences in the average adjusted change in vasomotor symptoms per day or in vasomotor symptom intensity between the herbal interventions and placebo at 3, 6, or 12 months, or for the average over all the follow-up time points, with 1 exception: At 12 months, the multibotanical plus soy intervention had higher (worse) symptom intensity relative to placebo ($P = 0.016$) (Table 2). The average difference in vasomotor symptoms per day between the placebo and herbal treatments groups was less than 1

symptom per day at 3 months and less than 0.6 symptom per day for the average over all the follow-up time points. The average adjusted difference for hormone therapy compared with placebo was -4.55 (95% CI, -6.51 to -2.59) vasomotor symptoms per day at 3 months ($P < 0.001$) and -4.06 (CI, -5.93 to -2.19) vasomotor symptoms per day for the average over all the follow-up time points ($P < 0.001$) (Table 2).

There were no statistically significant differences in the Wiklund Vasomotor Symptom Subscale score between any of the herbal interventions and placebo at 3, 6, or 12 months or for the average over all the follow-up time points (Table 2). The Wiklund Vasomotor Symptom Subscale score was statistically significantly lower with hormone therapy than with placebo at all follow-up time points.

Additional Analyses

There were no statistically significant differences in hot flashes per day or night sweats per day between any of the herbal interventions and placebo at 3, 6, or 12 months or for the average over all the time points, with 1 exception: At 3 months, the black cohosh group had 0.38 less night sweat per day than the placebo group (CI, -0.72 to -0.04 ; $P = 0.030$) (Table 3). The difference between the herbal treatments and placebo was less than 0.6 hot flash per day and less than 0.4 night sweat per day at any time point; the differences in the average over all the time points were even smaller. The differences in hot flashes per day and night sweats per day between hormone therapy and placebo were statistically significant at all times points; over all follow-up time points, the average difference was nearly -3 hot flashes per day and nearly -1 night sweat per day (Table 3).

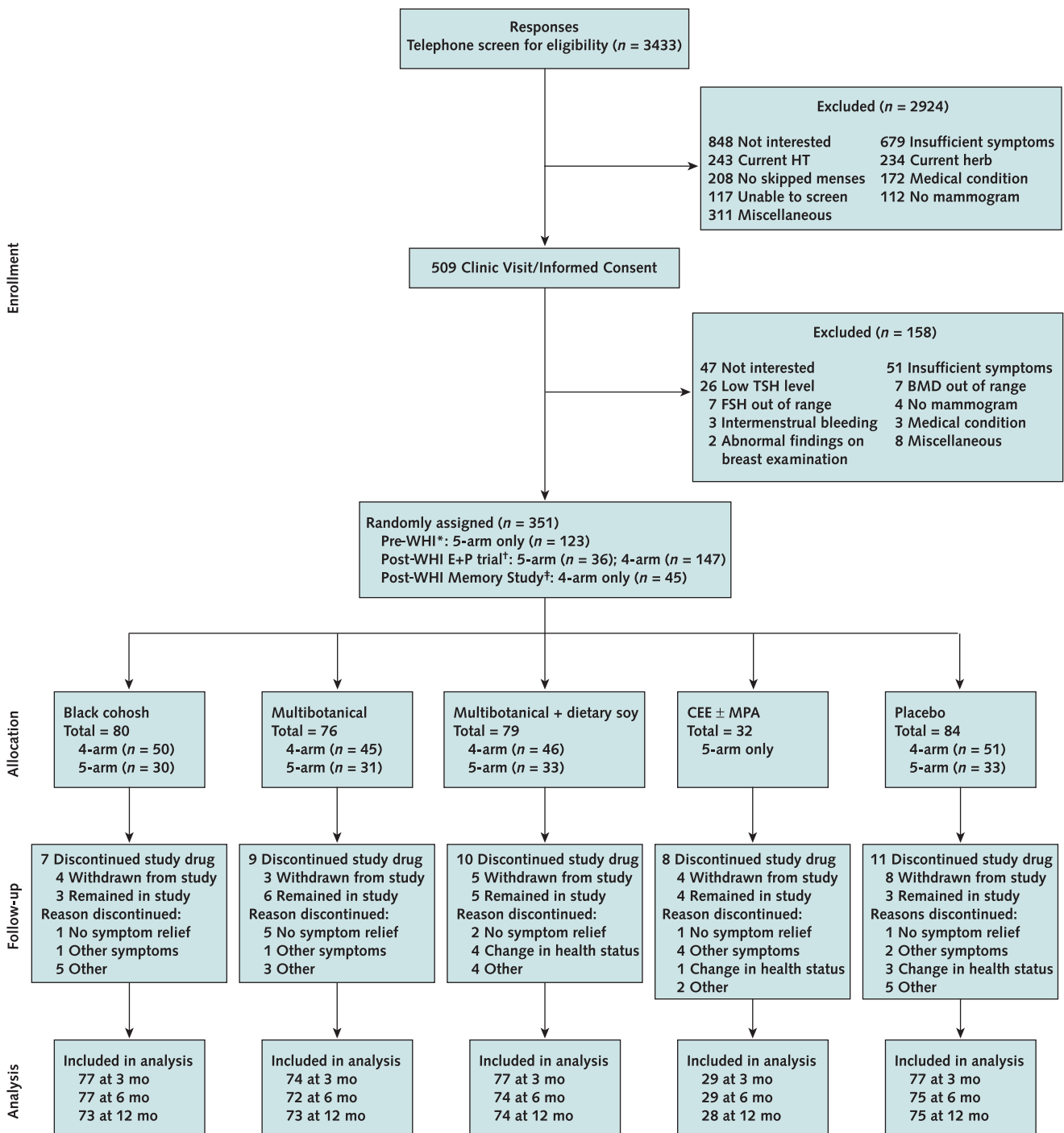
There were no statistically significant differences in the Wiklund Menopause Symptom Scale score between any of the herbal interventions and placebo at 3, 6, or 12 months or for the average over all the time points (Table 3). All differences between hormone therapy and placebo were statistically significant at all times (Table 3).

As-treated analyses, limited to women with at least 80% adherence, and separate analyses for women in the 4-arm and 5-arm randomization schemes, yielded similar results (data not shown). Results did not vary (no statistically significant treatment by subgroup interaction) when results were examined by baseline number of vasomotor symptoms (<7 vs. ≥ 7 per day), 4-arm versus 5-arm randomization scheme, baseline menopausal status, previous use of hormone therapy, hysterectomy (yes or no), or BMI (not obese [<30 kg/m²] vs. obese) (data not shown).

Adverse Events and Adherence

Women assigned to hormone therapy reported more breast pain ($P < 0.001$) and menstrual disorders ($P = 0.04$) compared with placebo (Table 4). There were no statistically significant differences between any of the 4 groups and placebo in the proportion of women with up-

Figure 1. Participant recruitment and retention, Herbal Alternatives for Menopause Trial (HALT).



Reasons for discontinuing therapy are not mutually exclusive. All participants received allocated intervention. *In the original enrolled plan, all participants were enrolled in 1 of 5 groups. †After publication of the Women's Health Initiative (WHI) estrogen-progestin (E + P) trial (2), women were given the option of 4-arm (without conjugated equine estrogen [CEE]) or 5-arm randomization. ‡After publication of the WHI Memory Study (8, 9), randomization to CEE was stopped and only 4-arm randomization (that is, random assignment to herb or placebo, excluding hormone therapy) was used. BMD = bone mineral density; FSH = follicle-stimulating hormone; HT = estrogen with or without progestin; MPA = medroxyprogesterone acetate, 2.5 mg (women without a uterus were randomly assigned to CEE only); soy = counseling to increase dietary soy; TSH = thyroid-stimulating hormone.

Table 1. Baseline Clinical and Demographic Characteristics by Randomization Group

Characteristic	All Participants (n = 351)	Black Cohosh Group (n = 80)	Multibotanical Group (n = 76)	Multibotanical plus Soy Counseling Group (n = 79)	Conjugated Equine Estrogen with or without Medroxyprogesterone Acetate Group (n = 32)	Placebo Group (n = 84)
Mean age (SD), y	52.2 (2.4)	52.0 (2.2)	52.2 (2.5)	52.5 (2.5)	52.3 (2.6)	52.0 (2.5)
Mean body mass index (SD), kg/m ²	28.6 (6.2)	27.3 (5.0)	28.4 (6.3)	28.4 (5.7)	31.5 (7.9)	29.2 (6.4)
Race/ethnicity, n (%)						
White	323 (93)	73 (91)	72 (99)	74 (95)	30 (94)	74 (88)
African-American	9 (3)	3 (4)	1 (1)	3 (4)	0 (0)	2 (2)
Other	15 (4)	4 (5)	0 (0)	1 (1)	2 (6)	8 (10)
Greater than high school education, n (%)	331 (95)	77 (96)	72 (97)	75 (95)	28 (88)	79 (94)
Menopausal transition (vs. postmenopausal), n (%)	183 (52)	39 (49)	39 (52)	43 (54)	20 (63)	42 (50)
Hysterectomy*, n (%)	38 (11)	9 (11)	7 (9)	8 (10)	3 (9)	11 (13)
Previous hormone therapy, n (%)	140 (40)	32 (40)	31 (41)	32 (41)	10 (31)	35 (42)
Mean vasomotor symptoms per day (SD), n	6.5 (3.7)	6.7 (3.0)	6.2 (3.6)	6.5 (3.9)	6.8 (4.9)	6.2 (3.7)
Hot flashes	4.6 (3.1)	4.7 (2.5)	4.4 (3.0)	4.6 (3.2)	5.0 (4.4)	4.3 (3.0)
Night sweats	1.9 (1.2)	2.0 (1.2)	1.8 (1.1)	1.9 (1.2)	1.8 (1.0)	1.9 (1.2)
Mean vasomotor symptom intensity (SD)†	1.80 (0.39)	1.78 (0.39)	1.78 (0.39)	1.77 (0.35)	1.82 (0.40)	1.85 (0.41)
Average symptoms moderate to severe (vs. mild), n (%)	101 (29)	21 (26)	20 (28)	22 (26)	12 (38)	26 (31)
Mean Wiklund Menopause Symptom score (SD)	2.3 (1.2)	2.2 (1.2)	2.2 (1.1)	2.2 (1.2)	2.1 (1.0)	2.5 (1.2)
Mean Wiklund Vasomotor Symptom Subscale score (SD)	4.5 (2.0)	4.4 (1.9)	4.3 (1.9)	4.3 (2.1)	4.5 (2.0)	4.9 (2.0)
Average ≥7 vasomotor symptoms per day, n (%)	120 (34)	33 (41)	23 (30)	28 (35)	12 (38)	24 (29)

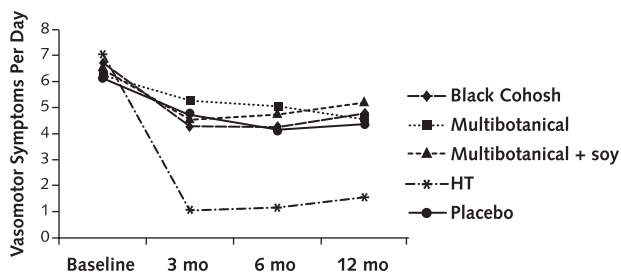
* Women with hysterectomy had at least 1 ovary.
† 1 = mild; 2 = moderate; 3 = severe.

per or lower gastrointestinal symptoms; nausea and vomiting; fatigue, asthenia, or malaise; or headaches or migraine. Too few severe adverse events occurred to make meaningful group comparisons (1 case of endometrial cancer in the multibotanical plus soy group 2.8 months after randomization; 1 case of breast cancer in the multibotanical group 4.7 months after randomization).

Over the 12-month follow-up period, the overall study sample on average took 86% of their pills; among individual study groups, adherence was 88% for black cohosh,

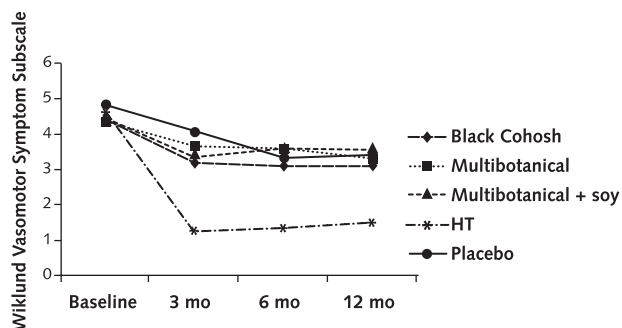
80% for multibotanical, 87% for multibotanical plus soy, 87% for hormone therapy, and 82% for placebo. These adherence figures include all 351 women; adherence was set to 0 for those who dropped out or stopped using study medication (Table 4). The primary reasons for discontinuation of study medication use or study withdrawal were no symptom relief (n = 10), other symptoms (n = 8), or change in health status (n = 8) (Figure 1).

Figure 2. Adjusted mean number of vasomotor symptoms per day, by study group.



Adjusted for age (continuous), body mass index (kg/m², continuous), hysterectomy (yes or no), previous use of hormone therapy (HT) (yes or no), menopausal status (menopausal transition vs. postmenopausal), and randomization arm (4-arm without hormone therapy vs. 5-arm with hormone therapy).

Figure 3. Adjusted mean Wiklund Vasomotor Symptom Subscale scores, by study group.



Adjusted for age (continuous), body mass index (kg/m², continuous), hysterectomy (yes or no), previous use of hormone therapy (HT) (yes or no), menopausal status (menopausal transition vs. postmenopausal), and randomization arm (4-arm without hormone therapy vs. 5-arm with hormone therapy).

Table 2. Difference in Adjusted Mean Change in Vasomotor Symptom Frequency and Intensity and Wiklund Vasomotor Symptom Subscale Score between Intervention and Placebo Groups*

Variable	Black Cohosh Group (n = 80)		Multibotanical Group (n = 76)		Multibotanical plus Soy Counseling Group (n = 79)		Conjugated Equine Estrogen with or without Medroxyprogesterone Acetate Group (n = 32)	
	Difference in Mean Change vs. Placebo (95% CI)	P Value vs. Placebo	Difference in Mean Change vs. Placebo (95% CI)	P Value vs. Placebo	Difference in Mean Change vs. Placebo (95% CI)	P Value vs. Placebo	Difference in Mean Change vs. Placebo (95% CI)	P Value vs. Placebo
Vasomotor symptoms per day (hot flashes plus night sweats)								
3 mo	-0.96 (-2.03 to 0.11)	0.079	0.41 (-0.67 to 1.50)	0.45	-0.53 (-1.60 to 0.54)	0.33	-4.55 (-6.51 to -2.59)	<0.001
6 mo	-0.48 (-1.63 to 0.66)	0.41	0.80 (-0.36 to 1.96)	0.178	0.32 (-0.83 to 1.47)	0.59	-3.86 (-5.73 to -2.00)	<0.001
12 mo	-0.18 (-1.30 to 0.93)	0.74	0.09 (-1.03 to 1.20)	0.88	0.49 (-0.62 to 1.60)	0.39	-3.76 (-5.76 to -1.76)	<0.001
Treatment effect over all follow-up time points	-0.54 (-1.47 to 0.38)	0.25	0.43 (-0.50 to 1.37)	0.36	0.09 (-0.83 to 1.02)	0.84	-4.06 (-5.93 to -2.19)	<0.001
Vasomotor symptom intensity (1 = mild, 2 = moderate, 3 = severe)								
3 mo	0.03 (-0.08 to 0.14)	0.59	0.08 (-0.03 to 0.19)	0.174	0.03 (-0.08 to 0.14)	0.60	0.07 (-0.17 to 0.31)	0.57
6 mo	0.01 (-0.11 to 0.12)	0.91	0.09 (-0.03 to 0.21)	0.126	0.06 (-0.06 to 0.17)	0.35	-0.13 (-0.34 to 0.08)	0.23
12 mo	0.05 (-0.07 to 0.17)	0.46	0.11 (-0.02 to 0.23)	0.089	0.15 (0.03 to 0.27)	0.016	0.05 (-0.15 to 0.26)	0.63
Treatment effect over all follow-up time points	0.03 (-0.07 to 0.12)	0.57	0.09 (0.00 to 0.19)	0.063	0.08 (-0.02 to 0.17)	0.108	0.00 (-0.19 to 0.18)	0.97
Wiklund Vasomotor Symptom Subscale score								
3 mo	-0.47 (-1.18 to 0.24)	0.098	0.15 (-0.57 to 0.87)	0.88	-0.23 (-0.94 to 0.48)	0.28	-2.60 (-3.74 to -1.46)	<0.001
6 mo	0.20 (-0.52 to 0.91)	0.90	0.80 (0.07 to 1.52)	0.062	0.72 (-0.01 to 1.44)	0.057	-1.78 (-2.80 to -0.76)	<0.001
12 mo	0.10 (-0.68 to 0.88)	0.83	0.44 (-0.34 to 1.22)	0.43	0.57 (-0.21 to 1.35)	0.27	-1.77 (-2.79 to -0.75)	<0.001
Treatment effect over all follow-up time points	-0.06 (-0.67 to 0.55)	0.48	0.46 (-0.15 to 1.08)	0.30	0.35 (-0.26 to 0.96)	0.41	-2.05 (-3.02 to -1.08)	<0.001

* All analyses were adjusted for age (continuous), body mass index (kg/m², continuous), hysterectomy (yes or no), previous use of hormone therapy (yes or no), menopausal status (menopause transition vs. postmenopausal), and randomization arm (4-arm without hormone therapy vs. 5-arm with hormone therapy). Estimates of difference in mean change from baseline vs. placebo, along with P values and 95% CIs, from mixed-model analysis that used data from baseline and all 3 follow-up time points (total, n = 349 for adjusted analyses).

DISCUSSION

In this large, randomized, double-blind trial, none of the 3 herbal treatments had clinically meaningful effects on any of the primary outcomes. As expected, hormone therapy resulted in a clinically important decrease in vasomotor symptom frequency and Wiklund scores throughout 1 year of treatment.

At least 5 randomized, placebo-controlled trials of black cohosh and menopausal symptoms have been published (16–20). All were short-term (≤12 weeks), and most were small, typically randomly assigning 30 to 60

women per group. Among 5 trials that examined frequency of hot flashes (16–19, 21), the only trial reporting a positive effect for black cohosh also found no effect of conjugated equine estrogen versus placebo (18); this result raises concerns about the validity of the findings. When menopause rating scales were used, 2 trials reported a positive effect of black cohosh (16, 18), 3 reported no difference from placebo (17, 19, 21), and 1 did not report main trial effects (20). The only trial that investigated a multibotanical containing black cohosh found no differences in vasomotor symptom frequency or menopause scale scores com-

Table 3. Difference in Adjusted Mean Change in Frequency of Hot Flashes and Night Sweats and Wiklund Menopause Symptom Scale Scores between Intervention and Placebo Groups*

Variable	Black Cohosh Group (n = 80)		Multibotanical Group (n = 76)		Multibotanical plus Soy Counseling Group (n = 79)		Conjugated Equine Estrogen with or without Medroxyprogesterone Acetate Group (n = 32)	
	Difference in Mean Change vs. Placebo (95% CI)	P Value vs. Placebo	Difference in Mean Change vs. Placebo (95% CI)	P Value vs. Placebo	Difference in Mean Change vs. Placebo (95% CI)	P Value vs. Placebo	Difference in Mean Change vs. Placebo (95% CI)	P Value vs. Placebo
Hot flashes per day								
3 mo	-0.59 (-1.43 to 0.26)	0.174	0.30 (-0.56 to 1.15)	0.50	-0.34 (-1.19 to 0.50)	0.42	-3.55 (-5.24 to -1.86)	0.0002
6 mo	-0.26 (-1.19 to 0.67)	0.59	0.55 (-0.40 to 1.50)	0.26	0.32 (-0.62 to 1.26)	0.51	-2.89 (-4.52 to -1.26)	0.001
12 mo	-0.28 (-1.16 to 0.60)	0.53	-0.05 (-0.93 to 0.84)	0.92	0.32 (-0.56 to 1.20)	0.48	-3.15 (-4.84 to -1.47)	<0.001
Treatment effect over all follow-up time points	-0.38 (-1.13 to 0.37)	0.33	0.27 (-0.49 to 1.03)	0.49	0.10 (-0.65 to 0.85)	0.80	-3.20 (-4.82 to -1.58)	<0.001
Night sweats per day								
3 mo	-0.38 (-0.72 to -0.04)	0.030	0.11 (-0.23 to 0.46)	0.52	-0.18 (-0.53 to 0.16)	0.29	-0.98 (-1.40 to -0.56)	<0.001
6 mo	-0.23 (-0.57 to 0.11)	0.182	0.23 (-0.12 to 0.57)	0.198	0.00 (-0.34 to 0.34)	1.00	-0.98 (-1.40 to -0.56)	<0.001
12 mo	0.08 (-0.30 to 0.47)	0.67	0.12 (-0.27 to 0.51)	0.54	0.16 (-0.23 to 0.54)	0.43	-0.60 (-1.08 to -0.13)	0.015
Treatment effect over all follow-up time points	-0.18 (-0.48 to 0.12)	0.25	0.15 (-0.15 to 0.46)	0.32	-0.01 (-0.31 to 0.29)	0.95	-0.85 (-1.26 to -0.45)	<0.001
Wiklund Meno- pause Symptom Subscale score								
3 mo	-0.15 (-0.47 to 0.17)	0.23	-0.04 (-0.36 to 0.28)	0.57	-0.10 (-0.42 to 0.22)	0.35	-0.87 (-1.29 to -0.46)	<0.001
6 mo	0.07 (-0.26 to 0.41)	0.86	0.35 (0.01 to 0.68)	0.068	0.25 (-0.08 to 0.58)	0.23	-0.37 (-0.90 to 0.16)	0.028
12 mo	-0.03 (-0.40 to 0.33)	0.83	0.14 (-0.23 to 0.51)	0.54	0.03 (-0.34 to 0.40)	0.99	-0.49 (-0.93 to -0.05)	0.013
Treatment effect over all follow-up time points	-0.04 (-0.33 to 0.26)	0.64	0.15 (-0.15 to 0.44)	0.45	0.06 (-0.23 to 0.35)	0.90	-0.58 (-0.98 to -0.18)	<0.001

* All analyses were adjusted for age (continuous), body mass index (kg/m², continuous), hysterectomy (yes or no), previous use of hormone therapy (yes or no), menopausal status (menopause transition vs. postmenopausal), and randomization arm (4-arm without hormone therapy vs. 5-arm with hormone therapy). Estimates of difference in mean change from baseline vs. placebo, along with P values and 95% CIs, from mixed-model analysis that used data from baseline and all 3 follow-up time points (total, n = 349 for adjusted analyses).

pared with placebo (22). Thus, the totality of the evidence does not consistently support a short-term effect of black cohosh on menopausal symptoms.

Effects of herbal products, such as black cohosh, may be sensitive to dose, extraction method, plant type, and coadministration of other herbs. The total daily triterpene glycoside dose in our black cohosh product was 5 mg, comparable to the 2 to 4 mg found in Remifemin (Schaper & Brümmer GmbH, Salzgitter, Germany), the most widely used product. Like Remifemin, our black cohosh (fingerprinted and verified to be *Actaea racemosa*) (7) was standardized to 27-deoxyactin. Remifemin is an isopropyl alcohol extract, whereas the products we tested are ethanol

extracts. The implications of these different extraction techniques are unknown.

The literature on the other ingredients in the multibotanical is limited. Randomized trials have shown no improvement in vasomotor symptoms with dong quai (23) or Siberian ginseng (24). We are unaware of any study that has examined how the other components of the multibotanical affect vasomotor symptoms, although similar formulas are prescribed by naturopathic clinicians (7) and sold as over-the-counter supplements.

We reviewed 16 randomized clinical trials that tested whole soy or soy isoflavone supplements for vasomotor symptoms (25–40). Most were 12-week trials (range, 4 to

52). Eight studies found statistically significant improvements in at least 1 menopause symptom measure (26–28, 31, 33, 35, 37, 39). The magnitude of benefit was a 25% to 55% decrease in frequency or severity of menopause symptoms. Only 3 short-term studies evaluated dietary soy and vasomotor symptoms (38–40); 1 found a statistically significant improvement in vasomotor symptoms after 12 weeks of a soy- and flax-enriched diet (39).

To our knowledge, ours is the longest and largest placebo-controlled, double-blind trial to date, and we included both placebo and hormone therapy as benchmark comparison groups. Findings from our study indicate that trials longer than 12 weeks are necessary to evaluate the sustainability of effects. Adherence and retention were high. We included women in the menopausal transition, and women with 2 or more vasomotor symptoms per day (compared with the 7 to 8 required in Food and Drug Administration-monitored drug trials [13]), because women with fewer symptoms are a key target for herbal therapies. Our findings were similar for women with 7 or more versus fewer than 7 symptoms per day. Although we found no evidence of significant side effects, only a larger and longer trial could provide reassurance in this regard. Our results are generalizable to white, relatively well-educated women who have an average of at least 2 vasomotor symptoms per day. We conducted independent testing of the herbal products; no contaminants were found, and key constituents were present in the amounts specified by the manufacturers (7).

An important question in a trial that does not find statistically significant treatment effects is whether the negative findings were due to a true lack of clinically impor-

tant effects or a lack of statistical power. The confidence intervals for our primary outcome of symptoms per day can be used to determine the effect size that can be “ruled out” by our results (Table 2). Over all 3 follow-up time points, one can rule out reductions beyond 1.5 symptoms per day from black cohosh and 1.0 symptom per day from the multibotanical treatments. Whether these are clinically important effects is debatable, but we would argue that most women would not think so. It is important to emphasize that these are the largest possible effects that are consistent with our data. Our best estimates of effect are far less; the average reduction in symptoms per day over the entire follow-up period was less than 0.01 symptom per day, combining results for the 3 herbal groups, all of whom received black cohosh.

Treatments used in naturopathic practice motivated our choice of interventions. The whole-person approach used by most naturopathic physicians differs significantly from the treatments selected for our study, and this might have affected response to therapy. Time spent with the patient on counseling about diet, exercise, and emotional issues related to menopause; dose revisions; and additional supplements are important aspects of the naturopathic strategy for managing menopausal symptoms. We could not replicate this approach.

In summary, there is a pressing need for safe and effective interventions for vasomotor symptoms. Regrettably, this trial and the totality of the evidence indicates that black cohosh used in isolation, or in a multibotanical product, has little potential to play an important role in relief of vasomotor symptoms.

Table 4. Women with Adverse Events, Mean Adherence, and Reasons for Withdrawal or Discontinuation of Medication Use by Treatment Group over 12 Months of Follow-up

Variable	Black Cohosh Group (n = 80)	Multibotanical Group (n = 76)	Multibotanical plus Soy Counseling Group (n = 79)	Conjugated Equine Estrogen with or without Medroxyprogesterone Acetate Group (n = 32)	Placebo Group (n = 84)
Adverse events					
Menstrual disorders, n (%)	10 (13)	8 (11)	14 (18)	19 (59)*	17 (20)
Breast discomfort, n (%)	0	1 (1)	2 (3)	5 (16)†	3 (4)
Gastrointestinal upset, n (%)	12 (15)	11 (14)	8 (10)	4 (13)	13 (15)
Headache, n (%)	12 (15)	8 (11)	12 (15)	6 (19)	16 (19)
Fatigue, asthenia, or malaise, n (%)	12 (15)	7 (9)	12 (15)	6 (19)	8 (10)
Myalgia or arthralgia, n (%)	11 (14)	9 (12)	9 (11)	1 (3)	10 (12)
Adherence					
Average medications taken, %	88	80	87	87	82
Reasons for study medication discontinuation or study withdrawal, n (%)					
No symptom relief	1 (1.3)	5 (6.6)	2 (2.5)	1 (3.1)	1 (1.2)
Other symptoms	1 (1.3)	1 (1.3)	–	4 (12.5)	2 (2.4)
Change in health status	–	–	4 (5.1)	1 (3.1)	3 (3.6)
Other	5 (6.3)	3 (3.9)	4 (5.1)	2 (6.3)	5 (6.0)

* $P < 0.001$ vs. placebo.

† $P = 0.04$ vs. placebo.

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Appendix Table. Consolidated Standards of Reporting Trials (CONSORT) Requirements for Controlled Trials of Herbal Interventions*

Criteria	Black Cohosh: Single Herb Product		Multibotanical Product	
		Black Cohosh	Alfalfa	Boron Citrate
Latin binomial name	<i>Actaea racemosa</i>	<i>Actaea racemosa</i>	<i>Medicago sativa</i>	NA
Botanical authority				NA
Family name	Ranunculaceae	Ranunculaceae	Fabaceae	NA
Common names	Black bugbane, black snakeroot, bugwort, rattleroot, rattletop, rattleweed, macrotys	Black bugbane, black snakeroot, bugwort, rattleroot, rattletop, rattleweed, macrotys	Alfalfa, lucerne, purple medik, trefoil	Boron
Proprietary product name (i.e., brand name) or extract name; manufacturer	CimiPure (Naturex, Avignon, France)	†	†	†
Is product authorized (licensed, registered) in United States?	Yes, trademarked	No trademark or registration	No trademark or registration	No trademark or registration
Parts of plant used to produce the product or extract	Rhizome and root	Root	Leaf	NA
Type of product used (e.g., raw, fresh, or dry, extract), type and concentration of extraction solvent, ratio of herbal drug to extract	70% ethanol extract	Water and alcohol 4:1 extract	No solvents 4:1 extract	NA
Method of authentication of raw materials		GC	TLC	HPLC
Lot number of the raw material	M008250	SB01-0160	220100-50	021390910
State whether a voucher specimen (i.e., retention sample) retained; if so, where it is kept or deposited, and reference number	Yes, voucher specimen 51680, deposited at the New York Botanical Garden	No—past time of retention	No—past time of retention	No—past time of retention
Product dosage per capsule	80 mg	50 mg	100 mg	20 mg
Content (e.g., as weight, concentration; may be given as a range where appropriate) of all quantified herbal product constituents, both native and added, per dosage unit form	Per capsule: 80 mg of black cohosh, 510 mg of rice flour			
Added materials (binders, fillers, and other excipients)	Rice flour	None	None	None
Standardization	Triterpene glycosides	None	None	Boron
Product's chemical fingerprint and methods used	HPLC, CE	HPLC, CE	HP-TLC	HPLC, CE
For standardized products, quantity of active/marker constituents per dosage unit form	2.5%	NA	NA	NA
Amount detected	Triterpene glycosides, 3.125%	Triterpene glycosides, 4.4%	L-canavanine Alfalfa juice, 20% extract, 1 mg/g Alfalfa leaf, 4:1 extract, 3 mg/g	0.92 mg
Was a sample of the product (i.e., retention sample) retained? If so, where it is kept or deposited?	Yes			

* All analyses were performed by ConsumerLab.com. Specifics of special testing/purity testing are as follows (abbreviations used in tables defined at end of footnote): 1. Chlorinated pesticide screens were tested on the black cohosh and the multibotanical finished products, evaluated by GC/MS. The detection limit level was set at 50 parts per billion. The following were tested and were not found: pentachlorobenzene, tetrachloroaniline, hexachlorobenzene, α -benzene hexachloride (BHC), pentachloronitrobenzene, lindane, β -BHC, heptachlor, pentachloroaniline, δ -BHC, aldrin, pentachlorothioanisole, heptachlor, epoxide, γ -chlordane, endosulfan I, α -chlordane, dieldrin, endrin, endrin aldehyde, endosulfan sulfate, dichloro-diphenyl-trichloroethane, dichlorodiphenyldichloroethylene, dichloro-diphenyl-dichloroethane, endosulfan II, methoxychlor, and endrin ketone. 2. Black cohosh, and the multibotanical were tested for heavy metals by inductively coupled plasma–mass spectroscopy. The black cohosh product contained $<0.06 \mu\text{g}$ of lead, $<0.06 \mu\text{g}$ of cadmium, and $0.97 \mu\text{g}$ of arsenic. The multibotanical finished product contained $<0.49 \mu\text{g}$ of lead, $<0.0714 \mu\text{g}$ of cadmium, and $1.16 \mu\text{g}$ of arsenic. 3. Alfalfa was tested for L-canavanine, an antinutrient, by using HP-TLC. The alfalfa leaf and juice extract raw material had 1 mg/g of L-canavanine in the juice extract (20% extract) and 3 mg/g in the leaf (4:1 extract). 4. Screening for estrogenic drug substances was detected by GC/MS. The following were tested and not found: diethylstilbestrol, estradiol, estrone, estriol, ethynyl estradiol, and tamoxifen. CE = capillary electrophoresis; GC = gas chromatography; HPLC = high-performance liquid chromatography; HP-TLC = high-performance thin-layer chromatography; MS = mass spectroscopy; NA = not available; TLC = thin-layer chromatography.

† Progyne (Progena, Albuquerque, NM, Lot 1051504).

‡ Per capsule: 50 mg of black cohosh, 100 mg of alfalfa, 1 mg of boron citrate, 50 mg of chaste tree, 100 mg of dong quai, 50 mg of false unicorn, 50 mg of licorice, 100 mg of oats, 100 mg of pomegranate, 100 mg of siberian ginseng; no filler or other constituents.

Appendix Table—Continued

Multibotanical Product						
Chaste Tree	Dong Quai	False Unicorn	Licorice	Oats Straw	Pomegranate	Siberian Ginseng
<i>Vitex agnus-castus</i>	<i>Angelica sinensis</i>	<i>Chamaelirium luteum</i>	<i>Glycyrrhiza glabra</i>	<i>Avena sativa</i>	<i>Punica granatum</i>	<i>Eleutherococcus senticosus</i>
Verbenaceae	Apiaceae	Liliaceae	Fabaceae	Poaceae	Lythraceae	Araliaceae
Chaste berry, Monk's pepper, Abraham's balm, chaste lamb-tree, safe tree, Indian-spice, wild pepper	Dong quai, dang gui, tang-kuei	Starwort, helonias root, blazing star root, devil's bit, false unicorn	Lacrisse, sweet licorice, licorice root	Oats	Pomegranate	Ginseng
†	†	†	†	†	†	†
No trademark or registration	No trademark or registration	No trademark or registration	No trademark or registration	No trademark or registration	No trademark or registration	No trademark or registration
Berry	Root	Root	Root	Straw	Fruit	Root
Dry powder	Water and alcohol 4:1 extract	Water and alcohol 4:1 extract	Water and alcohol 4:1 extract	Water and alcohol 10:1 extract	Dry powder	Water and alcohol 0.8% extract
GC	GC	TLC	TLC	GC	GC	GC
38699C	S801-0031	14C1-6	20012450	S801-0136C-J	L5029P	SG001006C
No—past time of retention	No—past time of retention	No—past time of retention	No—past time of retention	No—past time of retention	No—past time of retention	No—past time of retention
50 mg	100 mg	50 mg	50 mg	100 mg	100 mg	100 mg
‡	‡	‡	‡	‡	‡	‡
None	None	None	None	None	None	None
None	None	None	None	None	None	Eleutherosides B and E
HPLC, CE	HPLC, CE	HPLC, CE	HPLC, CE	Not tested	HP-TLC	HPLC, CE
NA	NA	NA	NA	NA	NA	0.8%
Agnuside, 0.024%	Ligustilide, <0.001%; ferulic acid, 0.016%	Diosgenin (free) Not detected	Glycyrrhizic acid, 14%	Not tested	Polyphenolics Not detected	Eleutherosides B and E, 1.6%

Yes—for both products, a retention sample is being stored at the Group Health Center for Health Studies