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MENOPAUSE

Phyto-Female Complex for the relief of hot flushes, night sweats and quality of sleep: Randomized, controlled, double-blind pilot study

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Abstract

Objective. To determine the efficacy and safety of the herbal formula Phyto-Female Complex (SupHerb, Netanya, Israel; ingredients: standardized extracts of black cohosh, *dong quai*, milk thistle, red clover, American ginseng, chaste-tree berry) for the relief of menopausal symptoms.

Methods. A randomized, double-blind, placebo-controlled trial in 50 healthy pre and postmenopausal women, aged 44–65 years, to whom oral Phyto-Female Complex or matched placebo was prescribed twice daily for 3 months. A structured questionnaire on the frequency and intensity of menopausal symptoms was administered weekly from one week before throughout the 3-month treatment period, followed by biochemical tests, breast check, and transvaginal ultrasonography.

Results. The women receiving Phyto-Female Complex reported a significantly superior mean reduction in menopausal symptoms than the placebo group. The effect of treatment improvements in menopausal symptoms increased over time; by 3 months there was a 73% decrease in hot flushes and a 69% reduction of night sweats, accompanied by a decrease in their intensity and a significant benefit in terms of sleep quality. Hot flushes ceased completely in 47% of women in the study group compared with only 19% in the placebo group. There were no changes in findings on vaginal ultrasonography or levels of relevant hormones (estradiol, follicle-stimulating hormone), liver enzymes or thyroid-stimulating hormone in either group.

Conclusion. Phyto-Female Complex is safe and effective for the relief of hot flushes and sleep disturbances in pre- and postmenopausal women, at least for 3 months' use.

Keywords: *Phyto-female complex, menopause, symptoms*

Introduction

According to the US Census Bureau as reported by the Food and Drug Administration [1], there were about 37.5 million US women reaching or currently at menopause (aged 40–59 years) in 2000. The reduction in estrogen levels during menopause may cause a range of symptoms of varying severity that affect quality of life, such as hot flushes, night sweats, sleep disturbances, fatigue, depression and reduction in libido. Although hormone replacement therapy (HRT) has been used for years to relieve menopausal symptoms, recent studies have raised concerns regarding its safety, especially in women with a personal or family history of breast or uterine cancer or other estrogen-dependent cancers, and women with or at risk of cardiovascular disease [2]. It was

suggested that even short-term use (1–2 years) can increase the risk of congestive heart disease, stroke and venous thromboembolic disease [3,4]. The risk rises in the presence of specific factors, such as older age, overweight or obesity, and factor V Leiden status [5]. As a result, women are increasingly turning to alternative therapies.

The growing popularity of herbal medicine has been fueled by a virtual explosion of scientific information in the last 20 to 30 years. Studies have shown that phytoestrogens, which are natural plant compounds, possess estrogenic or antiestrogenic activity and that they exert their effects through receptor-dependent and/or -independent mechanisms. Phytoestrogens may also serve as chemoprotective agents. Other botanical herbs used for menopausal symptoms include red clover,

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black cohosh, *dong quai*, chaste-tree berries and ginseng [6–31].

Phyto-Female Complex (SupHerb, Netanya, Israel) is a new herbal preparation specifically designed for relief of menopausal symptoms. Thus, the aim of the present study was to conduct a randomized, placebo-controlled efficacy study of the use of Phyto-Female Complex to relieve menopausal symptoms, mainly vasomotor symptoms such as hot flushes and night sweats, in peri- and postmenopausal women.

Materials and methods

The study was conducted at five community gynecological clinics of the General Health Services, the major health maintenance organization in Israel. The protocol was approved by the ethics committee of Rabin Medical Center and written informed consent was obtained from all participants.

The study sample included 50 healthy pre and postmenopausal women aged 45–65 years. Eligibility for the study was limited to women who met the following criteria: amenorrhea for at least 6 months, elevated follicle-stimulating hormone (FSH) level ($>30 \mu\text{g/ml}$), and hot flushes and/or night sweats at least three times daily. Clinical tests, blood sampling for hormonal profile, estradiol, FSH, blood glucose, cholesterol, liver enzymes (alanine transaminase, ALT and aspartate aminotransferase, AST) and thyroid-stimulating hormone (TSH), in addition to transvaginal ultrasonography and breast examination, were performed at onset and at completion of the study (13 weeks). Participants were also asked not to consume any soy or phytoestrogen products in their diet and to complete a questionnaire on a daily basis, one week before entering the study (the pre-study period) and every day during the trial, on number of hot flushes and night sweats and number of awakenings at night due to vasomotor symptoms. Symptom intensity and sleep quality were subjectively assessed on a scale of 1 to 5. Clinic visits were scheduled at the end of weeks 4, 8 and 12. In each clinic visit adverse events were assessed.

The patients were randomized into two groups, to receive either Phyto-Female Complex ($n=25$) or placebo ($n=25$). Each capsule of Phyto-Female Complex contains standardized extracts of the following herbs: black cohosh (*Cimicifuga racemosa*) root extract, 100 mg (2.5 mg triterpen glycoside, 2.5%); *dong quai* (*Angelica sinensis*) root extract, 75 mg (7.5 mg ligustilides, 1%); milk thistle (*Silybum marianum*) herb extract, 75 mg (60 mg silymarin, 80%); red clover (*Trifolium pratense*) flower extract, 50 mg (4 mg isoflavone, 8%); American ginseng (*Panax quiquefolium*) root extract, 50 mg (12.5 mg ginsenosides, 25%); and chaste-tree berry (*Vitex agnus castus*) fruit extract, 50 mg (2.5 mg vitexin, 5%). The complex is prepared according to Good Manufacturing Practice GMP

standards and analysis is certified (SupHerb). Phyto-Female Complex is marketed in Israel as a food supplement. The placebo capsules were outwardly identical to the study preparation.

Statistical analysis

Data were compared between groups and within groups, before treatment (baseline) and at the end of treatment, using Student's paired two-tailed t test (heteroskedastic test). Significance was set at $p < 0.05$.

Results

The background data and findings for the Phyto-Female Complex and comparison groups are shown in Table I. There were no significant differences between groups in mean age, body mass index, clinical chemistry profile, and baseline severity of vasomotor symptoms. The initial study sample included 50 women. Six women were withdrawn from the study due to missing data. Seven patients (five in the placebo group, two in the study group) dropped out of the study during the first four weeks and two (placebo group) during weeks 4–8 owing to lack of compliance or deciding voluntarily to discontinue participation. Women in the placebo group felt aggravation of or no change in symptoms and decided to stop the treatment. The remaining 35 patients (16 in the placebo group, 19 in the study group) satisfactorily completed the 12 weeks of the trial.

Women receiving Phyto-Female Complex already showed a significant reduction in the number of hot flushes and night sweats (percentage change from baseline) at the end of week 2 of the trial: 25% reduction in total number of daily hot flushes ($p=0.044$) and 23% reduction in night sweats ($p=0.037$), vs. 8% and 15%, respectively, in the placebo group. By the end of week 12, the number of hot flushes was reduced by a mean of 73% in the study group and 38% in the placebo group ($p=0.026$), and the number of night sweats was reduced by 69% and 29% respectively ($p=0.027$) (Figure 1 and Table II). The decrease in number of hot flushes was accompanied by a decrease in their intensity: at the end of the study, intensity scores were 80% lower than baseline (percentage of the average intensity experienced by the same woman before treatment) for the Phyto-Female Complex group but only 35% lower in the placebo group ($p=0.002$) (Table II). During the study, aggravation of symptoms was reported in 22% of the women in the placebo group; 52% reported no change and 26% reported only a mild response, including alleviation of hot flushes in 19%. Overall, 30% of this group ceased treatment before the end of the trial. By contrast, none of the patients in the study group had a worsening of symptoms and 81% reported an

Table I. Background data on peri- and postmenopausal women treated with Phyto-Female Complex herbal combination or placebo.

Characteristic	Phyto-Female Complex (n=21)	Placebo (n=23)	p Value
Age (years)	55.3 ± 5.4	59.0 ± 7.3	NS
Years in menopause	6.88 ± 4.77	8.95 ± 6.44	NS
No. who previously used HRT	12	13	NS
Height (cm)	1.63 ± 0.05	1.64 ± 0.05	NS
Weight (kg)	65.80 ± 9.90	70.58 ± 10.47	NS
No. of hot flushes*			
Baseline	5.57 ± 2.57	5.06 ± 2.98	NS
End of treatment	1.56 ± 1.11	2.90 ± 2.20	0.01
No. of night sweats*			
Baseline	3.18 ± 1.40	2.76 ± 1.43	NS
End of treatment	1.00 ± 0.80	1.98 ± 1.40	0.03
Intensity of hot flushes score†			
Baseline	3.14 ± 1.05	3.45 ± 1.06	NS
End of treatment	0.53 ± 0.67	2.17 ± 1.53	0.002
Sleep quality score†			
Baseline	3.58 ± 1.14	2.57 ± 1.53	NS
End of treatment	1.06 ± 1.04	2.05 ± 1.17	0.001
<i>Chemistry profile</i>			
AST (units) U/L			
Baseline	19.00 ± 3.38	19.98 ± 6.60	NS
End of treatment	25.27 ± 14.39	25.80 ± 10.30	NS
ALT (units) U/L			
Baseline	18.00 ± 5.85	21.80 ± 10.53	NS
End of treatment	21.77 ± 10.08	28.80 ± 16.90	NS
TSH (units) ml U/L			
Baseline	2.86 ± 1.16	1.85 ± 0.95	NS
End of treatment	2.95 ± 1.74	2.06 ± 0.98	NS
E ₂ (units) pg/ml			
Baseline	109.78 ± 30.00	104.14 ± 34.70	NS
End of treatment	89.73 ± 30.00	70.30 ± 25.25	NS

HRT, hormone replacement therapy; AST, aspartate aminotransferase; ALT, alanine transaminase; TSH, thyroid-stimulating hormone; E₂, estradiol; NS, not significant; data are expressed as mean ± standard deviation; *average daily number; †self-rated on a scale of 1 to 5.

amelioration of menopausal symptoms. The hot flushes stopped in 47% of the study group by the third month (Table III).

In relation to sleep quality rating, mean score at baseline was 2.57 ± 1.53 in the placebo group and 3.58 ± 1.14 in the study group (the lower the score, the higher the quality; Table I). Women taking the herbal complex reported a 52% reduction at the end of week 8 and a 70% reduction at the end of the trial, meaning that the women moved to the 'good sleeper' (score of 1) category. In the placebo group, scores at week 12 were reduced by only 21% compared with baseline ($p=0.001$) (Figure 2 and Table II).

Neither group had significant differences from baseline in estradiol, FSH, liver enzymes (ALT, AST) and TSH levels (Table I). There was no evidence of endometrial thickness changes by transvaginal ultrasonography.

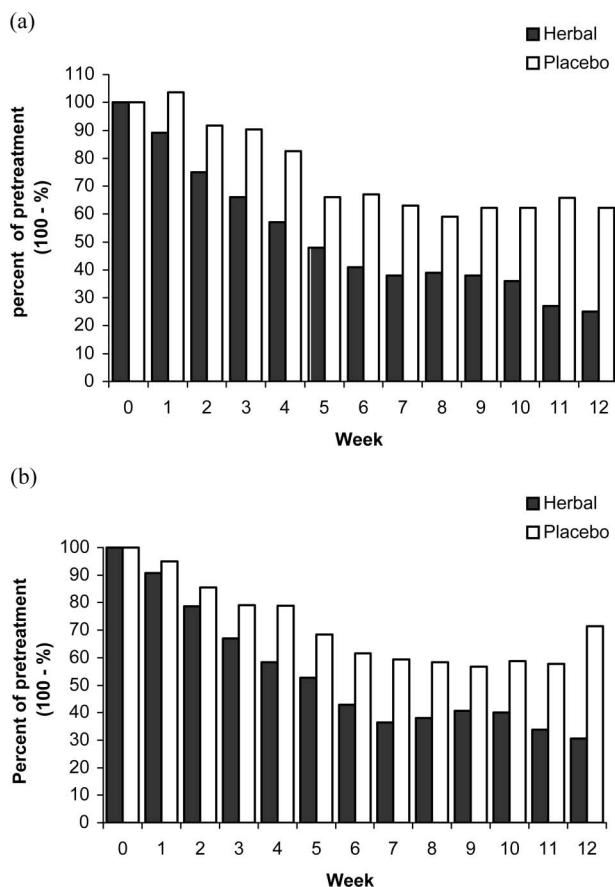


Figure 1. Decrease in the average number of (a) daily hot flushes and (b) night sweats compared with baseline in peri- and postmenopausal women treated with Phyto-Female Complex herbal combination or placebo.

Discussion

The present research work provides new data exploring the effect of an oral complex combining various herbal compounds on the relief of menopausal symptoms. Positive clinical evidence has been reported for some of the compounds found in the present combination, however in a single fashion. This is perhaps the first report to date to analyze the effect of a herbal combination on the relief of vasomotor symptoms and quality of sleep in peri- and postmenopausal women.

The results of our 12-week study suggest that Phyto-Female Complex is significantly effective in relieving menopausal symptoms, including both nocturnal and diurnal hot flushes and sleep disturbances, in comparison to placebo. The relief of hot flushes was observed as early as the end of week 2. The number of hot flushes and night sweats decreased progressively during the study period. The Phyto-Female Complex also significantly improved sleep quality by as early as the end of week 8, and even more at the end of the study. No side-effects were reported during the study and the complex was tolerated well.

Table II. Percentage change in vasomotor symptoms from baseline (before treatment) reported by women participating in each treatment group.

Symptom/treatment	Week 0	Week 2	Week 4	Week 8	Week 12	<i>p</i> Value*
Daily hot flushes[†]						
Phyto-Female Complex	5.6 ± 2.5	25 ± 3	43 ± 3	53 ± 5	73 ± 5	0.026
Placebo	5.1 ± 3.0	7.6 ± 3.0	18 ± 4	45 ± 5	5 ± 58	
Intensity of hot flushes[‡]						
Phyto-Female Complex	3.1 ± 1.0	21 ± 3	34 ± 3	62 ± 3	81 ± 3	0.002
Placebo	3.5 ± 1.0	6.6 ± 1.0	19 ± 3	35 ± 4	35 ± 5	
Night sweats[†]						
Phyto-Female Complex	3.2 ± 1.4	23 ± 3	35 ± 3	60 ± 3	69 ± 4	0.027
Placebo	2.7 ± 1.4	15 ± 3	21 ± 4	42 ± 5	29 ± 6	
Sleep quality[†]						
Phyto-Female Complex	3.5 ± 1.1	12 ± 4	28 ± 4	52 ± 4	70 ± 4	0.001
Placebo	2.5 ± 1.5	0.8 ± 4.0	20 ± 4	41 ± 6	21 ± 4	

*Data are expressed as mean ± standard deviation; **p* value for the comparison between Phyto-Female Complex vs. placebo after 12 weeks of treatment; [†]average number; [‡]self-rated on a scale of 1 to 5.

The use of alternative therapies for menopausal symptoms has been growing since the 1980s. Black cohosh, probably the most widely studied medicinal herb, has a long tradition as a beneficial remedy for joint, muscle and nerve aches, and rheumatism [11,12]. Its use since the late 1950s for the treatment of menopausal symptoms, menstrual disorders and premenstrual syndrome has been widely reported [9]. The majority of clinical trials have shown black cohosh to be effective for the relief of vasomotor symptoms. New evidence-based efficacy and safety data have been reported for the isopropanolic extract of black cohosh [29]. Wuttke and colleagues [12] described black cohosh as a selective estrogen receptor modulator and recommended it as an alternative to HRT; others found that it enhanced the antiproliferative effect of tamoxifen [13–15]. In studies in ovariectomized rats, black cohosh did not induce mammary-tumor-stimulating effects, endometrial proliferation or hormone level changes [16], indicating that the mechanism whereby black cohosh alleviates hot flushes differs from that of HRT. Accordingly, Burdette and associates [17] reported that black cohosh acts as a partial agonist of the serotonin receptor, which regulates body temperature. Applying a recombinant cell bioassay method, others failed to find measurable estrogen activity in black cohosh, *dong quai* and chaste-tree berry [18]; thus, these non-hormonal treatments may reduce menopausal symptoms without increasing the risk of breast cancer. According to the recent systematic review and meta-analysis of Nelson and co-workers [30], non-hormonal therapies may be most useful for highly symptomatic women who cannot take estrogen but are not the optimal choice for most women.

Ginseng has been used in Chinese medicine as an adaptogen to increase the body's resistance to physical and biological stress. It is used to treat symptoms of anxiety, counteract weakness, fatigue

Table III. Outcome of treatment with Phyto-Female Complex herbal combination and placebo in peri- and postmenopausal women during the 12-week study period.

Outcome	Phyto-Female Complex	Placebo
Aggravation of symptoms	0	22
No change	19	52
Amelioration of symptoms	81	26
Hot flushes stopped	47	19

Findings represent the percentage of women in each particular group.

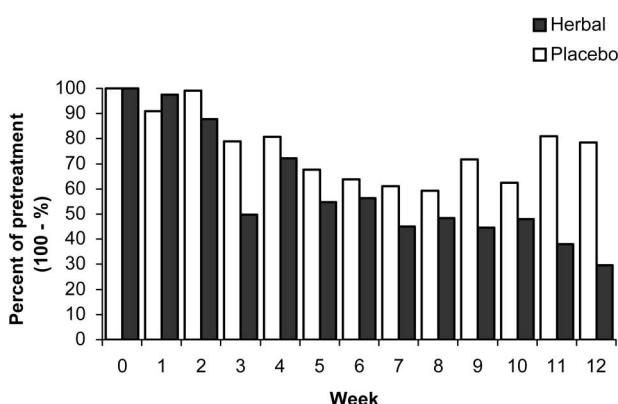


Figure 2. Decrease in sleep score (sleep quality) compared with baseline in peri- and postmenopausal women treated with Phyto-Female Complex herbal combination or placebo.

and impaired concentration, and enhance physical performance, immune function and sexual function. Wiklund and colleagues [19] reported that use of the standardized ginseng extract by postmenopausal women was associated with a statistically significant improvement in quality of life, general well-being and positive affect.

The chaste-tree berry has been used for female reproductive problems since the time of ancient

Greece, and has recently been found to contain selective estrogen receptor- β activity [20]. Red clover has been reported to affect hot flushes [21,22], plasma lipid levels [23], arterial compliance [24,25] and bone mineral density [26]. Huntley and Ernst [27] evaluated the possible adverse effects of herbs used to treat menopausal symptoms and their interaction with other drugs. They found that the evidence for black cohosh was promising and that red clover may be more effective for severe menopausal symptoms. A randomized controlled trial compared the efficacy and safety of two isoflavones supplements derived from red clover extract with placebo, in symptomatic menopausal women. The study provided evidence for a biological effect of one of the isoflavone supplements. However, neither supplement had a clinically significant effect compared with placebo. The authors suggested that even women with less symptomatic symptoms may benefit from treatment [31].

The preparation used in the present study contained a combination of standardized extracts of these herbs. Our results suggest that the Phyto-Female Complex preparation can serve as a safe alternative to HRT, at least for 3 months' use. This short-term pilot trial tested the preparation for a limited time because this is the minimal period needed to show any differences between treatment groups and the placebo effect. At the end of the study there was a significant decrease in hot flushes of more than 35% between the active and the placebo group, demonstrating the efficiency of Phyto-Female Complex. Furthermore, each woman served as her own reference for a climacteric symptom scale recorded one week before entering the study. This strengthens the results of the study. The Phyto-Female Complex was significantly superior to placebo regarding hot flushes (number and intensity), night sweats and quality of sleep, in spite of the small size of groups and short period of treatment. Overall, patients in the intervention group reported less difficulty with sleep quality and less fatigue during the day. No patient ceased therapy due to adverse side-effects. Longer-term studies in a larger number of women are needed to verify our findings.

Disclaimer

The first author has interest in product tested in this study-scientific consultant.

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References

1. US Food and Drug Administration. September is national menopause awareness month! Menopause and hormones: 'what can you believe' campaign spearheaded by FDA's Office of Women's Health; FDA Press Release P04-94 [Internet]. Washington (DC): FDA; revised version [modified 2004 Sep 29; cited 2007 Jan 10]. Available from: <http://www.fda.gov/bbs/topics/news/2004/NEW01121.html>
2. Herrington DM, Howard TD. From presumed benefit to potential harm – hormone therapy and heart disease. *N Engl J Med* 2003;349:519–521.
3. Geller ML, Chelebowski RT. HT and breast cancer risk. *Fertil Steril* 2003;80(Suppl 4):5–9.
4. Crandall C. Low dose estrogen therapy for menopausal women: a review of efficacy and safety. *J Womens Health (Larchmt)* 2003;12:723–747.
5. Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR. Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. *J Am Med Assoc* 2004;293:1573–1580.
6. Piersen CE. Phytoestrogens in botanical dietary supplements: implications for cancer. *Integr Cancer Ther* 2003;2:120–138.
7. Tesch BJ. Herbs commonly used by women: an evidence-based review. *Am J Obstet Gynecol* 2003;188(Suppl):S44–S55.
8. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized controlled trials. *Ann Intern Med* 2002;137:805–813.
9. Kam IW, Dennerhy CE, Tsourounis C. Dietary supplement use among menopausal women attending a San Francisco health conference. *Menopause* 2002;9:72–78.
10. Liske E, Hanggi W, Henneicke-von Zepelin HH, Boblitz N, Wustenberg P, Rahlfz VW. Physiological investigation of a unique extract of black cohosh (*Cimicifugae racemosae rhizoma*): a 6-month clinical study demonstrates no systemic estrogenic effect. *J Womens Health Gend Based Med* 2002;11:163–174.
11. Blumenthal M, Busse WR, Goldberg A, Klein S, Rister RS, translators. German Commission E monographs: Therapeutic monographs on medicinal German Commission plants for human use. Austin (TX): American Botanical Council; 1998.
12. Wuttke W, Jarry H, Becker T, Schultens A, Christoffel V, Gordow C, Seidlova-Wuttke D. Phytoestrogens: endocrine disruptors or replacement for hormone replacement therapy? *Maturitas* 2003;44(Suppl 1):S9–S20.
13. Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, Lo KM, Moore A, Rosenman PJ, Kaufman EL, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol* 2001;19:2739–2745.
14. Hernandez Munoz G, Pluchino S. *Cimicifuga racemosa* for the treatment of flushes in women surviving breast cancer. *Maturitas* 2003;44(Suppl 1):S59–S65.
15. Bodinet C, Freudenstein J. Influence of *Cimicifuga racemosa* on the proliferation of estrogen receptor-positive human breast cancer cells. *Breast Cancer Res Treat* 2002;76:1–10.
16. Freudenstein J, Dasenbrock C, Nisslein T. Lack of promotion of estrogen-dependent mammary gland tumors *in vivo* by an isopropanolic *Cimicifuga racemosa* extract. *Cancer Res* 2002;62:34448–34452.
17. Burdette JE, Liu J, Chen SN, Fabricant DS, Piersen CE, Barker EL, Pezzuto JM, Mesecar A, Van Breemen RB, Farnsworth NR, et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J Agric Food Chem* 2003;51:5661–5670.

18. Oerter Klein K, Janfaza M, Wong JA, Chang RJ. Estrogen bioactivity in *fo-ti* and other herbs used for their estrogen-like effects as determined by a recombinant cell bioassay. *J Clin Endocrinol Metab* 2003;88:4077–4079.
19. Wiklund IK, Mattsson LA, Lindgren R, Limoni C. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group. *Int J Clin Pharmacol Res* 1999;19:89–99.
20. Jarry H, Spengler B, Prozel A, Schmidt J, Wuttke W, Christoffel V. Evidence for estrogen receptor β -selective activity of *Vitex agnus-castus* and isolated flavones. *Planta Med* 2003;69:945–947.
21. van de Weijer PH, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* 2002;42:187–193.
22. Umland EM, Cauffield JS, Kirk JK, Tomason TE. Phytoestrogens as therapeutic alternatives to traditional hormone replacement in postmenopausal women. *Pharmacotherapy* 2000;20:981–990.
23. Schult TM, Ensrud KE, Blackwell T, Ettinger B, Wallace R, Tice JA. Effect of isoflavones on lipids and bone turnover markers in menopausal women. *Maturitas* 2004;48:209–218.
24. Nestel PJ, Pomeroy S, Kay S, Komesaroff P, Behrsing J, Cameron JD, West L. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *J Clin Endocrinol Metab* 1999;84:895–898.
25. Teede HJ, McGrath BP, DeSilva L, Cehun M, Fassoulakis A, Nestel PJ. Isoflavones reduce arterial stiffness: a placebo-controlled study in men and postmenopausal women. *Arterioscler Thromb Vasc Biol* 2003;23:1066–1071.
26. Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2004;79:326–333.
27. Huntley AL, Ernst E. A systematic review of herbal medicinal products for the treatment of menopausal symptoms. *Menopause* 2003;10:465–476.
28. Pockaj BA, Loprinzi CL, Sloan JA, Novotny PJ, Barton DL, Hagenmaier A, Zhang H, Lambert GH, Reeser KA, Wisbey JA. Pilot evaluation of black cohosh for the treatment of hot flashes in women. *Cancer Invest* 2004;22:515–521.
29. Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke-von Zepelin HH. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol* 2005;105:1074–1083.
30. Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, Nicolaidis C, Walker M, Humphrey L. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *J Am Med Assoc* 2006;295:2057–2071.
31. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. *J Am Med Assoc* 2003;290:207–214.