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To cite this article: Rossella E Nappi, Barbara Malavasi, Benedetta Brundu & Fabio Facchinetti (2005) Efficacy of *Cimicifuga racemosa* on climacteric complaints: A randomized study versus low-dose transdermal estradiol, Gynecological Endocrinology, 20:1, 30-35, DOI: [10.1080/09513590400020922](https://doi.org/10.1080/09513590400020922)

To link to this article: <https://doi.org/10.1080/09513590400020922>



Published online: 07 Jul 2009.



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MENOPAUSE

Efficacy of *Cimicifuga racemosa* on climacteric complaints: A randomized study versus low-dose transdermal estradiol

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Abstract

Objective To investigate, in a randomized clinical study, the efficacy of an isopropanolic aqueous extract of *Cimicifuga racemosa* (CR) on climacteric complaints in comparison with low-dose transdermal estradiol (TTSE₂). Hormonal parameters, lipid profile and endometrial thickness were also evaluated.

Methods Sixty-four postmenopausal women were enrolled and over the course of 3 months filled in a diary recording the number of hot flushes per day. Other climacteric symptoms (vasomotor and urogenital symptoms) as well as anxiety and depression, were evaluated at baseline and after 3 months. Gonadotropins (follicle-stimulating hormone (FSH), luteinizing hormone (LH)), prolactin (PRL), 17 β -estradiol (17 β -E₂) and cortisol, lipid profile (total cholesterol high-density lipoprotein (HDL)/low-density lipoprotein (LDL)-cholesterol, triglycerides, liver function (glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase) and endometrial thickness were measured. Patients were randomly allocated to receive, for 3 months, either 40 mg isopropanolic aqueous CR extract daily or 25 μ g TTSE₂ every 7 days plus dihydrogesterone 10 mg/day for the last 12 days of the 3-month estradiol treatment.

Results Both CR and low-dose TTSE₂ significantly reduced the number of hot flushes per day ($p < 0.001$) and vasomotor symptoms ($p < 0.001$), starting at the first month of treatment. Such a positive effect was maintained throughout the 3 months of observation, without any significant difference between the two treatments. An identical effect was evident also for both anxiety ($p < 0.001$) and depression ($p < 0.001$) which were significantly reduced following 3 months of both CR and low-dose TTSE₂. Total cholesterol was unchanged by CR treatment but significantly ($p < 0.033$) reduced by 3 months of low-dose TTSE₂. A slight but significant increase of HDL-cholesterol ($p < 0.04$) was found only in women treated with CR, while LDL-cholesterol levels were significantly lowered by 3 months of both CR ($p < 0.003$) and low dose TTSE₂ ($p < 0.002$). Triglycerides were not affected by both treatments, nor was liver function. FSH, LH and cortisol were not significantly affected after the 3-month treatment, while PRL ($p < 0.005$) and 17- β E₂ ($p < 0.001$) were increased slightly only by low-dose TTSE₂. Endometrial thickness was not affected by either CR or low-dose TTSE₂.

Conclusions CR (40 mg/day) may be a valid alternative to low-dose TTSE₂ in the management of climacteric complaints in those women who cannot be treated with or just refuse conventional strategies.

Keywords: Herbal remedies, *Cimicifuga racemosa*, hot flushes, low dose hormone replacement therapy, transdermal estradiol

Introduction

The multitude of products and regimens for hormone therapy postmenopause serve the aim of minimizing the occurrence of side-effects and long-term health risks while improving compliance [1–3]. In this context, low-dose formulations of hormone therapy seem to be highly effective in treating climacteric symptoms and improving quality of life, without inducing bothersome hormone-related complaints [4]. In addition, good endometrial protection is present, with very low rates of unscheduled bleeding, and bone mineral density is preserved over time [5–8]. On the other hand, many postmenopausal women actively seek alternative treatments in an

effort to manage their symptoms with ‘natural’ strategies, particularly when they are at low risk for the long-term consequences of estrogen deficiency or, alternatively, when they have contraindications to conventional hormone therapy [9–12].

Among several popular herbal remedies available on the market, *Cimicifuga racemosa* (black cohosh) has been widely used to alleviate symptoms of the menopause such as hot flushes, anxiety and depression, and other gynecological complaints [13,14]. The isopropanolic aqueous extract of the rootstock of *C. racemosa* (CR) herb is an active ingredient with good safety and tolerability profiles [15]. Even though its efficacy for the treatment of menopausal symptoms has not been fully demonstrated in

rigorous clinical trials [16], a recent review of the literature on complementary and alternative medicines for the menopause supported the benefits of black cohosh for short-term use, but it did not establish limitations on treatment time [17]. Liske and colleagues reported that the currently recognized standard dose of CR rhizome (40 mg/day) is associated with improvement in menopause symptoms without evidence of estrogen-like effects in a 6-month study [18]. In addition, in clinic samples of postmenopausal women consuming CR, a lack of estrogenicity on endometrial and vaginal tissues has been shown [14,15,19]. On the other hand, the only double-blind, placebo- and conjugated estrogen-controlled study has recently proved the effectiveness of 40 mg/day of the herbal drug in improving climacteric complaints, including hot flushes, psychic symptoms and vaginal atrophy [20]. Moreover, given the lack of uterotrophic effects together with a slight effect on bone turnover, the authors proposed that CR contains substances with selective estrogen receptor modulation (SERM) activity [20]. Indeed, the mechanisms of action of this herbal medicine are still controversial. Recent animal and *in vitro* experiments support the notion that CR may function as a 'natural' SERM, having diverse activities – both estrogenic and antiestrogenic – at multiple sites, including the brain, bone, uterus, vagina, mammary gland and the fat tissue [21,22]. Other mechanisms involving a modulation of dopaminergic and serotonergic function have been also postulated to explain the biological activity of CR extracts on vasomotor and psychic symptoms [23,24].

That notwithstanding, in the present randomized clinical study our aim was to investigate the efficacy of 40 mg/day of the isopropanolic aqueous CR extract on climacteric complaints in comparison with a low-dose therapy with transdermal estradiol (TTSE₂ 25 µg 7-day patch) and 12 days of dihydrogesterone (10 mg/day) over 3 months. Hormonal parameters, lipid profile and endometrial thickness were also evaluated.

Materials and methods

This prospective study was carried out at the Departments of Obstetrics and Gynecology of the Universities of Pavia and Modena, Italy. Among patients presenting for clinical evaluation of menopausal status, 64 subjects (age range 45–55 years; body mass index range 19–27 kg/m²) were enrolled. Inclusion criteria were spontaneous menopausal status of at least 6 months with follicle-stimulating hormone (FSH) level > 30 mUI/l, presence of hot flushes (at least five per day) and endometrial thickness < 5 mm. Exclusion criteria were previous hormone therapy or having any contraindications to hormonal treatments.

The observational period lasted 3 months, during which women filled in a diary recording the number

of hot flushes per day. Moreover, we evaluated other climacteric symptoms (vasomotor and urogenital symptoms) using the Greene scale [25], and both anxiety and depression using the Symptom Rating Test (SRT) [26].

At the first visit women underwent a general medical and gynecological history, a gynecological examination, an ultrasound evaluation of endometrial thickness and a clinical interview for menopausal symptoms. The same day patients provided blood samples for the determination of gonadotropins (FSH and luteinizing hormone (LH)), prolactin (PRL), 17β-estradiol (17β-E₂) and cortisol, total cholesterol high-density lipoprotein (HDL)/low-density lipoprotein (LDL)-cholesterol, triglycerides. Transaminases (glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase) were also determined to monitor liver function.

Patients were randomly allocated on the basis of a computer-generated number list into two groups, comparable in terms of age, body mass index and months since menopause, to receive either:

- (1) 40 mg/day of isopropanolic aqueous CR extract (Remifemin[®]; OmeoPiacenza, Italy) for 3 months;
- (2) TTSE₂ 25 µg every 7 days (Estraderm[®]; Novartis Farma, Italy) for 3 months plus dihydrogesterone 10 mg/day (Dufaston[®], Solvay, Italy) for the last 12 days of the 3-month estradiol treatment.

Follow-up evaluation, including review of the hot flushes diaries and administration of the Greene scale, was performed monthly, while the SRT, blood sampling and ultrasound evaluation of endometrial thickness were conducted after 3 months (at the end of treatment).

Data are expressed as mean ± standard deviation. Within- and between-subject analysis was performed using the paired Student *t* test and one-way analyses of variance, when appropriate.

Results

Table I reports the baseline characteristics of the women treated with CR and low-dose TTSE₂. One patient dropped out, stopping CR after 2 months because of nausea. Four patients consuming CR and five patients taking low-dose TTSE₂ completed the

Table I. Baseline characteristics (mean ± standard deviation) of the women treated with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol (TTSE₂).

	[CR (n = 32)]	[TTSE ₂ (n = 32)]	<i>p</i> Value
Age (years)	50.5 ± 2.1	50.9 ± 1.8	0.37
Menopause (months)	9.0 ± 2.9	9.1 ± 3.0	0.87
Body mass index (kg/m ²)	22.9 ± 2.2	22 ± 2.1	0.40

study but refused to provide a blood sample at follow-up.

Effects of treatments on climacteric symptoms

As shown in Figure 1, both CR and low-dose TTSE₂ reduced significantly the number of hot flushes per day ($p < 0.001$) and the Greene score for vasomotor symptoms ($p < 0.001$), starting at the first month of treatment. Such a positive effect was maintained throughout the 3 months of observation, without any significant difference between the two treatments.

Figure 2 shows that CR was significantly effective in reducing both anxiety ($p < 0.001$) and depression ($p < 0.001$) measured by SRT following 3 months of treatment, compared with baseline. Such an effect was identical to that obtained in postmenopausal women treated with low-dose TTSE₂ for both anxiety ($p < 0.001$) and depression ($p < 0.001$).

On the other hand, we did not find any significant effect of CR on urogenital symptoms, which remained unchanged from baseline (1.1 ± 0.2) to the third month (1.1 ± 0.2), while a trend toward significance ($p < 0.056$) was evident in postmenopausal women taking low-dose TTSE₂ (score from 1.2 ± 0.2 to 1.0 ± 0.2).

Effects of treatments on hormones, lipid profile and endometrial thickness

Table II reports data regarding hormones and lipid profile obtained in the two treatment groups. While total cholesterol was unchanged by CR treatment, 3 months of low-dose TTSE₂ were effective in lowering total cholesterol levels significantly ($p < 0.03$) below baseline. On the other hand, a slight but significant increase of HDL-cholesterol ($p < 0.04$) was found in women treated with CR, while no difference was evident in women taking low-dose

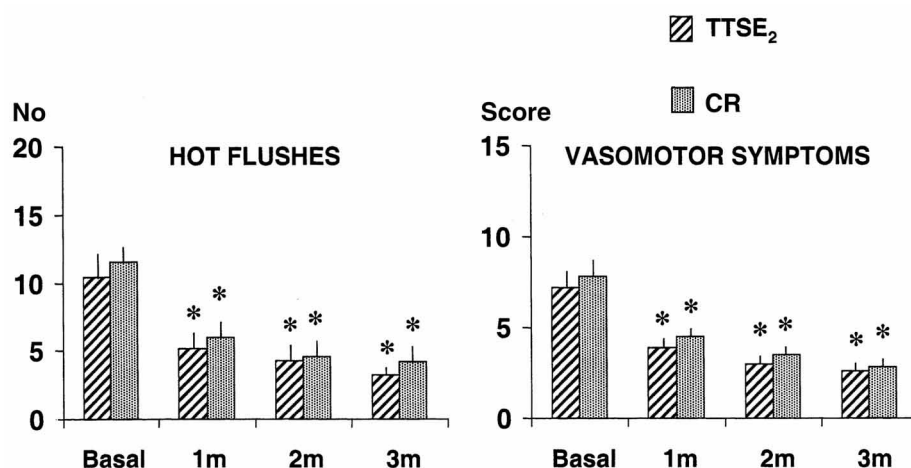


Figure 1. Mean (\pm standard deviation) number of hot flushes per day recorded in a diary throughout the 3 months of treatment and mean Greene score for vasomotor symptoms recorded monthly in postmenopausal women treated with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol (TTSE₂). Significance (*) is reported in the text.

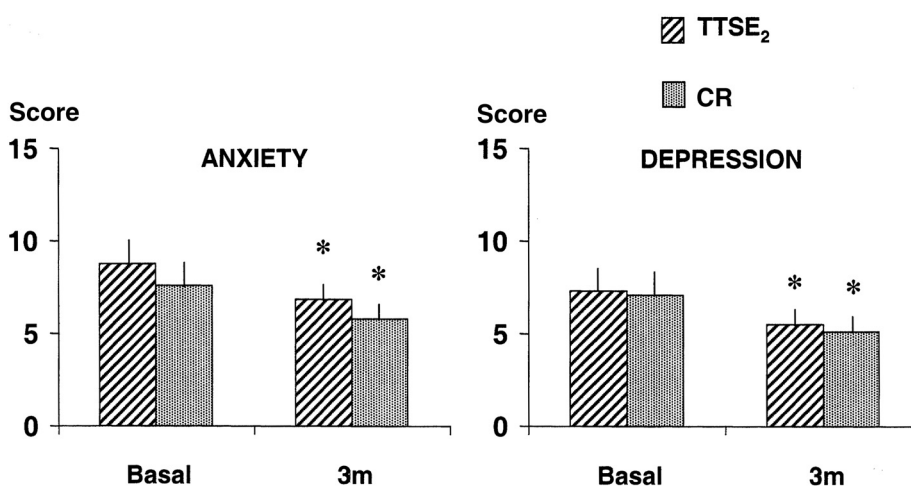


Figure 2. Mean (\pm standard deviation) Symptom Rating Test score for anxiety and depression recorded before and after 3 months of treatment with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol (TTSE₂). Significance (*) is reported in the text.

Table II. Effects of *Cimicifuga racemosa* (CR) and low-dose transdermal estradiol (TTSE₂) on lipid profile, liver function and hormones (mean \pm standard deviation) following 3 months of treatment.

	CR			TTSE ₂		
	Basal (<i>n</i> = 32)	3 months (<i>n</i> = 27)	<i>p</i> Value	Basal (<i>n</i> = 32)	3 months (<i>n</i> = 27)	<i>p</i> Value
Total cholesterol (mg/dl)	222.8 \pm 33.1	221.8 \pm 30.08	NS	247.4 \pm 26.5	239.4 \pm 26.2	0.03
HDL-cholesterol (mg/dl)	51.6 \pm 1.8	53.1 \pm 1.7	0.04	70.2 \pm 16.5	69.2 \pm 16.7	NS
LDL-cholesterol (mg/dl)	153.8 \pm 39.0	146.1 \pm 34.4	0.003	153.5 \pm 18.2	146.0 \pm 15.7	0.002
Triglycerides (mg/dl)	115.5 \pm 50.5	112.5 \pm 42.3	NS	121.1 \pm 63.5	123.5 \pm 61.4	NS
GOT (U/l)	14.6 \pm 3.4	14.5 \pm 3.8	NS	19.0 \pm 2.4	18.8 \pm 2.8	NS
GPT (U/l)	20.9 \pm 4.6	20.8 \pm 5.1	NS	25.4 \pm 3.1	24.4 \pm 4.2	NS
FSH (IU/l)	57.4 \pm 13.9	59.6 \pm 17.1	NS	52.6 \pm 20.1	52.3 \pm 12.4	NS
LH (IU/l)	28.8 \pm 8.9	30.8 \pm 10.8	NS	28.7 \pm 12.8	30.7 \pm 11.1	NS
17 β -E ₂ (pg/ml)	19.0 \pm 5.6	18.7 \pm 5.0	NS	18.7 \pm 6.6	22.5 \pm 5.7	0.001
PRL (ng/ml)	10.9 \pm 3.5	10.4 \pm 3.4	NS	13.1 \pm 4.9	14.6 \pm 6.5	0.005
Cortisol (nmol/l)	134.2 \pm 32.4	129.1 \pm 4.1	NS	122.0 \pm 4.9	130.2 \pm 22.2	NS

HDL, high-density lipoprotein; LDL, low-density lipoprotein; GOT, glutamic-oxalacetic transaminase; GPT, glutamic-pyruvic transaminase; FSH, follicle-stimulating hormone; LH, luteinizing hormone; 17 β -E₂, 17 β -estradiol; PRL, prolactin; NS, not significant.

TTSE₂ after 3 months. Concerning LDL-cholesterol levels, they were significantly lowered by 3 months of both CR ($p < 0.003$) and low-dose TTSE₂ ($p < 0.002$), while levels of triglycerides were not affected by either treatment.

Liver function was normal at baseline and unchanged after 3 months (Table II).

Gonadotropin profile was not affected significantly by both treatments, while PRL ($p < 0.005$) and 17- β E₂ ($p < 0.001$) were increased slightly only by low-dose TTSE₂ following 3 months. Plasma cortisol levels were unchanged under both treatments.

Finally, endometrial thickness was not affected by either CR or low-dose TTSE₂, remaining unchanged from baseline to the third month in both CR-treated women (from 3.8 ± 0.2 to 3.6 ± 0.2) and the low-dose TTSE₂ group (3.7 ± 0.1 to 3.7 ± 0.1). No evidence of vaginal bleeding was recorded throughout the study under both treatments, while two cases of spotting were reported by women taking low-dose TTSE₂.

Discussion

The present study revealed that both CR and low-dose TTSE₂ were equally effective in relieving hot flashes and emotional symptoms, mainly anxiety and depression, in postmenopausal women. On the other hand, slight differences were found in lipid profile according to treatment. Indeed, low-dose TTSE₂ significantly reduced total cholesterol and LDL-cholesterol with no effect on HDL-cholesterol and triglycerides, while CR caused a slight but significant increase of HDL-cholesterol and a significant decrease of LDL-cholesterol, without affecting total-cholesterol and triglycerides. Both treatments did not display any effects on plasma gonadotropin levels, did not stimulate endometrial growth and did not cause any significant side-effects.

That being so, 40 mg/day CR may be a valid alternative to low-dose TTSE₂ in the management of

climacteric complaints in those women who cannot be treated with or just refuse conventional strategies.

The positive clinical effect of CR on both menopausal symptoms and markers of bone metabolism has recently been compared with that of conjugated estrogens in a 3-month, placebo-controlled study [20]. Hot flushes were significantly improved, as were psychic complaints, by the use of herbal extracts that were able to positively affect the metabolic marker of bone formation, alkaline phosphatase, much more than conjugated estrogens. However, in the above study, a standard dose (0.6 mg) of conjugated estrogens was used despite recent focus on the necessity of reconsidering the role of standard hormone therapy oriented toward the use of a low-dose regimen [1]. To our mind, low-dose TTSE₂ seemed more appropriate for a comparison, given its high efficiency and tolerability [27]. Indeed, women who are good candidates for a 'natural' treatment are less prone to accept a standard-dose conventional hormone therapy, with possible consequences on their attitude to report symptoms on a self-administered scale for menopausal complaints [10–12].

Our study is limited by the absence of a placebo group and, even though the effectiveness of CR over placebo has recently been proved by Wuttke and associates [20], the need to produce well-controlled confirmatory results with black cohosh was reported by several authors and is still necessary [13–18]. However, the present results add some pieces of information to the challenge of herbal remedies in menopausal practice, from both the clinical and the safety point of view. Although the positive action of CR on vasomotor and psychological symptoms is confirmed [14,15,18,20], at variance with the literature [20], we did not find any significant effect on urogenital symptoms. Moreover, we cannot even support the controversial notion that CR reduces hot flashes by acting on LH pulsatility in postmenopausal women [18,28]. On the other hand, the positive

action of CR on emotional symptoms seems to corroborate the idea that CR may act as a neuromodulatory substance within hypothalamic–limbic structures [23,24]. Indeed, standard CR treatment restores the sensitivity of opiate receptors which have been lost at menopausal transition (A. D. Genazzani *et al.*, personal communication).

The confirmatory finding of a lack of effect at endometrial level is in keeping with the evidence that CR has selective activities not only in rat tissues but also in postmenopausal women [22,29–32]. Indeed, in experimental systems, CR antagonized estradiol proliferative activities in human mammary cancer-derived cell line MCF-7 [33], while it showed an osteoprotective effect measured by computer-assisted tomography in ovariectomized rats [22] that was supported by an increase in osteoblast and a slight decrease in osteoclast activity in women [20]. Thus, the estrogenic potency of herbal remedies and other phytoestrogens is significant, especially for estrogen receptor β , and they may trigger several biological responses that are evoked by the physiological estrogens [34]. That being so, it is worth reporting that some data are available on the use of CR for a period of 12 months in reducing the number and severity of hot flushes induced by tamoxifen in young, premenopausal, breast cancer survivors [35], while in a recent randomized, placebo-controlled trial lasting only 2 months the positive activity of CR on hot flushes was not confirmed in breast cancer survivors stratified on tamoxifen use [36].

The controversial picture of soy-derived phytoestrogens as protective agents in lipid metabolism [37] is now enriched by our evidence that a herbal remedy such as CR was capable of lowering LDL-cholesterol and slightly increasing HDL-cholesterol, without affecting total cholesterol and triglycerides. This effect was different from what we observed with low-dose TTSE₂, which confirmed its ability of exerting a positive action on lipid profile, mainly by lowering total and LDL-cholesterol [38].

Finally, from the perspective of regulating the market by improving the monitoring of manufacturers that should be able to ensure that herbs contain pure ingredients [39], it seems important to underline that the herbal treatment used in this study did not affect liver function and hormonal profile, being well-tolerated by almost all postmenopausal women recruited.

In conclusion, CR (40 mg/day) may be considered a consistent and safe option to counteract specific symptoms in menopausal practice.

References

- Grimes DA, Lobo RA. Perspectives on the Women's Health Initiative trial of hormone replacement therapy. *Obstet Gynecol* 2002;100:1344–1353.
- Schneider HP, Gallagher JC. Moderation of the daily dose of HRT: benefits for patients. *Maturitas* 1999;33:S25–S29.
- Ettinger B. Personal perspective on low-dosage estrogen therapy for postmenopausal women. *Menopause* 1999;6:273–276.
- Gambacciani M, Genazzani AR. Hormone replacement therapy: the benefits in tailoring the regimen and dose. *Maturitas* 2001;40:195–201.
- Archer DF, Dorin M, Lewis V, Schneider DL, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on endometrial bleeding. *Fertil Steril* 2001;75:1080–1087.
- Brynhildsen J, Hammar M. Low dose transdermal estradiol/norethisterone acetate treatment over 2 years does not cause endometrial proliferation in postmenopausal women. *Menopause* 2002;9:137–144.
- Evans SF, Davie MW. Low and conventional dose transdermal oestradiol are equally effective at preventing bone loss in spine and femur at all post-menopausal ages. *Clin Endocrinol (Oxf)* 1996;44:79–84.
- Gambacciani M, Ciapponi M, Cappagli B, Genazzani AR. Effects of low-dose continuous combined conjugated estrogens and medroxyprogesterone acetate on menopausal symptoms, body weight, bone density, and metabolism in postmenopausal women. *Am J Obstet Gynecol* 2001;185:1180–1185.
- 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.
- Gingrich PM, Fogel CI. Herbal therapy use by perimenopausal women. *J Obstet Gynecol Neonatal Nurs* 2003;32:181–189.
- Newton KM, Buist DS, Keenan NL, Anderson LA, LaCroix AZ. Use of alternative therapies for menopause symptoms: results of a population-based survey. *Obstet Gynecol* 2002;100:18–25.
- Gass ML, Taylor MB. Alternatives for women through menopause. *Am J Obstet Gynecol* 2001;185:S47–S56.
- McKenna DJ, Jones K, Humphrey S, Hughes K. Black cohosh: efficacy, safety, and use in clinical and preclinical applications. *Altern Ther Health Med* 2001;7:93–100.
- Lieberman S. A review of the effectiveness of *Cimicifuga racemosa* (black cohosh) for the symptoms of menopause. *J Womens Health* 1998;7:525–529.
- Liske E. Therapeutic efficacy and safety of *Cimicifuga racemosa* for gynaecologic disorders. *Adv Ther* 1998;15:45–53.
- Borrelli F, Ernst E. *Cimicifuga racemosa*: a systematic review of its clinical efficacy. *Eur J Clin Pharmacol* 2002;58:235–241.
- Huntley A, Ernst E. A systematic review of the safety of black cohosh. *Menopause* 2003;10:58–64.
- Liske E, Hanggi W, Henneicke-von Zepelin HH, Boblitz N, Wustenberg P, Rahlfs 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.
- Israel D, Youngkin EQ. Herbal therapies for perimenopausal and menopausal complaints. *Pharmacotherapy* 1997;17:970–984.
- Wuttke W, Seidlova-Wuttke D, Gorkow C. The *Cimicifuga* preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas* 2003;44:867–877.
- Wuttke W, Jarry H, Becker T, Schultens A, Christoffel V, Gorkow C, Seidlova-Wuttke D. Phytoestrogens: endocrine disruptors or replacement for hormone replacement therapy? *Maturitas* 2003;44:S9–S20.
- Seidlova-Wuttke D, Jarry H, Becker T, Christoffel V, Wuttke W. Pharmacology of *Cimicifuga racemosa* extract BNO 1055 in rats: bone, fat and uterus. *Maturitas* 2003;44:S39–S50.

23. Jarry H, Metten M, Spengler B, Christoffel V, Wuttke W. *In vitro* effects of the *Cimicifuga racemosa* extract BNO 1055. *Maturitas* 2003;44:S31–S38.
24. Winterhoff H, Spengler B, Christoffel V, Butterweck V, Lohning A. *Cimicifuga* extract BNO 1055: reduction of hot flushes and hints on antidepressant activity. *Maturitas* 2003;44:551–558.
25. Greene JG. A factor analytic study of climacteric symptoms. *J Psychosom Res* 1976;20:425–430.
26. Fava GA, Kellner R, Perini GI, Fava M, Michelacci L, Munan F, Evangelisti LP, Grandi S, Bernardi M, Mastrogiacomo I. Italian validation of the Symptom Rating Test (SRT) and Symptom Questionnaire (SQ). *Can J Psychiatry* 1983;28:117–123.
27. Utian WH, Burry KA, Archer DF, Gallagher JC, Boyett RL, Guy MP, Tachon GJ, Chadha-Boreham HK, Bouvet AA. Efficacy and safety of low, standard, and high dosages of an estradiol transdermal system (Eslim) compared with placebo on vasomotor symptoms in highly symptomatic menopausal patients. The Eslim Study Group. *Am J Obstet Gynecol* 1999;181:71–79.
28. Duker EM, Kopanski L, Jarry H, Wuttke W. Effects of extracts from *Cimicifuga racemosa* on gonadotropin release in menopausal women and ovariectomized rats. *Planta Med* 1991;57:420–424.
29. Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K. *Cimicifuga* and *Melbrosia* lack oestrogenic effects in mice and rats. *Maturitas* 1996;25:149–153.
30. 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;62:3448–3452.
31. Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. *Menopause* 2002;9:145–150.
32. Wuttke W, Jarry H, Westphalen S, Christoffel V, Seidlova-Wuttke D. Phytoestrogens for hormone replacement therapy? *J Steroid Biochem Mol Biol* 2002;83:133–147.
33. Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G. Antiestrogenic activities of *Cimicifuga racemosa* extracts. *J Steroid Biochem Mol Biol* 2002;80:125–130.
34. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson JA. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. *Endocrinology* 1998;139:4252–4263.
35. Hernandez Munoz G, Pluchino S. *Cimicifuga racemosa* for the treatment of hot flushes in women surviving breast cancer. *Maturitas* 2003;44:S59–S65.
36. 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.
37. Fitzpatrick LA. Soy isoflavones: hope or hype? *Maturitas* 2003;44:S21–S29.
38. Godsland IF. Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974–2000. *Fertil Steril* 2001;75:898–915.
39. Tesch BJ. Herbs commonly used by women: an evidence-based review. *Am J Obstet Gynecol* 2003;188:S44–S55.