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Black cohosh (*Cimicifuga racemosa*) is a non-estrogenic alternative to hormone replacement therapy

Wolfgang Wuttke* and Dana Seidlová-Wuttke

Abstract

Hormone replacement therapy is still a popular and most effective treatment for vasomotor symptoms and bone loss prevention in the postmenopause but it is not without risks. This has driven many climacteric women to seek for alternatives, chiefly natural products. Phytoestrogens containing soy or red clover preparations, however, when taken at the recommended daily doses, proved to be ineffective to ameliorate climacteric complaints and to prevent osteoporosis. *Cimicifuga racemosa* (CR) preparations, on the other hand, have been shown to ease climacteric distress. There is a widespread, but false, belief that the efficacy of CR preparations is linked to the presence of phytoestrogens in the plant. This review aims at summarizing the available *in vitro* and *in vivo* evidence showing that compounds in CR extracts do not bind to oestrogen receptors and thus do not exert any estrogenic effects in the uterus and mammary gland, as shown *in vivo* in experiments on ovariectomized rats and clinically in postmenopausal women. Studies in ovariectomized rats and in women suffering from climacteric complaints have indicated that substances with neurotransmitter-like activities affect beneficially postmenopausal symptoms such as hot flushes. Some of these compounds, such as actein-like triterpenes with GABA-ergic activity and a serotonin analogue, are present and have been identified in the CR extracts. We conclude that these activities explain most likely the beneficial effects of CR extracts on climacteric complaints.

Keywords: Black cohosh; *Cimicifuga racemosa*; Hormone replacement therapy; Climacteric complaints; Menopause; Non-oestrogenic effects

Review

Hormone replacement therapy (HRT) is still the most effective treatment of menopausal symptoms, providing also some help in the prevention of osteoporosis. Fastidious or serious side effects however, limit its use. HRT has been shown, for instance, to increase mammary cancer [1–5] and in the Women's Health Initiative (WHI) study the administration of a combination of conjugated estrogens with medroxyprogesterone acetate over more than 8 years resulted in an increased risk for lethal cardiovascular events [1], which led to its premature termination. Such events actually occur only when HRT is started late in the postmenopause, whereas it may in fact protect against cardiovascular diseases when immediately started at the onset of the menopause [6].

Women are looking for HRT substitutes to ameliorate climacteric complaints, particularly hot flushes. The ideal products would not be estrogenic in the uterus and in the mammary gland and augment blood clotting. Herbal remedies are increasingly recognized as an alternative to hormones and physicians and patients are willing to use them. There is also clinical evidence that selected herbal medicinal products may exert positive effects in some of the conditions typical of the menopausal period.

Far East Asian women, who traditionally eat large amounts of soy, develop breast cancer less often than Caucasian women: when Japanese women, however, migrate to the US and change their dietary habits, their female children develop mammary cancers at frequencies observed in the Caucasian population. This has generated the belief that soy, possibly because of the estrogenic isoflavones it contains, may prevent mammary cancer. In fact, in adult rats, a reduction of 7,12-dimethylbenz(a)anthracene

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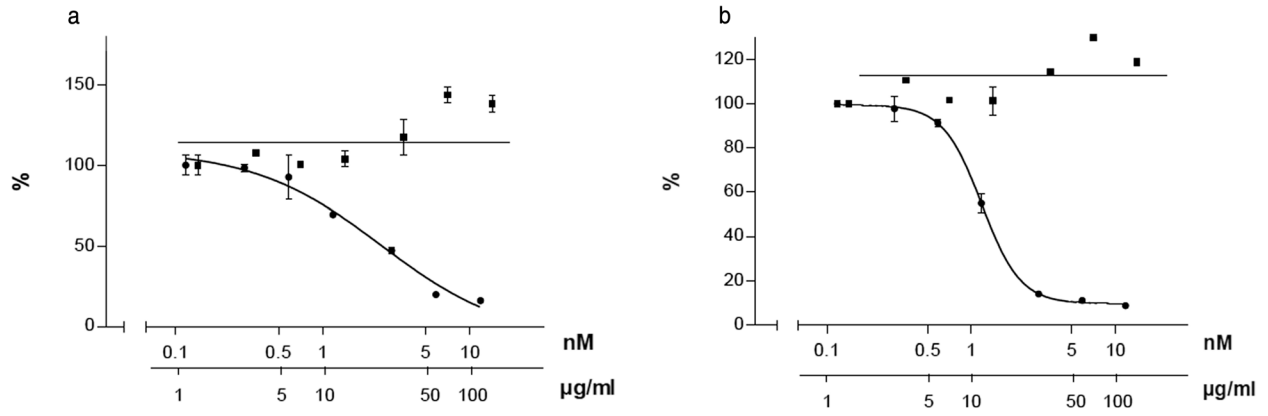

Fig. 1 Estradiol (E2) displaces radioactively labeled E2 from recombinant human. **a** oestrogen receptor (ER) ERα; (**b**) ERß. The BNO 1055 CR extract does not displace the radiolabeled E2 from both receptor subtypes

(DMBA)-induced mammary cancers by more than 50 % was achieved by the isoflavone genistein, but only when the soy isoflavone was administered at peripubertal time [7, 8]. The authors of these studies have suggested that early events are crucial for cancer protection and this has been confirmed in several other studies that have also elucidated the underlying molecular mechanisms [9]. There is now increasing evidence that this applies also to humans: In fact, recent studies have shown that Japanese girls who migrated after puberty to the US developed significantly less mammary carcinomas than those who went to the US before puberty or their Caucasian counterparts [10].

Soy or red clover preparations containing estrogenic isoflavones have been intensively investigated, but in most double blind, placebo controlled clinical studies carried out using the recommended daily doses of 50 mg isoflavones these products had no significant effects on climacteric complaints [11–14] and no bone protective effects could be observed [13, 15, 16]. At this dosage the isoflavones did not exert any effects on the mammary gland and the uterus; on the other hand, 3-4-fold higher amounts of the daily recommended dose, often used by women in the hope of obtaining a better efficacy, may exert undesired estrogenic effects.

Cimicifuga racemosa (black cohosh)

Non-hormonal treatment with natural remedies may be an option and *Cimicifuga racemosa* (CR; synonym: *Actaea racemosa*) is probably the most promising available alternative. Its clinical efficacy and safety in climacteric symptoms have been evaluated in several studies with mainly positive outcomes. Traditionally, CR has been used by indigenous American Indians for aching muscles and joints, neuralgias, rheumatoid arthritis, menstrual cramps and more general gynecological complaints. CR originates from the US and it is now grown systematically in Europe. CR extracts have been marketed since 1956 in Germany and the scientific knowledge on this herbal medicine has been summarized in several monographs, among them and prominently the ESCOP monograph [17], leading to the publication of the Community Herbal Monograph on *Cimicifuga racemosa* (L.) Nutt. rhizoma by the EMA Herbal Medicinal Products Committee [18]. Preparations on the food supplement market containing Asian *Cimicifuga* species that have never been clinically tested and may contain quite different compounds are not covered by the Community Monograph and cannot be considered similar to the CR extracts.

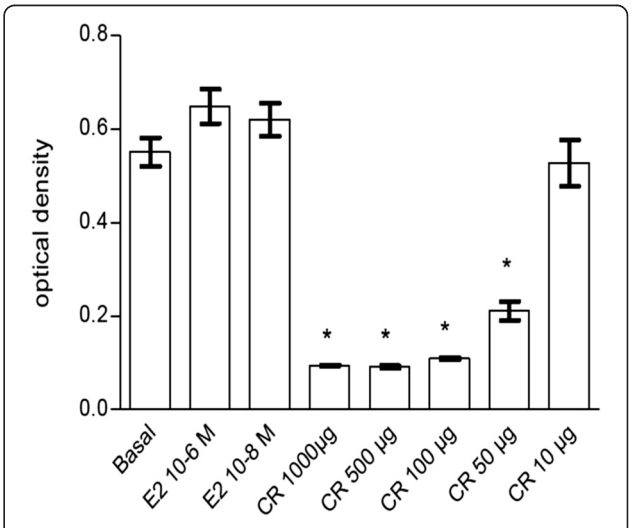

Fig. 2 Effects of CR BNO 1055 on the proliferation on MCF-7 cells. The proliferation of the ERα expressing human mammary cancer derived MCF7 cell line is stimulated by estradiol (E2). The BNO 1055 CR extract inhibits proliferation of these cells dose dependently

Cimicifuga racemosa has no estrogenic activity and does not bind to estrogen receptors (ER)

Almost thirty years ago an isopropanolic extract of *CR* was described to contain the estrogenic isoflavone formononetine [19] but subsequent studies on a variety of CR extracts did not confirm this finding. *In silico*, *in vitro* and *in vivo* animal and clinical evidence, gathered mainly in experiments carried out with the aqueous/ethanolic CR extract BNO 1055*, indicates that all CR extracts tested so far contain no estrogenic compounds.

Estrogenic compounds should bind to estrogen receptors (ER). Both ERα and ERß have been cloned and used in *in vitro* binding studies with the BNO 1055 CR extract [20]. No compound contained in the extract bound to the recombinant ERα or ERß (Fig. 1a, b).

Estrogenic compounds stimulate the proliferation of estrogen receptive human mammary carcinoma cells. In the MCF-7 carcinoma cell line, the most widely used cell line with estrogen reception properties, the proliferation is inhibited rather than stimulated by an isopropanolic extract of CR [21–23] or by the BNO 1055 CR extract [20] (Fig. 2). Mammary gland tissue and MCF-7 cells express aromatases that can increase the availability of estrogens in mammary glands by aromatizing androgens into estrogens. This conversion was inhibited by an ethanolic CR extract in MCF 7 cells [24], which would suggest some mammary cancer protective effects of the extract.

Effects by CR in the mammary gland and the uterus were tested in ovariectomized (ovx) rats, an OECD recommended model for the study of putatively estrogenic effects [25]. Animals were treated orally with the BNO 1055 CR extract for 3 months. Control animals received either sham or estrogen treatment. The extract did not affect the lobuloalveolar and duct apparatus of the ovx rats whereas estradiol (E2) containing food resulted in a

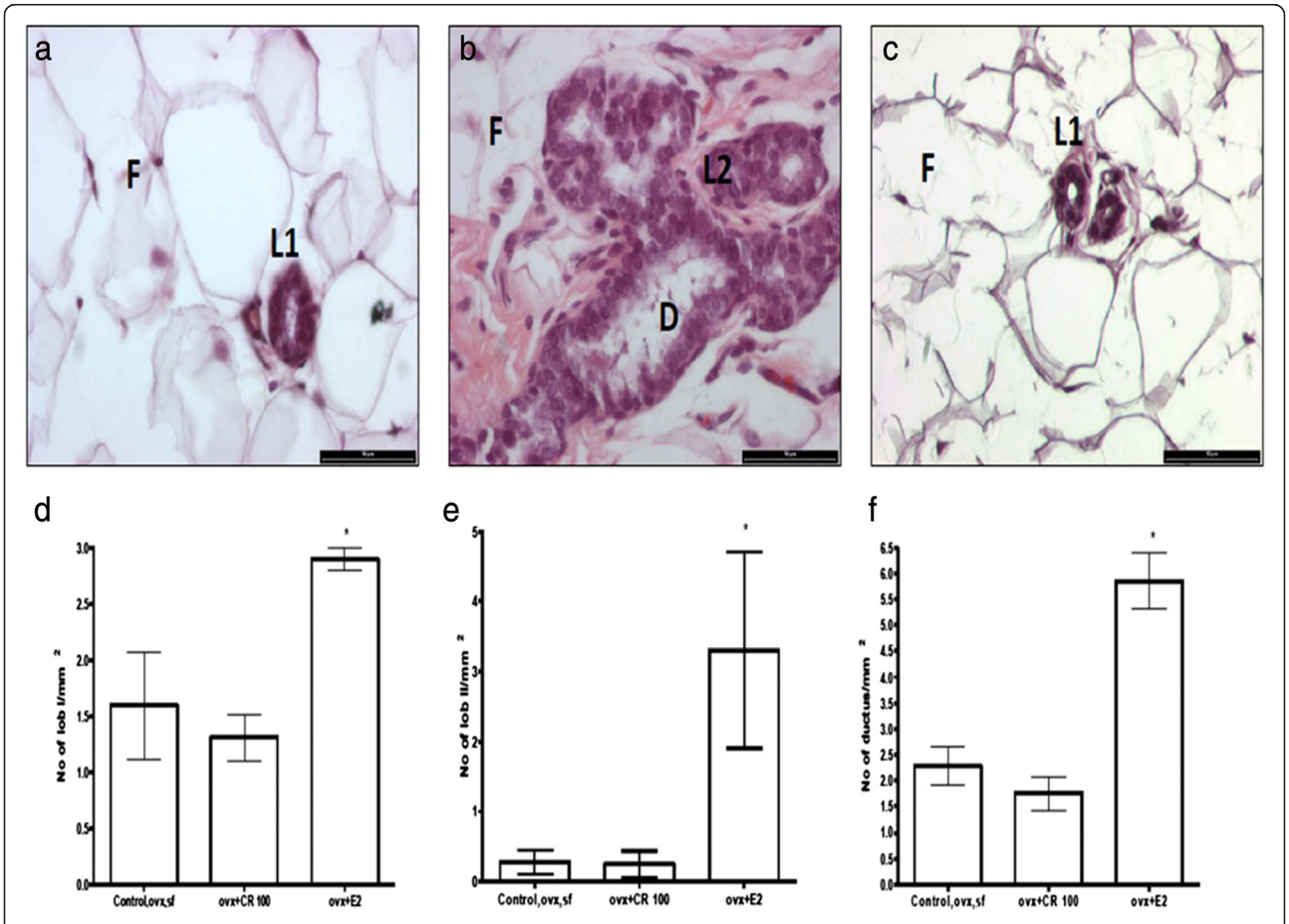

Fig. 3 a-**c** Histological appearance of mammary glands of (**a**) control ovx, (**b**) ovx + E2, (**c**) ovx + CR BNO 1055. Estradiol (E2) stimulated the number of lobuli in the mammary glands (**b**), but not in the sham (**a**) and in the BNO 1055 CR extract treated animals (**c**). D: duct; F: fat; L1: Lobulus 1; L2: Lobulus 2. **d**-**f** Histomorphometric evaluation of the histologic preparations after 3 months per food in ovx rats. **d** Effects of E2 and CR on number on lobulus 1/mm^2; (**e**) Effects of E2 and CR on lobulus 2/mm^2; (**f**) Effects of E2 and CR on number of ducts/mm^2. E2 yielded a significant stimulation of lobuli type 1 (**d**) and 2 (**e**) and ducts (**f**) (*$p < 0.05$ vs control, ovx). CR: *Cimicifuga racemosa* BNO 1055; E2: Estradiol; lob: Lobulus; ovx: ovariectomised; sf: soy free food (*$p < 0.05$ vs. sham and vs. CR treated)

massive stimulation of the lobuli and duct (Fig. 3a-f) [26]. Sprague–Dawley rats treated with DMBA developed typical mammary tumor structures that were inhibited by oral administration of an isopropanolic CR extract [27].

In a large, 6-month, clinical study in early postmenopausal women, BNO 1055 did not affect mammary gland density, as determined by mammography, or endometrial thickness [28]. An isopropanolic CR extract tested in 65 women who underwent mammography and fine needle aspiration biopsies of the breast did not increase mammographic breast density or cell proliferation [29]. In a prospective, observational study carried out in 50 breast cancer patients under Tamoxifen treatment therapy, an isopropanolic CR extract administered during 6 months reduced significantly psycho-vegetative symptoms as measured by the Menopause Rating Scale (MRS) [30]. A recently published case control study involving 949 breast cancer patients demonstrated that the use of several black cohosh preparations had significant breast cancer protective effects [31]. Finally, the effects of the intake of 2.5 % triterpenes derived from CR extracts were compared to those of an extract containing trace amounts of triterpenes and no specific estrogenic effects on the breast were observed [32].

The evidence gathered so far suggests, therefore, a protective rather than a harmful effect on the mammary gland.

The uterine weight of ovx rats increases in response to an estrogenic stimulus [25]. In studies utilizing this animal model several CR extracts did not cause any increase in uterine weight [20]. Uterine histology and the expression of estrogen-regulated genes in the uterus remained unaffected, while treatment with E2 exerted typical estrogenic effects (Fig. 4a, b) [33].

In a placebo-controlled, clinical study the BNO 1055 CR extract had no effects on the endometrium, as opposed to an estrogen preparation that stimulated the increase of the endometrium thickness as measured by vaginal ultrasound [34]. In the longest clinical safety study ever conducted with CR, the same CR preparation was tested for one year and endometrial safety assessed by histological evaluation of the tissue. No case of endometrial abnormality was detected in more than 300 tested patients [28].

Efficacy of CR in climacteric complaints

Ovariectomised rats suffer from hot flushes [35–38] that occur as frequently as the LH pulses. Kapur et al. [39] have shown that the skin temperature of ovx rats increases at regular intervals (Fig. 5) and as a result of these pulses the mean skin temperature of ovx rats is significantly higher than in the intact individuals. Very likely the overactive pulse generator produces hot flushes also in ovx rats, similarly as in postmenopausal women. An effect of the aqueous-ethanolic BNO 1055 CR extract and of an isopropanolic CR extract on hot flushes in ovx rats has been demonstrated [39, 40]. Ovx rats had a higher skin temperature than animals treated with the BNO 1055 CR extract (Fig. 6). It can therefore be safely concluded that CR extracts do not reduce hot flushes in ovx rats through estrogenic but rather through non-estrogenic, neurotransmitter-like substances.

Clinical studies

Several clinical trials have reported that black cohosh extracts reduce hot flushes. Most of these studies, however,

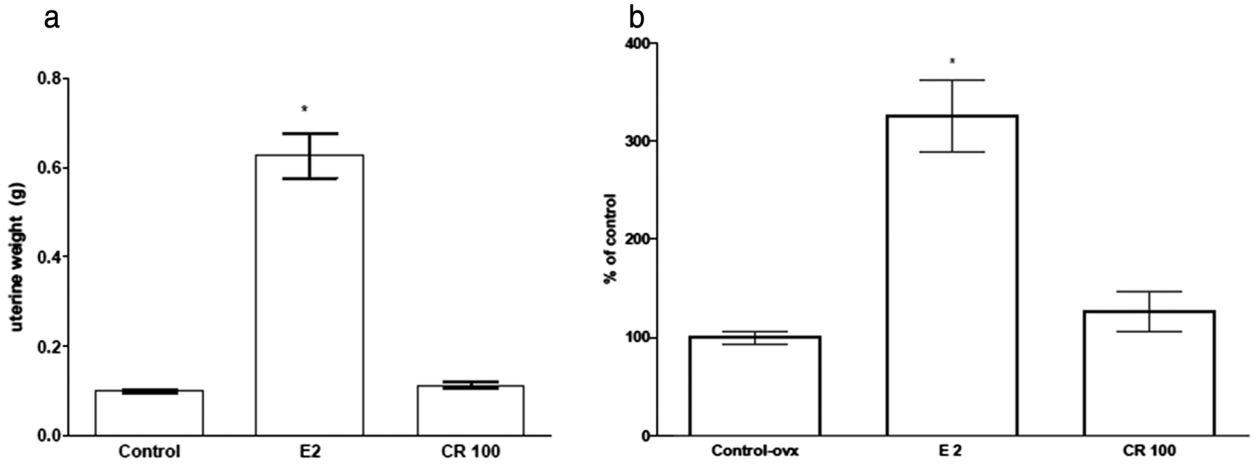

Fig. 4 Effects of E2 and CR BNO 1055 (12 weeks p.o.) in ovx rats on (**a**) uterine weight and (**b**) gene expression of IGF-1 in uterus. Uterine weights (**a**) and insulin like growth factor 1 (IGF1) gene expression (**b**) of ovx rats were significantly stimulated by E2. The stimulatory effect of E2 on uterine weights is partially mediated by E2-stimulated insulin like growth factor gene (IGF 1) (*$p < 0.05$ vs Control and vs. CR 100). CR: *Cimicifuga racemosa*; E: Estradiol; IGF: insulin like growth factor; ovx: ovariectomised

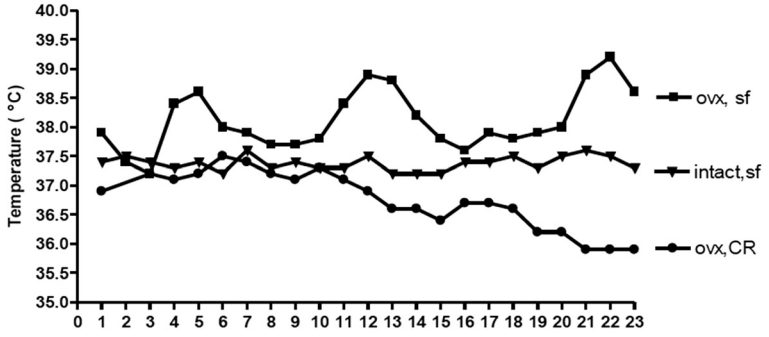

Fig. 5 Skin temperature of ovx and intact rats. Typical fluctuations of subcutaneously measured skin temperature in an ovx rat are not seen in intact or BNO 1055 CR extract treated animals (Scans every 5 min; n ovx, sf; intact, sf; Ÿ ovx). CR: *Cimicifuga racemosa*; ovx: ovariectomised; sf: soy free food

were open and uncontrolled or used too high extract dosages. A number of well-performed, double blind, placebo controlled studies, on the other hand, have demonstrated the beneficial effects of extracts of the CR rhizome on climacteric complaints.

Fourteen randomized, placebo or comparator controlled trials investigating various climacteric symptoms were identified (Tables 1–3). All trials using preparations of European origin and sold exclusively in pharmacies yielded positive results, with statistically significant improvement of climacteric complaints [30, 41–50]. In all but three studies either an isopropanolic or an aqueous/ethanolic extract of 40 mg of the dried plant rhizome (an amount equivalent to 4–8 mg of dry extract) were used. On the other hand, four (three US and one Australian) studies using much higher extract doses (up to 160 mg of dry extract, equivalent to 1600 – 3200 mg of the dried CR rhizome) yielded negative results [44, 47, 51, 52]. The outcomes of these trials can be interpreted in the light of the inverted U-shaped dose-effect curve (IUSDEC) pharmacodynamic properties typical of some pharmacologically active substances, most notably D2-receptor antagonists [53].

In addition, several and diverse products with different quality standards are present on the market and the use of a low-quality product may greatly affect the outcome of a clinical trial. For instance, the analytical profiles of 11 commercial CR preparations available on the U.S. market were analyzed by means of high-performance liquid chromatography: more than one-third of them showed signs of

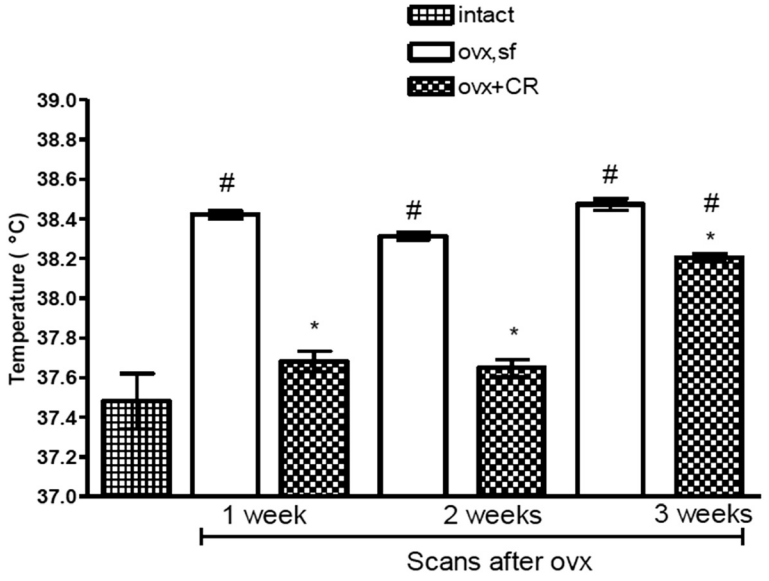

Fig. 6 Skin temperatures in untreated and CR treated rats after ovariectomy. The absence of hot flushes prior to ovx results in significantly lower skin temperature than in ovx rats. Skin temperature in the ovx CR BNO 1055 treated animals is also significantly lower than in the sham treated ovx animals (# $p < 0.05$ vs intact; * $p < 0.05$ vs ovx). CR: *Cimicifuga racemosa*; ovx: ovariectomised

Table 1 Short description of clinical studies with Cimiciduga racemosa preparations

Ref. (placebo or comparator controlled)	*Design*	Patient characteristics and age	Treatment, dose, and duration	Outcome measures	Finding and comments	Effects in short No = Ø Signif. pos = + Signif. neg = –
Wuttke et al., 2003 [34]	Randomized, double-blind, comparator and placebo-controlled	64 early postmenopausal women with 3 or more hot flushes daily	Aquous-ethanolic CR extract BNO 1055 (40 mg dried rhizome powder daily (equivalent to 4.5-8.9 mg dried extract)) vs 0.6 mg conjugated estrogens vs placebo. Duration, 3 mo	Menopause Rating Scale I. Frequency of nocturnal wake-up periods	Significantly better improvement of most climacteric complaints under CR an CE in comparison to placebo,	+
Osmers et al. 2005 [41]	Randomized, double-blind, placebo-controlled	304 early post-menopausal women	Isopropanolic CR extract (40 mg dried rhizome powder daily (equivalent to 5 mg dreid extract)), duration 12 weeks	Menopause Rating scale I.	Significantly better improvement of most climacteric complaints under CR an CE in comparison to placebo,	+
Nappi et al. 2005 [42]	Randomized, comparator controlled trial	64 postmenopausal women	Isopropanolic CR extract (40 mg dried rhizome powder daily (equivalent to 5 mg dried extract)) vs low-dos transdermal estradiol, duration 3 months	Diary recorded number of hot flushes per day	Identical improvement under CR and transdermal E2	+
Frei-Kleiner et al. 2005 [43]	Randomized, double-blind, placebo-controlled trial	122 postmenopausal women with 3 or more hot flushes per day	CR extracr Cr 99 vs placebo, duration 12 weeks	Kupperman Index and Menopause Rating Scale	Significant superiority of the CR extract in comparison to placebo.	+
Pockaj et al. 2006	Randomized, double-blind, placebo-controlled, trial, cross-over design	132 postmenopausal women	2x20 mg of a CR extract (probably equivalent to 2x200 mg dried root powder) for 4 weeks, then crossover to verum or placebo respectively	Hot flush score	Slightly better improvement under placebo in comparison to verum. Note: The dose was approximately 10-fold higher than in all other studies which had a positive outcome	-

CE conjugated oestrogens, *CR Cimicifuga racemosa*, *DB* double blind, *GCS* greene climacteric scale, *KMI* Kupperman menopause index, *MRS* menopause rating scale, *PM* postmenopausal, *RCT* randomised controlled trial

Table 2 Short description of clinical studies with Cimiciduga racemosa preparations preparations

Ref. (placebo or comparator controlled)	*Design*	Patient characteristics and age	Treatment, dose, and duration	Outcome measures	Finding and comments	Effects in short No = Ø Signif. pos = + Signif. neg = –
Newton et al. 2006 [44]	Randomized, double-blind, comparator and placebo-controlled	351 early postmenopausal women with 2 or more hot flushes daily	160 mg of a CR extract daily (probably equivalent to 1600 mg dried rhizome powder) vs a multibotanical preparation vs placebo vs 0.625 mg conjugated estrogens with or without 2 mg medroxyprogesterone- acetate, duration 1 year	Frequency and intensity of vasomotor symptoms (Wiklund Vasomotor Symptom Subscale)	Significant reduction under hormone treatment. No significant differences between CR and placebo, worsening of symptoms in multibotanical group. Note: the CR dose was approximately 40 fold higher than in the studies which yielded positive effects	-
Bai et al. 2007 [45]	Randomized, double-blind, comparator controlled	244 early post-menopausal women with Kupperman Index > or = 15	Isopropanolic CR extract (40 mg dried rhizome powder daily (equivalent to 5 mg dried extract)) vs 2.5 mg tibolone, duration 3 months.	Kupperman Menopause Index	CR preparation was as effective as tibolone in reducing KMI score	+
Oktem et al. 2007 [46]	Randomized, comparator controlled trial	120 women with climacteric symptoms	Aquous-ethanolic CR extract BNO 1055 (40 mg dried rhizome powder daily (equivalent to approximately 6.5 mg dried extract)) vs serotonin reuptake inhibitor fluoxetine, duration 6 months	Kupperman Menopause Index, Beck's Depression Scale	Hot flush score improved by 85 % vs 62 under fluoxetine, whereas fluoxetine was more effective than CR to reduce depressive symptoms	+
Geller et al. 2009 [47]	Randomized, double-blind, comparator and placebo-controlled	89 postmenopausal women with 35 or more hot flushes per week	128 mg of an ethanolic CR extract, vs 398 mg of a red clover extract (containing 120 mg isoflavones) vs 0.625 mg conjugated estrogens in combination with 2.5 mg medroxyprogesterone -acetate vs placebo, duration 12 months	Number of vasomotor symptoms and night sweats	No significant effects by both plant preparation Significant superiority of the hormone preparation. Note: the CR dose was approximately 25 fold higher than in the studies which yielded positive effects	–
Van der Sluijs et al. 2009 [52]	Randomized, double-blind placebo con-trolled trial	93 women women with 6 or more vasomotor symptoms per day	3150 mg dried rhizome powder (equivalent to approximately 300 mg CR extract) per day, duration 16 weeks	Greene Climacte5ric Sclae	No significantly more improvement in comparison to placebo Note: The CR dose was approximately 50 fold higher than in the studies which positive results	–

CE conjugated oestrogens, *CR Cimicifuga racemosa*, *DB* double blind, *GCS* greene climacteric scale, *KMI* Kupperman menopause index, *MRS* menopause rating scale, *PM* postmenopausal, *RCT* randomised controlled trial

Table 3 Short description of clinical studies with Cimiciduga racemosa preparations

Ref. (placebo or comparator controlled)	*Design*	Patient characteristics and age	Treatment, dose, and duration	Outcome measures	Finding and comments	Effects in short No = Ø Signif. pos = + Signif. neg = –
Rostock et al., 2001 [30]	Prospective observational trial. This non placbo controlled study was incorporated because of the importance of its outcome	50 breast cancer patients under tamoxifene	1 to 4 times 2.5 mg of an isopropanolic extract daily for 6 months	Menopause Rating Scale II	Hot flushes, sweating, sleep problems and anxiety improved significantly	+
Ross 2012 [48]	Randomized, double-blind, placebo-controlled	304 post-meno-pausal women	Isopropanolic CR extract (40 mg dried rhizome powder daily (equivalent to 5 mg dried extract)), duration 12 weeks	Number of hot flushes	Significantly better improvement of severety and number of hot flushes	+
Schellenberg et al. 2012 [49]	Randomized, comparator controlled trial	180 women with climacteric complaints	6.5 or 13 mg of the CR extract Ze 450 vs placebo, duration 12 weeks	Kuppermans's Menopausal Index.	Significant dose dependent improvement under CR	+
Mohammad-Alizadeh-Charandabi et al. 2013 [50]	Randomized, double-blind, placebo-controlled trial	84 early postmeno-pausal women	6.5 mg of a dried CR extracr vs placebo, duration 8 weeks	Greene Climacteric Scale	Significant more improvement by the CR extract of all GCS scores (vasomotor, psychiatric, physical and sexual symptoms)	+
Pokul and Porkhanova 2007 [55]-——————————————— Stefanovskaya et al. 2011 [56]	Prospective comparator controlled trial	226 oopher-ectomized women with estrogen dependant cancer	Aquous-ethanolic CR extract BNO 1055 (40 mg dried rhizome powder daily (equivalent to approximately 6.5 mg dried extract)) vs vitamins	Climacteric complaint questionnaire, Hamilton depression scale, sonography of mammary gland, urinary bladder tonus	Under BNO1055 significant improvement of psychosomatic complaints and increased bladder tonus. No change in mammary gland	+
	Comparator controlled study was incorporated because of the importance of its outcome	36 post-menopausal women with metabolic syndrome	Aquous-ethanolic 6.5 mg CR extract BNO 1055 6.5 mg vs vitamins for 6 months	Menopausal index, abdominal obesity, lipids	Reduction of psychsomatic complaints and of cholesterol, LDL, triglycerides and fasting glucose. . Increased HDL	+

CE conjugated oestrogens, *CR Cimicifuga racemosa*, *DB* double blind, *GCS* greene climacteric scale, *KMI* Kupperman menopause index, *MRS* menopause rating scale, *PM* postmenopausal, *RCT* randomised controlled trial

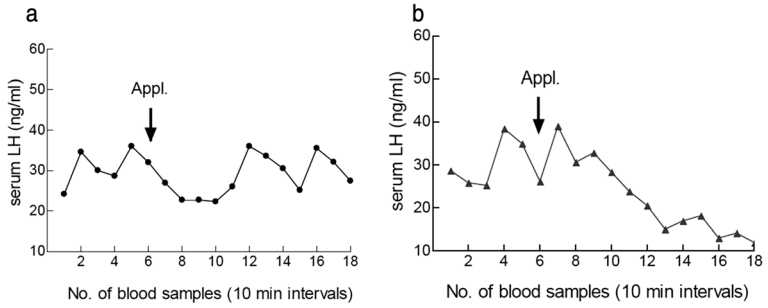

Fig. 7 Luteinizing hormone release in ovx rats. **a** Control, application of 2 % Cremophor; (**b**) ovx rats, application of E2 3.5 μg iv. Pulsatile LH release by the pituitary occurs at the same frequency as the subcutaneously measured temperature pulses (hot flushes). This suggests a common hypothalamic mechanism that generates hot flushes and LH pulses (**a**). Pulsatile LH release is strongly inhibited by an injection of estradiol (**b**). Appl: Application; E2: Estradiol; iv: intravenous

misbranding and adulteration and most likely contained other undeclared species than *C. racemosa* [54].

Table 1 includes three studies that further underline the efficacy of CR extracts. In one non-controlled study in mammary cancer patients [30], climacteric complaints were successfully alleviated by a CR extract. The other 2 studies were carried out in Russia. In one of them 126 oophorectomized women suffering from heavy climacteric complaints were treated with the BNO 1055 CR extract, while 120 received conventional systemic symptomatic therapy (diuretics, tranquilizers) [55]. Substantially larger beneficial effects were seen in the CR than in the control group.

Similar results were obtained in the second study [56] that included overweight and obese patients and reported additional beneficial effects on a number of metabolic parameters, including fasting glucose and insulin resistance.

CR effects on hot flushes

In all mammals in the reproductive state so far studied, regularly occurring Gonadotropin-releasing hormone (GnRH) pulses stimulate the pituitary gland to a normal pulsatile luteinizing hormone (LH) release; this happens in the presence of a normally working hypothalamic GnRH pulse generator. In the absence of estrogens, i.e. in postmenopausal women or in ovx rats, the GnRH pulse generator is overactive. This results in high serum LH pulses and therefore in significantly higher serum gonadotropin levels as compared to those found in normal or estrogen treated individuals. In the perimenopausal state many women experience climacteric complaints, of which the hot flushes are most troublesome. The occurrence of hot flushes correlates significantly with LH pulses in the blood [57], which are the result of phasic and synchronous overactivation of hypothalamic GnRH neurons. This causes a pulsatile GnRH release into the portal vessels that connect the hypothalamus to the anterior pituitary gland. The overactivity of the GnRH pulse generator is due to a dysregulated neurotransmitter release. An estrogen regulated, coordinated release of serotonin, γ-amino-butyric acid (GABA) and catecholamines (dopamine, norepinephrine) in the hypothalamus is of crucial importance for the occurrence of pulsatile LH release. Ovariectomy of rats results in the typical pulsatile LH release (Fig. 7a, b) also seen in postmenopausal women whereas estradiol inhibits it [58].

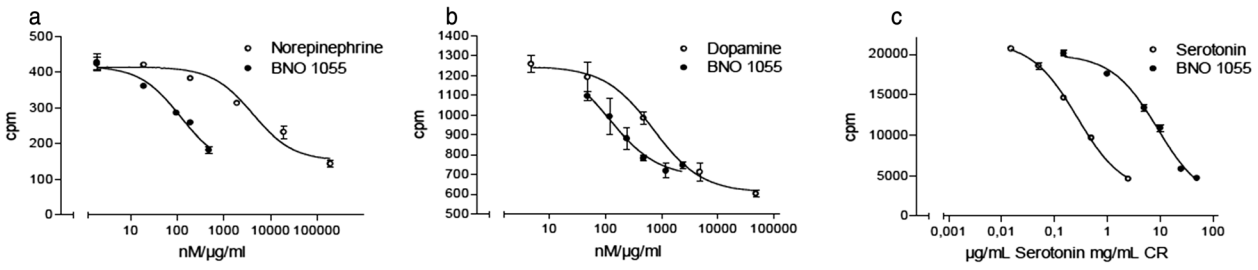

Fig. 8 Displacement curves of the BNO 1055 CR extract and the reference compounds dopamine (DA), norepinephrine (NE) or serotonin 5-HT in receptor binding assays (RBA). **a** Norepinephrine RBA; (**b**) Dopamine RBA; (**c**) Serotonin RBA. The receptor preparations originate from rat brain tissue. Radioactively labeled DA, NE and 5-HT bind to their respective receptors and substances with affinities to the respective receptor displace the radiolabeled neurotransmitter. This indicates that the BNO 1055 CR extract contains NE-, DA- and 5HT- mimetic substances. CR: *Cimicifuga racemosa*

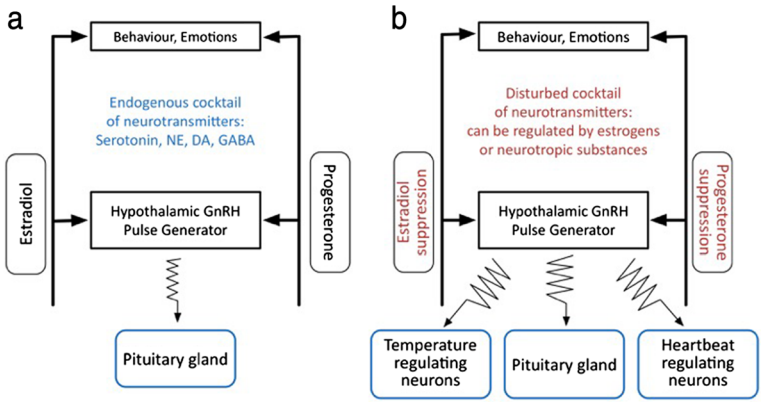

Fig. 9 Functional pictogram of the GnRH pulse generator, hot flushes and neurotransmitters. **a** individuals with functional ovaries such as premenopausal women or intact rodents; (**b**) oestrogen-deficient such as postmenopausal women or ovariectomized rodents. In the presence of functional ovaries a cocktail of stimulatory and inhibitory neurotransmitters in the hypothalamus [such as serotonin, norepinephrine (NE), dopamine (DA) and γ-aminobutyric acid (GABA)] causes regular, phasic and synchronous activation of GnRH-producing neurons, which results in normal pulsatile release of GnRH into the portal vessels connecting the hypothalamus with the anterior pituitary gland. This pulsatile pattern is important for the normal sensitivity of GnRH receptors of LH and FSH producing cells and therefore for normal reproductive health. The absence of ovarian steroids causes a dysbalance of neurotransmitters and the GnRH neurons are overstimulated, thus resulting in high GnRH pulses and consequently high LH and FSH levels in the serum. Under these conditions the dysregulated neurotransmitters spill over to temperature and heart regulating neurons, thus producing hot flushes and tachycardia

Recently we investigated whether or not the BNO 1055 CR extract contains substances that bind receptors of neurotransmitters known to be involved in the generation of hot flushes (Wuttke and Seidlová-Wuttke, unpublished). We could demonstrate that BNO 1055 contains substances that bind to dopamine, norepinephrine and serotonin (5-hydroxytryptamine: 5-HT) receptors isolated from rat brains (Fig. 8a-c). The serotoninergic substance is most likely 5-methyl-serotonin, the presence of which was already demonstrated in a CR extract [59]. In addition to dopaminergic, noradrenergic and serotoninergic substances the aqueous/ethanolic BNO 1055 CR extract contains GABAergic compounds. Clinically, GABAergic drugs such as Gabapentin and serotoninergic compounds such as the 5-HT reuptake inhibitor fluoxetine can reduce hot flushes [60]. Several triterpenes isolated from BNO 1055 were shown to bind to GABA receptors [61], hence substances with neurotransmitter like properties present in CR extracts may be at least partly responsible for the efficacy of CR extracts in preventing climacteric complaints. In the absence of estrogens or under conditions of blocked estrogen receptors, as under tamoxifen therapy, the release of these excitatory and inhibitory neurotransmitters appears to be exaggerated and they spill over to thermo- and cardioregulatory hypothalamic neurons, resulting in hot flushes and tachycardia attacks in many climacteric women (Fig. 9a, b).

In a 6-month clinical study in 120 climacteric patients comparing the serotonin reuptake inhibitor fluoxetine with an aqueous/ethanolic CR extract (120 patients, 6 months) the CR extract reduced 85 % of the climacteric complaints as measured by the Kupperman Menopause Index, as compared to 62 % in the fluoxetine group; fluoxetine, on the other hand and as expected, was more effective in reducing depression [46].

Inhibition of serotonin reuptake by neurons increases the availability of this neurotransmitter in the synaptic clefts. Mixed serotonin and norepinephrine (NE) reuptake inhibitors, which increase the availability of 5-HT and NE, and clonidine, an agonist of the α_2 NE receptor, proved to be effective in reducing climacteric complaints [62]: correspondingly, the CR derived serotonin analogue 5-methyl-serotonin is probably involved in the reduction of climacteric complaints, even if the amount of 5-methyl-serotonin alone present in the daily recommended CR dosage may not be sufficient to reduce hot flushes. The efficacy of CR extracts in reducing climacteric complaints is most likely the result of a synergistic effect of all neurotransmitter-mimetic compounds such as the structurally identified serotoninergic and GABAergic substances [59, 61] and still unidentified compounds binding to dopamine and norepinephrine receptors.

Common adverse events of CR extracts

In several placebo-controlled clinical trials the common adverse events which occurred under therapy with the 2 leading brands of CR preparation were evaluated and are listed in Tables 4 and 5 (Osmers et al. [38]). All adverse events, regardless of the judgement of causality, are listed for the 3 studies according to their frequency of occurrence.

Table 4 Incidence of Adverse Events /AE) in individual studies– by system organ class (MedDRA)

System organ class	Reported incidence by treatment groups						
	(KLI-DF-1 2001)					(BI 563.2)	
	Klimadynon 40 mg	CR BNO 1055 150 mg	CR BNO 1055 300 mg	CE 0.625 mg	Placebo	Menofem /Klimadynon 40 mg	Placebo
	N = 30	*N* = 33	*N* = 31	*N* = 34	*N* = 33	*N* = 152	*N* = 159
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Patients with AE	12 (40.0)	12 (36.4)	13 (41.9)	13 (38.2)	12 (36.4)	16 (10.5)	17 (10.7)
Blood and lymphatic disorders							1 (0.6)
Cardiac disorders							
Ear and labyrinth disorders	1 (3.3)				1 (3.0)		
Eye disorders		1 (3.0)					
Gastrointestinal disorders		2 (6.1)		4 (11.8)		2 (1.3)	2 (1.3)
General disorders and administration site conditions						1 (0.7)	1 (0.6)
Immune system disorders							2 (1.3)
Infections and infestations	2 (6.7)	3 (9.1)	1 (3.2)	6 (17.6)		5 (3.3)	4 (2.5)
Injury poisoning and procedural complications	2 (6.7)					1 (0.7)	
Investigations		4 (12.1)	3 (9.7)	1 (2.9)		1 (0.7)	2 (1.3)
Metabolism and nutrition disorders	1 (3.3)	2 (6.1)			1 (3.0)	4 (2.6)	5 (3.1)
Musculoskeletal and connective tissue disorders		1 (3.0)	1 (3.2)		2 (6.1)	1 (0.7)	2 (1.3)
Nervous system disorders	1 (3.3)	1 (3.0)				1 (0.7)	1 (0.6)
Psychiatric disorders		1 (3.0)					
Renal and urinary disorders							
Reproductive system and breast disorders	9 (30.0)	11 (33.3)	12 (38.7)	12 (35.3)	13 (39.4)	1 (0.7)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (3.3)				1 (3.0)		
Skin and subcutaneous disorders				1 (2.9)	1 (3.0)		
Surgical and medical procedures						1 (0.7)	
Vascular disorders	1 (3.3)						1 (0.6)

With the exception of a possible influence on lipometabolism, which up to now could not definitively be excluded, no common adverse events have been identified for *Cimicifuga racemosa* preparations.

Several years ago case reports were published which indicated possible hepatotoxic effects of CR preparations. For this reason an expert panel was called by the US American Food and Drug Administration (Workshop on the Safety of Black Cohosh in Clinical Studies; WORKSHOP SPONSORS: National Center for Complementary and Alternative Medicine NIH Office of Dietary Supplements National Institutes of Health Bethesda, Maryland) which took place on November 22, 2004). On the basis of extensive discussion of the reported cases the expert panel concludes that CR extract are unlikely to be hepatotoxic. Following publication of this expert opinion an evaluation of the 30 reports on liver toxicity by black cohosh concluded that liver damage was in no case probably or certainly due to the blamed preparations. Nevertheless the Dietary Supplement Information Expert Committee determined on the basis of these data that black cohosh preparations should be labeled to include a cautionary statement [63]. Several reviews however, substantiated the safety of *Cimicifuga racemosa* preparations [64, 65]. A recent meta-analysis evaluated 5 randomized, double blind and controlled studies in all of which no adverse effects on liver function were reported [66].

Conclusions

Cimicifuga racemosa extracts are traditionally used to ease climacteric complaints and a number of double-blind placebo-controlled studies have demonstrated this effect. Low or intermediate doses, however, are more effective than high doses. CR extracts do not contain

Table 5 Most common AE in the study by Osmers et al. (2005) [41] by system organ class (MedDRA)

System organ class	Remifemin 40 mg	Placebo	Total
	N = 153	*N* = 151	*N* = 304
	N	*N*	*N* (%)
Infections and infestations	13	19	32 (10.5)
Musculoskeletal and connective tissue disorders	15	10	25 (8.2)
Gastrointestinal disorders	8	7	15 (4.9)
Investigations	6	5	11 (0.4)
Nervous system disorders	4	5	9 (3.0)
Reproductive system and breast disorders	4	4	8 (2.6)
Psychiatric disorders	2	5	7 (2.3)
Skin and subcutaneous disorders	3	3	6 (2.0)
Blood and lymphatic disorders	1	1	2 (0.7)
Cardiac disorders	2		2 (0.7)
General disorders and administration site conditions	1	1	2 (0.7)
Vascular disorders	1	1	2 (0.7)
Injury poisoning and procedural complications	2		2 (0.7)
Metabolism and nutrition disorders	2		2 (0.7)
Ear and labyrinth disorders		1	1 (0.3)
Renal and urinary disorders	1		1 (0.3)
Respiratory, thoracic and mediastinal disorders		1	1 (0.3)

estrogenic compounds: they exert their efficacy through mechanisms linked to the presence of dopaminergic, noradrenergic, serotoninergic and GABAergic acting substances, but no estrogenic activity can be expected.

Competing interests

Wolfgang Wuttke and Dana Seidlová-Wuttke declare that they have no competing interests.

Authors' contributions

WW and DSW were advisors to Bionorica SE, Germany. They conducted the systematic review of the literature and drafted the first version of the manuscript. Both authors read and approved the present version of the manuscript. They thank Mr. Petrini for lingual help.

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