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Review

The non-estrogenic alternative for the treatment of climacteric complaints: Black cohosh (*Cimicifuga* or *Actaea racemosa*)

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ABSTRACT

In postmenopausal women estrogens in combination with progestins have beneficial effects on climacteric complaints and on osteoporosis but this hormone replacement therapy (HRT) bears the risk of increased mammary carcinomas and cardiovascular diseases. Phytoestrogens at low doses have little or no effects on climacteric complaints, at high doses they mimic the effects of estrogens. Therefore other plant derived substances are currently intensively investigated. Extracts of the rhizome of black cohosh (*Cimicifuga racemosa* = CR) did not bind to estrogen receptors and were shown to be devoid of estrogenic effects on mammary cancer cells in vitro and on mammary gland and uterine histology in ovariectomized rats. In addition in this rat model the special extract CR BNO 1055 inhibited the occurrence of hot flushes and development of osteoporosis.

In postmenopausal women CR BNO 1055 reduced major climacteric complaints as effectively as conjugated estrogens and significantly more than placebo. Similar data were published for other European CR preparations whereas 2 US American preparations were ineffective. This was most likely due to the too high doses or due to the adulteration with Asian Cimicifuga preparations. In all European studies neither effects in the uterus nor in mammary glands were observed.

The effective compounds in CR are most likely neurotransmitter-mimetic in nature: dopaminergic, noradrenergic, serotoninergic and GABAergic effects were demonstrated and some have been structurally identified. We conclude that CR extracts at low doses are effective to ameliorate climacteric complaints but are devoid of adverse estrogenic effects. These finding strengthens the role of CR extracts as substitutes for HRT.

This article is part of a special issue entitled: Special Issue on Phytoestrogens.

Contents

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1. Introduction

Many women after the 4th decade of their life experience menopausal symptoms and most find them distressing. Therefore hormone replacement therapy (HRT) was practiced for more than half a century but recently published clinical studies have questioned its safety. The 2 HERS studies questioned the safety of HRT in the cardiovascular system (for review see [1,2]). In the estrogen/progestin arm of the large Women's Health Initiative (WHI) it was shown that intake of a combination preparation containing conjugated estrogens and medroxyprogesterone acetate taken for a period of more than 8 years increased the risk for the development of mammary cancer. In hysterectomized women taking only estrogens such effects was not seen ([3], for review see [4,5]). In both arms significantly more cardiovascular incidences were observed which were later blamed to be due to the over aged study population (for review see [6]). In the British Million Women Study all in Great Britain available preparations were shown to increase the risk for breast cancer (for review see [7]).

It is undisputed that administration of progestin unopposed estrogens in uterus-intact women over more than 3 months is contraindicated because such treatment increases the risk for the development of an endometrial carcinoma (for review see [8]).

The recent insecurity about safety of HRT has led to efforts to find alternatives to classical hormone replacement therapy (HRT). Basic and clinical researchers, often supported by plant and food additive producing companies seek for such alternatives as complementary or alternative medicines (CAM). Ideally, a plant derived alternative for a HRT preparations should be devoid of estrogenic effects in the mammary gland and the uterus but should have beneficial effects on climacteric complaints and in the bone.

A large number of uncontrolled studies were published and most yielded positive results, i.e. most tested CAM preparations reduced climacteric complaints. This is due to a large placebo effect of any preparation on psychosomatic symptoms. Similarly, the weakness of many clinical studies using CAM preparations is enforced by the following: The literature about alternative methods for the treatment of gynecological diseases is plentiful and often ends with statements such as "more clinical studies with a larger number of patients need to be performed before final conclusions can be drawn".

2. Phytoestrogens

A good number of solid placebo-controlled studies on climacteric complaints and postmenopausal development of osteoporosis in females have been published. Preparations used in Western World utilizing CAM which are commonly prescribed for postmenopausal symptoms or osteoporosis often consist of phytoestrogen, primarily isoflavone containing plant extracts, which may provide a scientific basis for their action. Nowadays legal authorities, physicians and patients demand proof of efficacy in clinical studies and many studies were conducted and published in the past. However, many of them do not fulfill the criteria of evidence based medicine. Those fulfilling these criteria gave evidence that phytoestrogen containing preparations have weak, if any effects on climacteric complaints. Many preparations used in traditional Cines Medicine (TCM) contain often poorly characterized extracts of a variety of plants including plants containing phytoestrogens. Cell biological and animal experiments studying effects of phytoestrogen containing Asian plants are almost innumerous. However, due to different mixtures, durations and endpoints most results obtained with TCM preparations are not comparable to other studies, primarily those performed in the Western world. Most solid clinical studies utilizing phytoestrogens containing preparations were done in Western countries and reviews of their outcome on vasomotor symptoms, primarily hot flushes, concluded that phytoestrogens exert little or no effects (for different views see [9], see also Lewis et al., and Bedell et al., this volume).

3. Postmenopausal symptoms and diseases

In the life of women 5 global types of diseases may occur:

1. Life threatening are carcinomas, particularly breast cancer.
2. Peri- and postmenopausal women often develop psychosomatic symptoms of which most troublesome are climacteric complaints such as hot flashes.
3. As a result of the postmenopause women often develop osteoporosis. Particularly, a slim postmenopausal woman is prone to develop this disease because the fat cells of the female type fat distribution around the gluteal and thigh area (the so called pear fat distribution) express aromatases which are able to aromatize circulating androgens into estrogens which partially prevent osteoporosis and which are not produced in slim postmenopausal women [10].
4. Obesity: this has almost reached pandemic properties. In the United States more than one-third of the population is obese [11]. In Europe estimations go up to 30% and even in countries considered to be poor obesity is a major health threatening condition. Obesity is often related to poverty [10] because the socio-economic situation of poorer people is frequently associated with a lower education and with a high intake of high caloric fast food. This leads to other threatening effects in the aging population, the development of cardiovascular diseases which are often associated with obesity.
5. Infertility: estimations report that 30–40% of infertility is associated with obesity [12,13] of the male type (i.e. the apple type with large amounts of visceral fat) and the thereof resulting hyperandrogenemia in females [14]. Many of these symptoms/diseases are the result of the lack of estrogens in the postmenopause and can be largely omitted by HRT. Substitutes for HRT should therefore have beneficial effects on these symptoms/diseases as well, but should not have the undesired side effects of HRT.

3.1. The non estrogenic alternative: Cimicifuga racemosa

In many countries and after decades of arguments it is still not generally accepted – particularly by health authorities – that rhizomes of *C. (Actaea) racemosa* (CR) are not estrogenic. In the present review animal experimental and clinical data will be given that extracts of rhizomes of CR extracts have desired effects on climacteric complaints without stimulating mammary gland tissue. Own data stem from animal experimental and clinical investigations of a special aqueous/ethanolic extract known as CR BNO 1055.

C. racemosa (black cohosh) was originally used by indigenous North American Indians to treat a variety of women's diseases. Later

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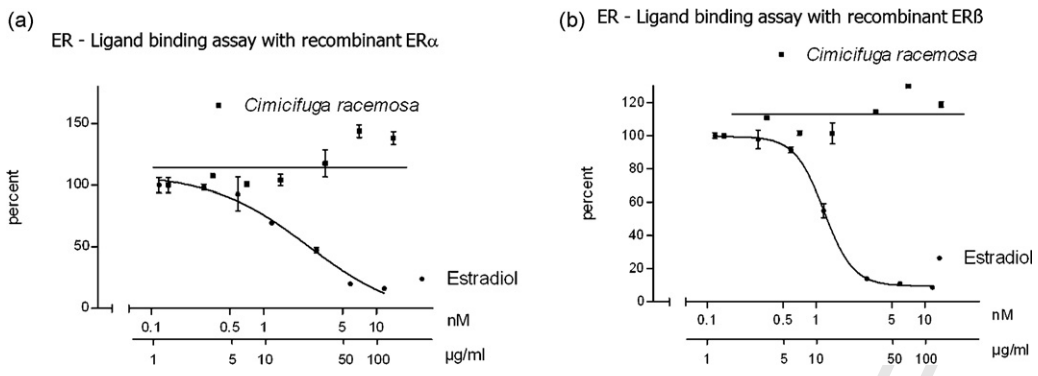


Fig. 1. Displacement curves of estradiol and CR BNO 1055 from recombinant estrogen receptors (ER). In ligand binding assay with ERα (a) and ERβ (b) increasing amounts of estradiol displaced the radiolabelled estradiol increasingly from both receptor-preparations, such activity was not seen with increasing amounts of CR BNO 1055. This indicates that no substance in CR BNO 1055 competes with the radiolabelled estradiol for both receptor subtypes.

it proved to be efficient to alleviate climacteric complaints. Few double blind, placebo controlled studies however were conducted and little is known about the mechanism of action. CR grew originally in North America but other *Cimicifuga* species grow in Far East Asian countries. Due to the hundred thousands of years of separation of the American from the Eurasian continent it is not surprising that the chemical constituents of *CR* are quite different from these Asian *Cimicifuga* species [15,16]. This is important because in many countries in which black cohosh extracts are sold as food supplements the preparations contain Asian *Cimicifuga* [17] for which no clinical data for their effectiveness are available. In Germany and in many East European countries CR extracts are medicines sold exclusively in pharmacies whereas in Anglo-American countries such extracts are sold as food supplements.

3.2. CR and estrogenicity: cell biological and animal experimental studies

3.2.1. The mammary gland

There is ample evidence that extracts of *C. racemosa* do not contain estrogenic compounds as they bind neither to ERα nor to ERβ (Fig. 1a and b) [18,19]. This does not exclude estrogenic effects which could be exerted via non genomic mechanisms. Therefore, a number of cell biologic investigations were performed. Estrogenic substances would stimulate proliferation of estrogen receptive human mammary carcinoma cells. The most widely used cell lines with these properties are the ERα receptive MCF-7 cells of which the proliferation is stimulated by estradiol 17-β but inhibited rather than stimulated by extracts of *CR* [20–22]. The aqueous/ethanolic CR BNO 1055 extract was dose dependently inhibitory to the proliferation of these cells (Fig. 2) and in another study a CR extract inhibited estradiol-stimulated proliferation of MCF 7 cells and of the estrogen receptive endometrial cancer Ishikawa cells [23]. Mammary gland tissue and MCF-7 cells express aromatases which can increase the availability of estradiol in mammary glands by aromatizing androgens into estrogens (for review see [24]). This conversion is profoundly inhibited by a *C. racemosa* extract [25] which would argue for a protective effect in the mammary gland.

Most convincing evidence for the absence of estrogenic, mammotrophic substances stems from animal experiments. In a variety of animal models CR extracts did not have estrogenic actions in the mammary gland. In experiments with ovx rats the CR BNO 1055 extract was shown not to stimulate proliferation of the lobuloalveolar and ductal apparatus and of their epithelial cells which, however, were profoundly stimulated by E2 (Fig. 3a–e) [26].

When Sprague–Dawley rats are treated with dimethylbenzanthracene (DMBA) they develop typical mammary tumors which were also profoundly inhibited by oral administration of an isopropanolic CR extract [27] and also the occurrence of spontaneously occurring mammary adenocarcinomas was inhibited by CR [22].

3.2.2. The uterus

It was already mentioned that proliferation of the Ishikawa cells, which originated from a human endometrial carcinoma, was inhibited by a CR extract [23]. As early as 1996 it was shown in an in vivo experiment that a CR extract did not stimulate uterine weights of ovariectomized (ovx) mice and rats [28]. The ovx rat is now a well-accepted model to study estrogenicity of compounds in a variety of organs and the Organization for Economic Co-operation and Development (OECD) proposes the uterotrophy assay in ovx rats as a standard model to study estrogenic effects [29]. In this model uterine weight and endometrial thickness – which increase in response to estrogens – remained unaffected (Fig. 4a and b) [30,31].

3.2.3. Hot flushes

Due to the lack of estrogens in postmenopausal women pituitary LH release occurs in high pulses at relatively regular intervals. These LH pulses are due to phasic and synchronous activation of hypothalamic GnRH neurons which results in pulsatile GnRH release into the portal vessels connecting the hypothalamus with the anterior pituitary. The GnRH pulse generator is overactive in the absence of estrogens, i.e. in the postmenopause. This results in high serum LH pulses and therefore in significantly higher serum gonadotropin levels in comparison to those found in intact or estrogen treated individuals. Similarly, the lack of estrogens in ovx rats results in high pulsatile LH release which can be profoundly inhibited by estradiol 17β (E2) (Fig. 5a and b). The overactivity of the

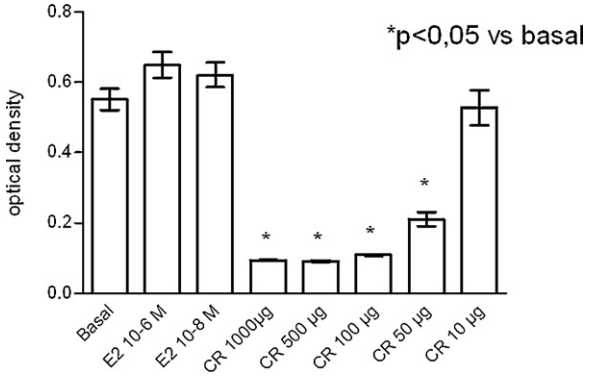
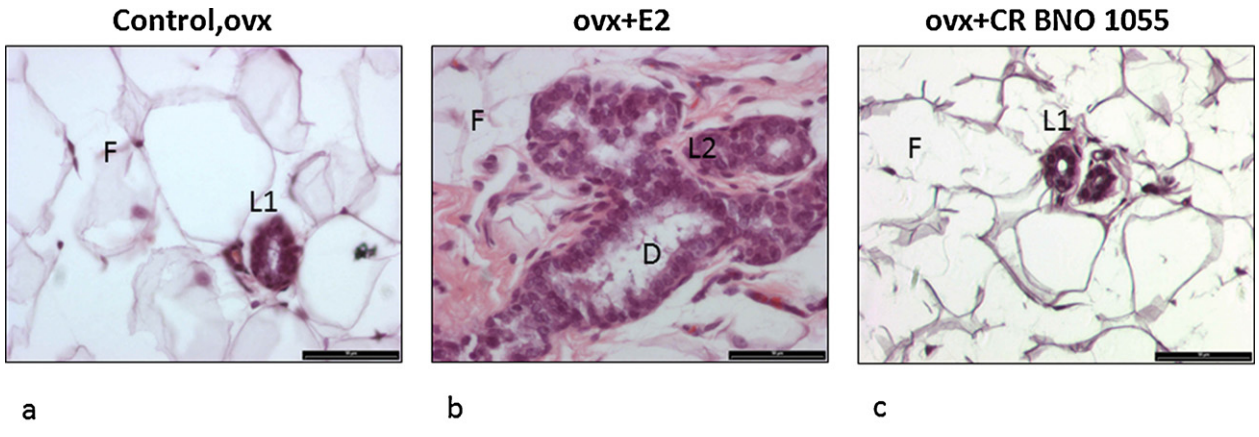


Fig. 2. Proliferation assay of MCF-7 cells. The CR BNO1055 extract inhibited dose dependently the proliferation of the estrogen receptor a receptive human mammary cancer MCF-7cell line.



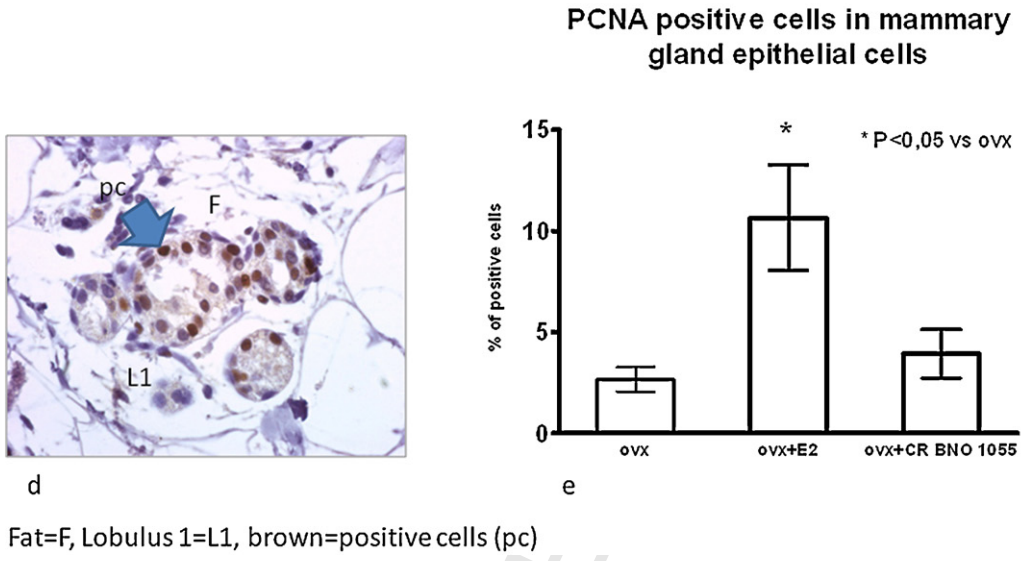


Fig. 3. Effects of estradiol (E2) and CR BNO 1055 in the mammary gland. Histological preparations of a mammary gland of (a) an ovx control rat, (b) of an ovx rat treated orally for 3 months with estradiol (0.05 mg/day) or (c) with CR BNO 1055 (30 mg/day). Note the much higher number of lobuli and ductus in the estradiol treated animal in comparison to the negative control and the CR BNO 1055 treated animal, indicating that the black cohosh extract did not contain estrogenic compounds. PCNA positive cells are numerous in mammary gland epithelia of ovx, E2-treated rats (d and e) while CR BNO 1055 did not change the number of PCNA positive cells (e).

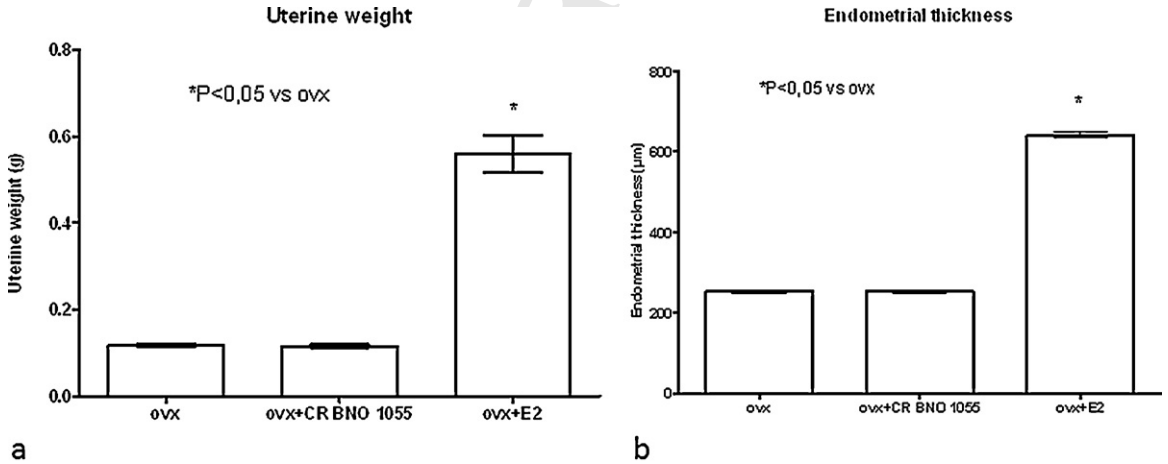


Fig. 4. Effects of estradiol (E2) and CR BNO 1055 in the uterus. Quantitative evaluation of (a) uterine weight and (b) endometrial thickness in ovx controls, ovx rats treated for 3 months with estradiol or CR BNO 1055. Note lack of stimulation of both parameters in the CR BNO 1055 treated animals. This confirms the absence of estrogenic activities in the black cohosh extract.

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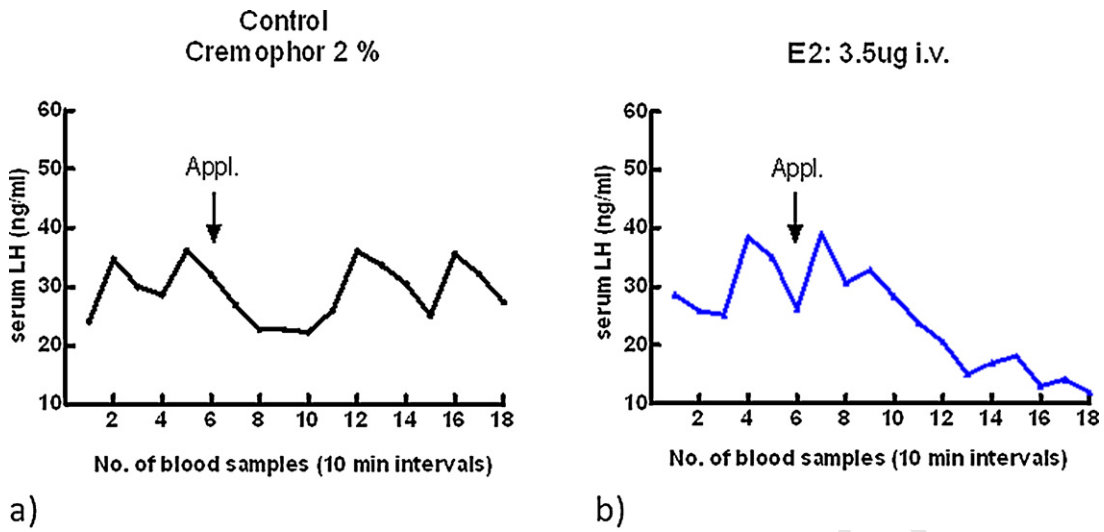

Fig. 5. Effects of estradiol on pulsatile LH release (a) serum LH in ovx rats is released in pulses which occur in approximately 20–30 min intervals and (b) these pulses are inhibited by E2. Arrows indicate the timepoint of administration.

GnRH pulse generator is due to a dysregulated neurotransmitter release. It is known that an estrogen regulated, coordinated release of serotonin, gamma aminobutyric acid (GABA) and catecholamines in the hypothalamus are of crucial importance for the occurrence of pulsatile LH release. In the absence of estrogens or under conditions of blocked estrogen receptors the release of these excitatory and inhibitory neurotransmitters is exaggerated and therefore neurotransmitters spill over to thermo- and cardioregulatory hypothalamic neurons which results in hot flushes and in many climacteric women in tachycardiac attacks. This is the reason why serum LH pulses and hot flushes occur often synchronously [32]. This is graphically exemplified in Fig. 6a and b.

Recently, we and others demonstrated that ovx rats have also hot flushes [33–36] which occur as frequently as the LH pulses and these pulses of increased skin temperature are not seen in intact or in CR BNO 1055 treated animals (Fig. 7). Hence, the mean skin temperature of ovx rats is significantly higher in these in comparison to intact or ovx CR BNO 1055 treated animals (Fig. 8).

3.2.4. Other organs

Lacking estrogens have negative impacts on bone metabolism. This is the reason why about 25–30% of postmenopausal women develop severe osteoporosis (for review see [37]). In cell biologic experiments a CR extract stimulated the formation of bone nodules in MC3T3-E1 preosteoblast cells [38] and a major constituent of CR, namely deoxyactein, stimulated osteoblast function [38].

The ovx rat is an excellent model to study development of osteoporosis and its prevention (for review see [39]). In this animal model the CR BNO 1055 extract had osteoprotective effects [39] of which the mechanisms of action remain unknown. Recently it was shown that the unpolar substances in CR BNO 1055 which contain primarily actein-related substance have osteoprotective

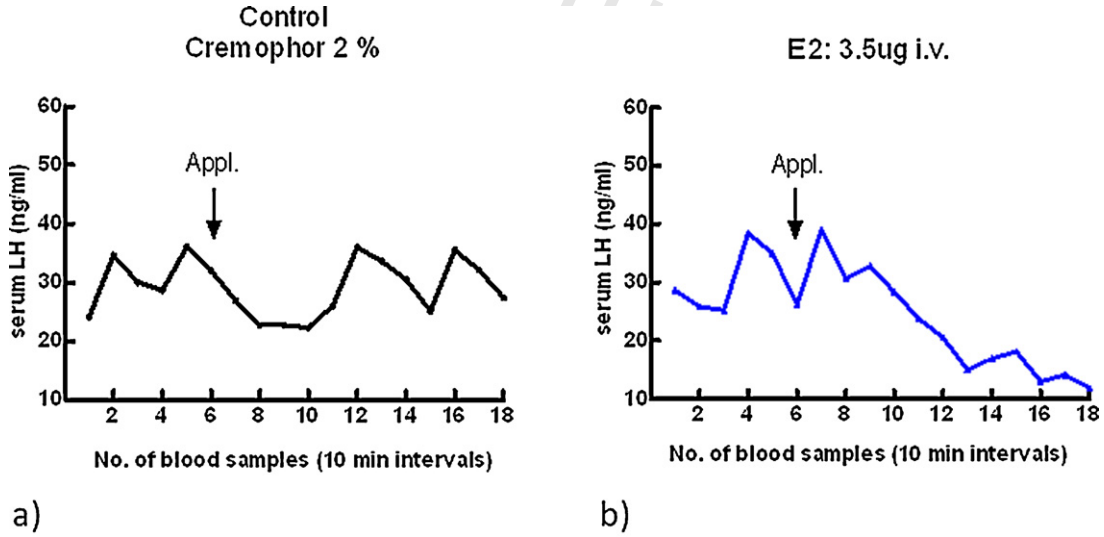

Fig. 6. Schematic drawing of the neuroendocrine circuit regulating the ovary. The GnRH pulse generator consists of hypothalamic GnRH neurons which are regulated by a variety of neurotransmitters. The left part of this graph details the situation in the presence of estrogens, i.e. in women and rats in the reproductive age. The ovarian estrogens signal the GnRH pulse generator the status of follicular development in the ovaries and exert a negative feedback to the GnRH pulse generator. The right part of the graph depicts the situation when ovarian estrogen production ceases. In this case the GnRH pulse generator becomes overactive in an attempt to stimulate ovarian function. Hence, the cocktail of excitatory and inhibitory neurotransmitters driving the GnRH neurons to become phasically and synchronously activated is dysregulated. This in turn activates closely neighbored temperature regulatory neurons which results in widening of skin blood vessels which is a hot flush. The neurotransmitters known to be involved in the generation of hot flushes are indicated in the right graph.

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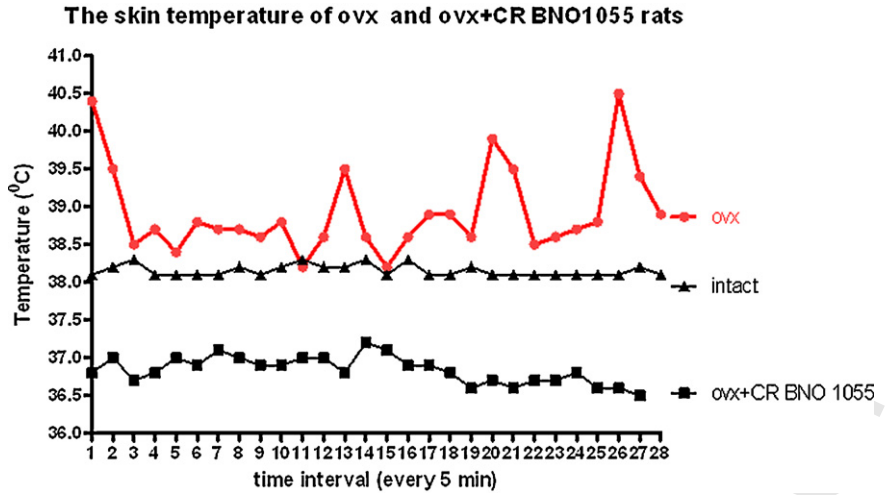

Fig. 7. Effects of estradiol and CR BNO 1055 on skin temperature. Subcutaneous temperature measured in 5 min intervals over a period of 140 min in an ovx rat treated orally for a period of 1 week with the black cohosh preparation CR BNO 1055 (11.27 mg/day) or fed with food containing no additive. Note the regularly occurring pulse of increased temperature in the ovx animal indicating the presence of hot flushes. Such flushes are not seen in intact and in the CR BNO 1055 treated animal.

effects [40]. The lack of estrogens causes not only osteoporosis but also cartilage tissue in joints deteriorates and this is the reason for the development of osteoarthritis in many elderly women. Following ovx of rats the cartilage layer in the knee joint is significantly smaller than in intact animals and this was largely prevented by the saponin fraction of CR BNO 1055) [41].

CR BNO 1055 had also no effects in a variety of organs which are not regulated by estrogens [42] and in a clinical trial it was devoid of effects on lipids, fibrinogen, glucose and insulin [43]. It appears, however, that CR extracts had anti-inflammatory effects [44,45].

3.3. Clinical studies

3.3.1. The mammary gland

A high mammographic density of mammary glands indicates a high risk for the development of breast cancer [46]. A number of clinical trials demonstrated with a variety of methods no estrogenic effects in mammary gland of women [47–49]. In a large, 12 months lasting study the investigated *C. racemosa* preparation Klimadynon did not affect the mammary gland density as determined by mammography [50]. In 2 other studies neither cell morphology [47] nor the proliferation marker Ki-67 [48] of mammary gland cells in nipple aspirates were affected by the treatment with CR. In the former of these 2 trials effects of a 12 weeks lasting intake of 2.5% black cohosh tri-terpenes were compared with an extract containing trace amounts of tri-terpenes. In this study the triterpene containing extract exerted no breast specific estrogenic effects but climacteric complaints were significantly relieved [47].

Hence, there is not only experimental but also convincing clinical evidence that *CR extracts* are not harmful but may actually protect the mammary gland. In fact a recently published case control study involving 949 breast cancer patients demonstrated that the use of black cohosh had a significant breast cancer protective affect [51].

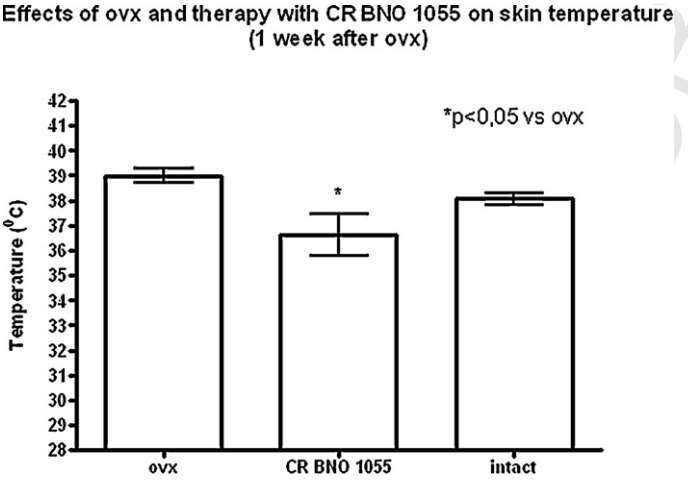

Fig. 8. Skin temperature is significantly reduced by CR BNO 1055. Mean subcutaneous skin temperatures in a group of ovx, ovx CR BNO 1055 (11.27 mg/day/animal) or ovx estradiol (0.154 mg/day) treated animals. Note the significant temperature lowering effects of CR BNO 1055 and estradiol.

3.3.2. The endometrium of the uterus

There are results of 2 clinical trials published in which the safety of the endometrium was investigated. In one large study the intake of CR BNO 1055 extract for 1 year was tested and endometrial safety was assessed by histological evaluation of the tissue. There was no case of endometrial abnormality present in the more than 300 tested patients [50]. In the other double blind, placebo controlled, 3 months lasting trial exposure to CR BNO 1055 vaginal cytology and endometrial thickness remained unaffected, whereas an conjugated estrogen preparation increased endometrial thickness and the number of superficial vaginal cells significantly [52]. This lack of effects of *C. racemosa* extracts in the endometrium is in line with animal experimental (see above and [30]) and also the major constituent of this extract – deoxyactein – had no effects on endometrial parameters including proliferation [53]. Hence, it can be concluded that *C. racemosa* extracts have no estrogenic effects in the endometrium and therefore, bare no risks for the uterus.

4. Climacteric complaints

The claim for all *C. racemosa* preparation is to ameliorate climacteric complaints. Indeed, with few exceptions (see below) most placebo-controlled clinical trials demonstrated amelioration of climacteric complaints, particularly of hot flushes. In most of these studies either the old Kupperman-Index or the more recent menopause rating scale 1 or 2 were used. Most placebo controlled clinical trials were conducted over an investigation period of 3 months. They proved unequivocally that placebo preparations reduced the psychosomatic symptoms of the climacteric syndrome

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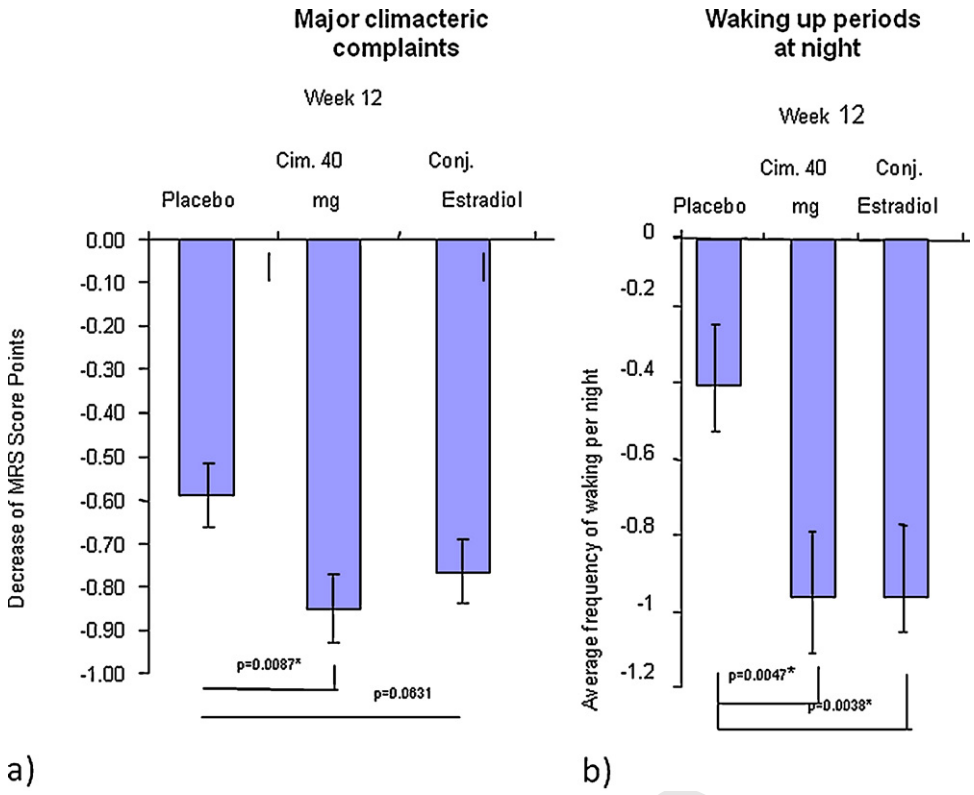

Fig. 9. Effects of Klimadynon on major climacteric complaints. Major climacteric complaints (left) as well as frequent wake up episodes at night (right) were significantly more reduced by Klimadynon and conjugated estrogens than by placebo.

by 30 up to 50%. Therefore, in the following we will only discuss placebo controlled trials.

In one study with CR BNO 1055 (the German preparation Klimadynon) the effects were compared to those of conjugated estrogen and of a placebo preparation. Reduction of these symptoms under both verum preparations was identical und superior to placebo (Fig. 9a) [54]. As noted in a diary that each of the patients had to fill out, the sleeping behavior, i.e. the frequency of wake up periods was significantly reduced (Fig. 9b). Another Swiss CR extract proved also to significantly ameliorate the severity hot flushes [55]. In 2 larger trials, one comprising 244 the other 304 postmenopausal patients, another German preparation was tested and a significant reduction of climacteric complaints was reported [56,57]. A Turkish trial compared the effects of the BNO 1055 containing preparation with the effects of fluoxetine, a serotonin reuptake inhibitor [58]. Both preparations proved to ameliorate climacteric complaints significantly. Finally, another large study with a German preparation reported significantly reduced climacteric complaints in 304 patients [59].

In contrast to the positive effects of these German/Swiss medications, the study of 4 US American food supplements yielded 3 negative results [59]. This may have the following reason: it appears that the dosage of the tested CR extracts may be of crucial importance. The German/Swiss medications contained 2×20 mg CR drug. A plant drug is the dried plant. The yield of an extracted and dried drug results in case of CR in 10–20% of its original weight. Hence, the German/Swiss preparations contained 10–20% of the weight of the drug, i.e. 4–8 mg extract. These were the doses tested in the studies that yielded positive results. The 2 negative results from the US American studies administered 15–25-fold the amounts used in the European trials. In one study 200 mg CR extract was used [60] which is roughly a 25 fold higher the amount of CR extract than were used in the German/Swiss studies. Similarly in the 2nd unsuccessful trial 15 fold higher amounts were tested [61]. Interestingly, also a moderate overdosage yielded negative results [62]. In another American trial the amount of triterpenes in the black cohosh preparation was standardized to 2.5% and its administration yielded a significant reduction of menopausal symptoms which was not seen when a triterpene-free extract was given [47].

The identity of many American black cohosh preparations is often unknown and they are on the market as food supplements. It was previously shown that many of them contain Asian Cimicifuga species for which no clinical data are available. The HPLC profiles of these Asian species look quite different from those of the CR species that grew originally in America [16]. The German/Swiss medications contain extracts of original CR rhizomes and these rhizomes stem from field planted CR that grew under rigidly controlled conditions. Hence, the German CR BNO 1055 containing medication proved in both, animal experiments and in placebo controlled clinical trials to effectively ameliorate climacteric symptoms. In line with these findings are results from other clinical trials using different extracts from authentic field grown CR.

In most counties in which CR extracts are sold as medication health authorities demand the information for the user that the extract should not be taken in cases of estrogen dependently growing tumors. This is primarily due to a very old report. In 1985 the presence of the estrogenic isoflavone formononetin was reported in a CR extract [63]. This could never be confirmed in subsequent analyses but was the reason for the note of caution. Isoflavones stimulate the growth of estrogenic events in vitro (such as proliferation of MCF 7 cells) and in vivo (such as uterine growth). As documented above such effects were never seen in any of the later experiments. Also newly developed HPLC methods to identify formononetin were employed to specifically look for the presence of this isoflavone in extracts of CR. These analyses clearly demonstrated that this compound was not present in a number of different extracts [64,65].

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The absence of estrogenic compounds in CR is clinically exorbitantly important. It is now internationally practiced to give antiestrogens such as tamoxifen or aromatase inhibitors as an adjuvant therapy to mammary cancer patients. These patients suffer frequently from severe climacteric complaints particularly hot flushes. A classical HRT application for these patients is of course contraindicated. Gynecologic oncologists are therefore often faced with the situation that the patient seeks for help to relieve of these troubling psychovegetative symptoms. The only non estrogenic alternative are extracts of the rhizome *CR*. Indeed, a prospective observational study was carried out in 50 breast cancer patients under tamoxifen treatment. In this trial a 6 months lasting therapy with a *CR* extract reduced psycho-vegetative symptoms as measured by the menopause rating scale significantly [66].

4.1. Active compounds in CR extracts

A good number of compounds that may be active to relieve climacteric complaints have been identified. A number of actein derived triterpenes are good candidates [66]. Ligand binding assays and cell culture experiments indicated the presence of dopaminergic and serotoninergic compounds in CR BNO 1055. As mentioned above hot flushes are causally related to the overactivity of the GnRH pulse generator which is due to a dysregulated neurotransmitter release. Thus, it is possible that the proven effect of CR BNO 1055 on hot flushes is caused by dopaminergic, adrenergic and serotoninergic compounds. In earlier experiments the CR extract BNO 1055 was shown to inhibit the release of prolactin from dispersed rat pituitary cells and this was antagonized by haloperidol, which proved dopaminergic activities in the extract [67]. The presence of dopaminergic compounds in CR BNO 1055 was further documented with a well characterized ligand binding assay with recombinant human dopamine receptors [67]. Recently the presence of the serotonin derivative N-methyl-serotonin was demonstrated in a CR extract [67]. GABAergic compounds such as GABApentin are also able to ameliorate climacteric complaints (for reviews see [68,69]). Therefore, the isolation of compounds mimicking the effects of GABA from CR BNO 1055 [70] may be another piece of the puzzle how CR extracts may be effective to reduce climacteric complaints. Hence, there are a number of neurotropic substances present in CR extracts which form a kaleidoscope of actions to effectively prevent climacteric complaints. Thus, it is clearly documented that CR extracts contain yet to be identified dopaminergic substances as well as N-methyl-serotonin and triterpenes with GABAergic effects. Each of these substances alone would most likely not be able to prevent these symptoms but together they appear to act synergistically and are therefore able to ameliorate climacteric complaints. Hence, the CR BNO 1055 extract may be a good non-estrogenic alternative for the treatment of women with climacteric complaints including breast cancer patients. But more studies with identically produced extracts, utilizing the same doses should be performed before definite conclusions can be drawn.

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