REVIEW

Nutrafoods (2018) 17:193-200
DOI 10.17470/NF-018-1007-4

Received: April 19, 2018
Accepted: May 15, 2018

Climacteric symptoms during adjuvant treatment in hormone-responsive breast cancer patients: the underestimated role of *Cimicifuga racemosa*

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ABSTRACT

The treatment of breast cancer is complex, with a wide variety of surgical, radiotherapeutic, chemotherapeutic, biological and endocrine options available. Although these therapies have improved survival rates, adjuvant treatment does have side-effects. The main adverse effects, such as vasomotor symptoms, classically represented by hot flushes and night sweats, are related to anti-hormone therapy, which aims to block the estrogen receptor or destroy estrogen-producing tissue. Options generally include selective estrogen receptor modulators (SERMs), GnRH analogues and aromatase inhibitors, which all cause climacteric symptoms in most breast cancer survivors and have a big impact on their quality of life and treatment compliance. Classically, hormone replacement therapy (HRT) has been the gold standard treatment for menopausal hot flushes. However, this treatment has risks, and should not be the first option in women with breast cancer or at high risk of developing the disease. Many alternatives to HRT such as tibolone, phytoestrogens and antidepressants have been proposed in recent decades, but results have been controversial regarding efficacy and safety, and consequently compliance is poor. Therefore, interventions to improve compliance with adjuvant hormonal therapy are required. Black cohosh or *Cimicifuga racemosa* isopropanolic extract (Remifemin®) is a herbal medication frequently used for alleviating menopausal symptoms. Several recent studies have shown that patients with mild menopausal symptoms usually experience spontaneous remission after taking black cohosh, while those with moderate to severe symptoms may experience some benefit. No adverse effects or estrogen activity were reported with this compound. This review examined the effectiveness of black cohosh extract for relieving symptoms and improving quality of life in breast cancer survivors and high-risk women with moderate to severe menopausal symptoms.

Keywords
Breast cancer
Endocrine treatment
Hot flushes
Cimicifuga racemosa

Endocrine therapy for breast cancer

Breast cancer is the most common cancer in women worldwide [1] with an estimated 1.67 million new cancer cases diagnosed in 2012 [2]. There is a wide variety of treatment options. Almost 80% of breast cancers are hormone receptor (HR) positive (estrogen receptor (ER) positive and/or progesterone receptor (PgR) positive) [3], so hormone therapy, commonly used for treating such cancers, is very effective but may have side effects such as premature menopause, which can have a serious impact on quality of life and treatment compliance. Endocrine-responsive cancers are a heterogeneous group of tumours and treatment decisions should take into consideration co-morbidities as well as the presence of other classic risk factors. Ever since oophorectomy was first shown to cause regression of advanced breast cancer more than a century ago, inhibition of estrogenic signalling has been the mainstay of endocrine management of ER-positive and/or PgR-positive disease [4]. Oophorectomy was abandoned when the US Food and Drug Administration approved tamoxifen citrate for use in advanced breast cancer in 1978. Selective estrogen receptor modulators (SERMs), such as tamoxifen, hinder the function of the ER by binding competitively to it. Moreover, tamoxifen also has some estrogen-agonist effects that help prevent bone demineralization in postmenopausal women and improve their lipid profiles. A large number of patients have been treated with SERMs either for clinical research or in clinical practice. Tamoxifen has been used clinically for breast cancer treatment for more than 30 years and has been able to reduce the recurrence rate by 42% and contralateral neoplasia by 47% [5]. Moreover, tamoxifen seemed to also reduce breast cancer incidence in healthy BRCA2 carriers by 62% but not in BRCA1 carriers. All available data on the use of tamox-

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ifen in the adjuvant setting of ER-positive breast cancer have been extensively reviewed in a recent meta-analysis which included over 83,000 women [6]. The authors reported a 38% reduction (HR 0.62, 95% CI 0.56 to 0.69) in breast cancer incidence. Unfortunately, tamoxifen increases the risk of endometrial cancer 2.4-fold and the risk of thromboembolic disease 1.9-fold [7] and consequently its use should be carefully individualized.

Aromatase inhibitors (AIs) which block the conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma, are another hormone treatment option. Modern third-generation AIs include the non-steroidal inhibitors, letrozole and anastrozole, and the steroidal inhibitor, exemestane. Recent reports of large trials conducted in the adjuvant setting indicate better outcomes among women given AIs than those given tamoxifen. In particular, initial adjuvant endocrine therapy with anastrozole or letrozole was found to significantly reduce the risk of relapse among postmenopausal women with endocrine-responsive disease when compared with tamoxifen [8, 9]. A recent meta-analysis of randomized trials of AIs compared with tamoxifen either as initial monotherapy or after 2–3 years of tamoxifen, confirmed that AIs result in significantly lower recurrence rates compared with tamoxifen either as initial monotherapy or after 2–3 years of administration [10].

These data suggest that in postmenopausal patients, AIs appear to confer greater benefit than tamoxifen, in particular during the first 5 years. Thus, although some patients at low risk or with a particular co-morbidity may be considered suitable for tamoxifen alone, AIs should be the gold standard of care for higher risk postmenopausal women with receptor-positive breast cancer and also for extended treatment (10 years), as suggested in a recent double-blind, placebo-controlled trial which showed higher rates of disease-free survival and a lower incidence of contralateral breast cancer after extended treatment [11].

Side effects of endocrine therapy

SERMs include tamoxifen (TAM) and raloxifene, which act as both estrogen agonists and antagonists. TAM has been used clinically for breast cancer treatment for more than 40 years in order to reduce the risk of both recurrence and contralateral neoplasia, but its use is often accompanied by an increased risk of other diseases, such as uterine cancer or thromboembolism, and side effects, particularly hot flushes and night sweats [12].

Moreover, aromatase, an enzyme of the cytochrome P450 super family and the product of the CYP19 gene, is expressed in various tissues, including subcutaneous fat, liver, muscle, brain, and normal and neoplastic breast tissue [13]. It is responsible for conversion of the adrenal androgen substrate androstenedione to estrogen in peripheral tissues [14], and is the main source of estrogen in postmenopausal women. AIs can reduce estrogen production by more than 90% [15]. However, this large reduction in estrogen activity is accompanied by the onset of major side effects. Generally, compared with tamoxifen, the use of AIs in postmenopausal women with early-stage breast cancer slightly increases the odds of developing cardiovascular disease and bone fractures but decreases the odds of developing venous thrombosis and endometrial carcinoma. The main side effects are frequently accompanied by minor AI-related symptoms as well as depression, fatigue and climacteric syndrome, which are caused by the lack of estrogens and impact on quality of life and treatment compliance. The principal side effects related to endocrine therapy are summarized in Figure 1.

Vasomotor symptoms in particular, classically represented by hot flushes accompanied by night sweats, are categorized as mild, moderate or severe and can be defined as a sensation of warmth accompanied by diffuse (principally on the face) erythema which occurs in episodic attacks. In 2011, Dent *et al* reported that 100% of women experienced hot flushes in AI trials [16]. The incidence of hot flushes is approximately 37% in initial AI therapy. However, the incidence of hot flushes increases to 42%–48% with sequential AI therapy following 2–3 years of tamoxifen use. Consequently, a pharmacological or alternative solution is required so that the patient's quality of life can be improved by reducing discomfort.

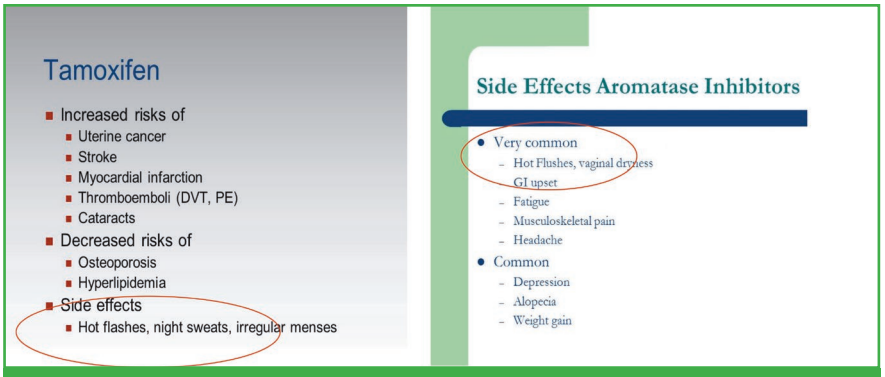

Figure 1 - Common side effects of endocrine therapy

Treatments for climacteric symptoms

The management of menopausal symptoms and the decreased quality of life in women treated for breast cancer are important and growing clinical concerns. Classically, HRT has been the gold standard treatment for menopausal hot flushes. However, this treatment carries risks, and should not be the first option in women with breast cancer or at high risk of developing the disease. In 1997 two independent randomized trials were started in Sweden to assess the effects of HRT after a diagnosis of breast cancer: the Hormonal Replacement After Breast Cancer – Is it Safe? (HABITS) study and the Stockholm trial. Following an interim safety analysis which showed a significant risk of recurrence in patients taking HRT in the two trials, both studies were prematurely halted in December 2003 [17, 18]. Similarly, tibolone, a synthetic steroid approved in several countries for the treatment of menopausal symptoms and for the prevention of osteoporosis, was shown in a recent double-blind randomized trial to increase the risk of breast cancer recurrence, although it relieved vasomotor symptoms and prevented bone loss [19]. In The Million Women Study, tibolone showed an intermediate risk of disease compared with other types of HRT. The study revealed that breast cancer incidence was significantly increased in current users with RRs of 1.30, 2.00 and 1.45 for estrogen only, estrogen-progestin and tibolone, respectively [20].

Alternative treatments

Postmenopausal women often seek alternative treatment in an effort to manage their symptoms with natural remedies, particularly when they have contraindications to HRT. Many clinical trials have investigated the effects of alternative therapies for the treatment of menopausal symptoms and, in particular, vasomotor hot flushes. Therapies can be divided into pharmacological alternatives and herbal alternatives. Alpha-adrenergic agonists, antidepressants and anticonvulsants are pharmacological alternatives, while phytoestrogens (soy products) and black cohosh are herbal alternatives (Fig. 2).

Figure 2 - Alternative treatments for climacteric symptoms

Phytoestrogens

Phytoestrogens are plant-derived compounds found in a wide variety of foods, most notably soy. Isoflavones, a class of phytoestrogens abundantly present in soy, have been shown to exert a weak estrogenic effect and have anti-carcinogenic properties [21]. It has been suggested that soy foods, which are widely consumed in Asia where the prevalence and incidence of breast cancer is very low, may contribute to the prevention of breast cancer. A number of epidemiological studies examining the association between soy foods or isoflavone intake and risk of breast cancer have yielded promising results [22]. In fact, the major soy isoflavones bind to ERs α and β, with a preference for the latter. Therefore, they are classified as selective ER modulators, which are used in breast cancer treatment and prevention. Thus, dietary intake of soy foods containing isoflavones would be expected to reduce breast cancer risk.

One of the first authoritative meta-analysis on 18 epidemiological studies has concluded that consumption of a high soy diet is associated with a small reduction in breast cancer risk (OR 0.86; 95% CI 0.75 to 0.79) and that this reduction is slightly larger in premenopausal women (OR 0.70; 95% CI 0.58 to 0.85) [23]. However, the authors concluded that this result should be interpreted with caution because of potential exposure misclassification, confounding, and the lack of a dose response, and stated that the use of phytoestrogens as an alternative for HRT cannot be advocated due to insufficient data on efficacy and safety. These results have been confirmed in prospective studies where soy isoflavone consumption was inversely associated with risk of breast cancer (RR 0.89) and recurrence (RR 0.84) [24]. It is generally accepted that in addition to reducing the risk of breast cancer in women at high risk, dietary soy intake may also benefit women who have a diagnosis of breast cancer. Nechuta *et al* [25] reported that soy food consumption after a diagnosis of breast cancer was associated with improved treatment outcomes and lower recurrence rates. In contrast, results regarding their efficacy on menopausal symptoms and in particular on hot flushes and night sweats are less conclusive. Their ability to affect vasomotor symptoms is weak and seems to be related to concentration and dose. In 2015, an important review found that most of the current literature shows that phytoestrogens have positive effects on breast cancer incidence and prognosis, but that their efficacy on menopau-

sal symptoms is probably minimal at best [26]. Moreover, an authoritative meta-analysis and systematic review published in 2016 found that phytoestrogen supplementation was associated with modest reductions in the frequency of hot flushes and vaginal dryness but no significant reduction in night sweats [27]. Finally, a Cochrane systematic review [28] of 43 randomized controlled trials on phytoestrogens for menopausal vasomotor symptoms found no conclusive evidence that phytoestrogen supplements effectively reduce the frequency or severity of hot flushes and night sweats in peri-menopausal and postmenopausal women.

These contrasting results of a positive effect on safety (breast cancer incidence and outcome) and a negative effect on efficacy (weak effect on menopausal symptoms) are principally due to the mechanisms of action of phytoestrogens and to their concentration and dose. After consumption, phytoestrogens undergo enzymatic conversion in the gut into metabolites which include a phenolic ring that competes for binding to ERs, which results in weak estrogenic activity [29]. The amount of phytoestrogens consumed varies greatly in different countries and cultures, and the three-fold lower risk of breast cancer, as well as lower serum concentrations of estrogen, in Asian women compared with their Western counterparts may be due to consumption of dietary phytoestrogens [30, 31]. The competition between hormones and phytoestrogens for the ERs slightly stimulates estrogen pathways into the cell, which could explain the low incidence of cancer in these populations. Unfortunately, the dietary dose which affects breast cancer is too low to also control vasomotor symptoms. The effect due to phytoestrogens consumed to reduce hot flushes looks very similar to ordinary estrogenic stimulation and for this reason they are not an option in women on breast cancer endocrine therapy or at high risk of developing the disease.

SSRI and SNRI

It is hypothesized that endorphin concentrations in the hypothalamus decrease with declining estrogen production, increasing the release of norepinephrine and serotonin. This lowers the set point in the thermoregulatory nucleus and leads to inappropriate heat-loss mechanisms. In the last few years, many trials have examined the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRI) on hot flushes, and several meta-analyses have been published [32–34]. In 2006, a systematic review of 10 studies on the use of antidepressants provided evidence of efficacy but found the effects were less than for estrogen. Moreover, most of the few trials that have been published have methodological deficiencies, generalizability is limited, and adverse effects and cost may restrict the use of these inhibitors for many women [35]. SSRIs and SNRIs can reduce hot flushes by 65% and begin working within the first week [36]. However, these drugs have some side effects including, most commonly, nausea and constipation. SNRIs have also been associated with increased blood pressure and should be used with caution in women with hypertension. Finally, women with a history of breast cancer and taking tamoxifen should avoid SSRIs, which have been shown to interfere with tamoxifen metabolism due its action on CYP2D6 [37, 38]. Alternative treatments to SSRIs and SNRIs sometimes in this setting are clonidine and gabapentin [39, 40]. The first drug is an anti-hypertensive agent and may relieve hot flushes by reducing peripheral vascular reactivity, while gabapentin is used to control partial seizures in adults with epilepsy. Trial results provide evidence of efficacy, however, effects are less than for estrogen, generalizability is limited, and adverse effects and cost may restrict use for many women. Finally, these therapies do not seem to be the optimal choice for most women.

Cimicifuga racemosa

Black cohosh, also known as *Cimicifuga racemosa* or *Actaea racemosa* (family *Ranunculaceae*), is a popular herb frequently used for a variety of women's health issues [41]. Several standardized extracts of black cohosh root and rhizome are available commercially. The most common black cohosh extract (BCE) is Remifemin®, which is a 40% isopropanolic extract. Black cohosh was used initially by Native Americans for a variety of complaints. It has been widely used for more than 50 years and was recently registered in Germany as a treatment for menopausal disorders, premenstrual syndrome, dysmenorrhea and menopausal symptoms [42, 43]. It is estrogen free and does not influence hormone levels, unlike estrogens and phytoestrogens such as soy. In addition, Cimicifuga roots and rhizomes contain triterpene glycosides and although the exact mechanisms underlying the effects of black cohosh have not been fully determined, its medical effects are likely related to the presence of these compounds [44].

Despite extensive studies, the pathogenesis of vasomotor symptoms and in particular, menopausal hot flushes, remains unclear. It is believed that estrogens play a major role in the maintenance of core temperature [45], and that they, or their absence, are involved in the initiation of menopausal hot flushes. Estrogen deprivation alters the activity of neurotransmitters such as serotonin, dopamine,

β-endorphin, γ-aminobutyric acid and their receptors which regulate several human processes, principally thermoregulation [46, 47]. In this scenario, BCE act as a partial receptor agonist and restores neurotransmitter activity and consequently thermoregulation. Moreover, BCE seems to inhibit the enzyme steroid sulfatase (STS) in mammary glands. STS has a very important role in the conversion of sulfated steroids, which are biologically inactive, into biologically active unsulfated steroid hormones, which support the development and growth of several hormone-dependent neoplasms, including breast cancer [48]. This ability is particularly important in breast cancer survivors where the action of this enzyme has been shown to be 10–500-fold higher than that of aromatase [49–51]. Finally, BCE seems to also have a protective effect on bone. Analysis of bone turnover markers indicated *Cimicifuga racemosa* (CR) had beneficial effects as it stimulated osteoblast activity but inhibited osteoclast activity [52]. No estrogenic action on the uterus or vagina has been identified. The actions of BCE are shown in Figure 3.

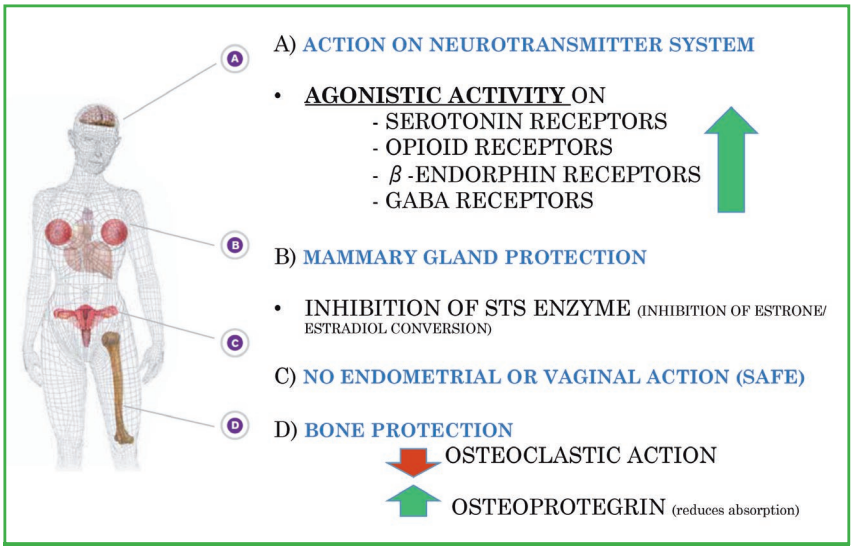

Figure 3 - Actions of isopropanolic extract of *Cimicifuga racemosa* (iCR)

CR has been extensively studied for over 40 years [53] but past reviews have not differentiated between extracts, quality and indications, resulting in inconsistent data and incorrect conclusions concerning safety and toxicity. However, the first review of herbal treatment options which differentiated by extract and indication for approximately 11,000 climacteric patients was recently published and reported consistently positive data regarding the efficacy and safety of the isopropanolic *Cimicifuga racemosa* extract (iCR) [54]. The large number of studies demonstrated a consistent Oxford level of evidence (LOE) of 1b (LOE 1a for safety), leading to a Grade of Recommendation (GR) of A. The authors conclude that the evidence is favourable and consistent regarding efficacy and suggest marketing authorization of CR products for the treatment of climacteric complaints (Fig. 4).

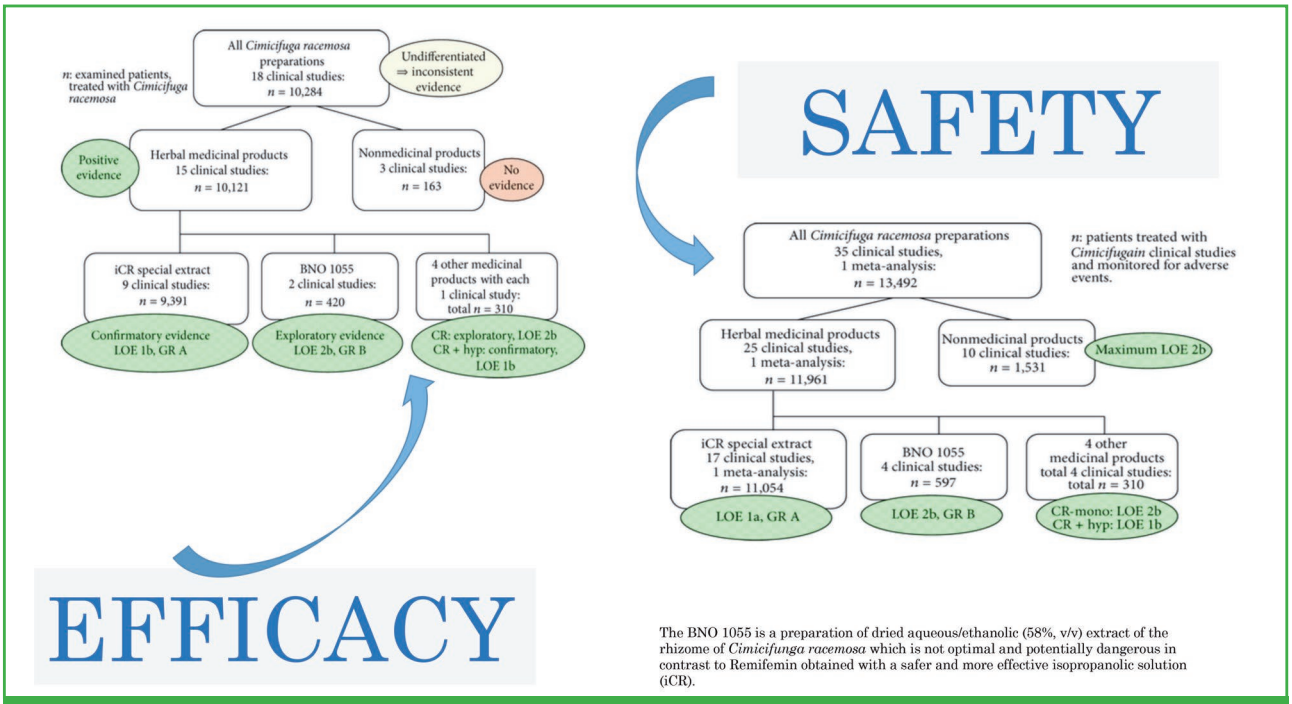

Figure 4 - Safety and efficacy

The results of the above review are supported by several studies which compared CR with other treatments used by menopausal women. First of all, iCR seems to reduce the frequency and intensity of hot flushes [55]. iCR also has a good safety–efficacy balance compared with both HRT and tibolone. A recent study showed that iCR and HRT had the same efficacy on hot flushes but that iCR did not have side effects [56]. Similar results were obtained regarding tibolone where the authors found that iCR is as good as tibolone for the treatment of mild to severe climacteric complaints, but clearly has a better safety profile, particularly regarding gynaecological adverse events [57]. Importantly, the lack of vaginal and uterine bleeding was confirmed in another study where iCR was compared to tibolone in patients with uterine fibroids [58].

The effect of iCR on breast tissue has also been analyzed. Studies have shown that iCR has no effect on the predictive and prognostic biomarkers of breast cancer risk, such as mammographic density and cellular proliferation. In an interesting study published in 2007 [59], the authors evaluated the effects of iCR on mammographic breast density and breast epithelial proliferation (Ki67 evaluation of random fine needle aspiration specimens) in 74 healthy, naturally postmenopausal women with climacteric symptoms and found that none of the women had any increase in mammographic breast density or in breast cell proliferation. These encouraging results on breast density have been confirmed in a more recent evaluation where the authors compared the effects of continuous combined hormone therapy, tibolone, black cohosh and placebo on digitized mammographic breast density in postmenopausal women [60]. Both HRT and tibolone significantly increased breast density (mean increases of 14.3%, $p<0.001$ and 2.3%, $p<0.001$, respectively) during treatment, while black cohosh and placebo did not. The difference in the increase in breast density between HRT on the one hand and tibolone, black cohosh and placebo on the other was highly significant ($p<0.0001$), and the authors concluded that black cohosh does not influence mammographic breast density. iCR has also been tested in breast cancer patients undergoing adjuvant endocrine treatment in order to evaluate its safety and its lack of effect on anticancer treatment efficacy. A pharmacoepidemiological observational retrospective cohort study investigated the influence iCR on recurrence-free survival after breast cancer [61]. The authors concluded that it is unlikely that the risk of breast cancer recurrence is increased in women who have received iCR treatment compared with women not treated with iCR. Moreover, after more than 6 years of follow-up, the rate of recurrence was 7.5% lower in a subgroup of these women who received both tamoxifen and iCR treatment than in women who received tamoxifen alone.

Finally, it has been suggested that black cohosh is hepatoxic. However, several meta-analyses of randomized controlled clinical trials have dismissed this possibility [62] and explained that hepatoxicity was caused by other compounds in the isopropanolic extract such as ethanol or methanol. In conclusion, the data suggest that iCR extract is not hepatotoxic.

Conclusion

The provision of anti-hormone therapy in breast cancer survivors is standard in early and hormone-responsive breast cancer, but several side effects of these therapies reduce the patient's quality of life and treatment compliance. Climacteric syndrome, and in particular hot flushes, are generally induced and/or aggravated by antiestrogen therapy. However, as estrogen supplementation is contraindicated in these patients, alternative pharmacological and phytoestrogen therapies are often used to control symptoms, but do have side effects or increase the risk of breast cancer recurrence. Consequently, a herbal alternative such as an isopropanolic extract of black cohosh (Remifemin®) seems to be a reasonable treatment approach in these breast cancer patients. Several recent and authoritative studies have shown that patients with moderate to severe climacteric symptoms might benefit as much from BCE as from HRT or other hormonal/non-hormonal therapy, but without the side effects.

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