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REVIEW

Weight gain in menopause: systematic review of adverse events in women treated with black cohosh

B. Naser[a], C. Castelo-Branco[b], H. Meden[c], M. J. Minkin[d], D. Rachoń[e], A.-M. Beer[f] and S. Pickartz[g]

[a]Pharmacovigilance, Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany; [b]Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine, University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [c]Swiss Institute for New Concepts and Treatments, Richterswil, Switzerland; [d]Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA; [e]Department of Clinical and Experimental Endocrinology, Medical University of Gdańsk, Gdańsk, Poland; [f]Hospital for True Naturopathy, Katholisches Klinikum Bochum, Blankenstein Hospital, Hattingen, Germany; [g]Medical Service, Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany

ABSTRACT

Weight gain is a frequent problem in perimenopausal and postmenopausal women. *Cimicifuga racemosa* (CR) is a popular treatment option for menopausal symptoms. The aim of this review was to investigate whether there is scientific evidence that CR causes weight gain. We searched our database for medically confirmed, spontaneous adverse events regarding weight gain, literature for case reports and randomized controlled trials. Thirty cases in total were spontaneously reported in 15 years. The causality was not considered certain/likely in any of the cases. A nurse (consumer) assessed the causality as possible. Only one case was published in the literature. However, no change in body fat composition was reported, and the causality seems unlikely. Of the 31 identified studies, 17 were double-blind placebo-controlled, five were double-blind reference-controlled and nine were open reference-controlled. In total, 1839 women were treated with CR for up to 12 months. Two studies reported weight gain as an adverse event; however, no significant differences in weight changes were observed between the groups. One case of weight gain (about 2 kg) was reported, but the authors did not specify in which treatment group. In conclusion, this study provides no scientific evidence that the use of *Cimicifuga racemosa* causes weight gain in menopausal women.

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Introduction

Rationale

Weight gain is very common among women in perimenopause and postmenopause. Nearly two-thirds of women aged 40–59 years are overweight with a body mass index (BMI) of >25 [1]. On average over 5 years, up to 2.1 ± 5.1 kg were gained in this age group [2]. Other studies suggested an increase of 4.0 ± 4.6 kg [3]. The evidence regarding menopause-related changes in body composition (increased fat mass, decreased lean mass) is mixed; some studies support an association and others do not [4]. Cross-sectional comparisons of premenopausal and postmenopausal women and other studies of women throughout the menopause transition have yielded evidence both for and against menopause as the mediator of changes in body composition [5]. The majority of evidence suggests that changes in weight are due to chronological aging whereas changes in body composition and fat distribution are primarily due to the cessation of ovarian function. Weight gain and increased BMI are related to anxiety, depression and low life satisfaction during menopausal transition [6,7]. Furthermore, common disorders in menopausal women can lead to weight gain: sleep disturbances induce adipogenesis, increase appetite and calory consumption and result in overweight and obesity [8]. However, menopause per se does not result in significant weight gain after adjustment for age [9]. Weight gain per se also does not appear to be affected by the hormonal changes after menopause [10].

Hormone therapy is generally accepted as the treatment of choice for the amelioration of menopausal symptoms. However, the Women's Health Initiative (WHI) Study has shown that numerous health concerns are associated with even short-term use of hormone therapy, including stroke, invasive breast cancer and venous thromboembolic disease [11–15]. Although subsequent analysis showed a reduction in cardiovascular diseases in women under the age of 60 years, a growing number of women worldwide use herbal therapies [16]. *Cimicifuga racemosa* (CR; black cohosh) with or without *Hypericum perforatum* (St. John's wort) is a successfully used, non-hormonal herbal alternative for the relief of menopausal symptoms with a positive benefit–risk profile [17–19].

Objectives

The aim of the current systematic review was to evaluate the scientific evidence regarding any association between the

CONTACT Belal Naser belal.naser@schaper-bruemmer.de Schaper & Brümmer GmbH & Co. KG, Bahnhofstraße 35, 38259 Salzgitter, Germany

intake of CR and weight gain from the most relevant sources of adverse events reporting.

Methods

Eligibility criteria and information sources

For the purpose of this review, we investigated the evidence of weight gain from the most relevant information sources used in the management of adverse events in pharmacovigilance: spontaneous reporting of adverse drug reactions (ADR); case reports in scientific literature; and clinical studies with a high Level of Evidence (LoE) according to the Oxford Center for Evidence-Based Medicine [20] (i.e. randomized controlled trials [RCTs]).

Data collection from spontaneous reporting

Cases of suspected adverse reactions from spontaneous reporting from worldwide reporting sources were included. However, only valid cases concerning weight gain under treatment with CR that were medically confirmed by a doctor or other health-care professional were included. Medical inquiries or reports from consumers as well as cases described on social media platforms were excluded.

Search in scientific literature

PubMed as well as our internal databases for pharmacovigilance and medical affairs were searched for any case reports from the literature of suspected adverse reactions concerning weight gain under treatment with CR. 'CR', 'isopropanolic extract of Cimicifuga (iCR)', 'Remifemin', 'black cohosh', 'Hypericum perforatum', 'St. John's wort' and/or 'weight gain', 'weight increased', 'increase of body weight' and 'BMI increase' were used as key words for the search strategy. No limitations for languages were set. Only valid cases with the four minimal criteria (identifiable source, identifiable patient, identifiable drug and identifiable adverse event) were reviewed.

Selection of clinical studies

Only RCTs using a preparation containing a CR extract to treat menopausal complaints were included in the analysis. CR as a mono preparation as well as combinations with other active ingredients were considered. There were no restrictions for therapy duration, CR dosage or extraction solvent. Clinical studies with a low LoE that did not include a control group were excluded. Due to treatment complexity and possible influence on body weight, studies in cancer patients were not considered.

Synthesis of results

Descriptive statistical methods were used for statistical analysis.

Cases from the three sources (RCTs and case reports from spontaneous reporting and the literature) were evaluated for the suspected drug (CR as a mono preparation or in combination with other active ingredients, such as *H. perforatum*, and regardless of the extraction solvent). The dose, duration of treatment, source, frequency, seriousness and outcome of ADRs were also considered. The causality was assessed in accordance with the World Health Organization (WHO) criteria [21]. In addition, the case documentation was evaluated regarding the quality of the available data.

Results

Spontaneous reporting

In the period covered by our database (2005–2020) about 17.4 million patients were treated with iCR as mono preparation worldwide. During the same time frame, 30 case reports of weight gain were found in the spontaneous reporting system (Table 1). Eighteen women were treated with a CR mono preparation and 12 with a combination of CR and *H. perforatum*. Twenty-four cases were reported by pharmacists and only two by physicians. Thirteen patients

Table 1. Number of cases of weight gain from the spontaneous reporting system for the time period 2005–2020.

Characteristics	*Total*
Substance	
Cimicifuga racemosa	18
Cimicifuga racemosa and *Hypericum perforatum*	12
Qualification	
Pharmacist	24
Physician	2
Other health-care professional	2
Other	2
Age at adverse event occurrence (years)	
40–49	6
50–59	7
>60	1
Unknown	16
Duration of therapy (weeks)	
24	1
12	2
8	2
4	3
2	1
1	2
Unknown	19
Daily dose	
2 × 1 tablet	1
4 × 2 tablets	2
Unknown	27
Outcome as per reporter	
Not recovered/not resolved	1
Recovered/resolved	6
Unknown	23
Changes in medication	
Dose not changed	1
Dose reduced	1
Drug withdrawn	9
Drug withdrawn due to adverse event	2
Unknown	17
Causality assessment by the reporter	
Not related	2
Not reported	21
Possible	2
Suspected	1
Unassessable/unclassifiable	3
Unlikely/remote	1

Table provides characteristics of the suspected drug, qualification of the reporters, age of patients, treatment details, the outcome and causality assessment of the adverse event as per reporter.

Table 2. Overview of weight gain in randomized controlled trials (RCTs).

Study	Design	Extract	Total	CR	Control	Duration	Results
Pkhaladze et al., 2020 [38]	Double-blind placebo-controlled study	eCR	198	148	50	12 weeks	No cases of weight gain were observed in either group
Mehrpooya et al., 2018 [39]	Double-blind reference-controlled study	eCR	80	40	40	8 weeks	None reported
Tanmahasamut et al., 2015 [40]	Double-blind placebo-controlled study	eCR	54	27	27	12 weeks	Adverse events were well tolerated and self-limited, requiring neither treatment nor study termination
Zhang et al., 2015 [41]	Reference-controlled study	iCR	98	49	49	12 weeks	None reported
Jiang et al., 2015 [42]	Double-blind placebo-controlled study	iCR	48	24	24	6 months	Safety measures did not yield any adverse event assigned to CR
Chen et al., 2014 [43]	Double-blind reference-controlled study	iCR	116	56	60	12 weeks	None reported
Mohammad-Alizadeh-Charandabi et al., 2013 [44]	Double-blind placebo-controlled study	eCR	84	42	42	4–8 weeks	No side-effects were reported in either group
Chen 2013 [25]	Reference-controlled study	iCR	120	60	60	12 weeks	Weight gain was common in the CR group when compared with Livial group; the difference had no statistical significance
Huang 2013 [45]	Reference-controlled study	iCR	172	86	86	12 weeks	None reported
Huang et al., 2013 [46]	Reference-controlled study	iCR	120	60	60	8 weeks	No significant changes existed in tested parameters before and after treatment
Schellenberg et al., 2012 [47]	Double-blind placebo-controlled study	eCR	180	120	60	12 weeks	As regards safety, no serious adverse events and 21 non-serious adverse events occurred in 20 patients. Weight gain was not reported in any of the groups
Sun et al., 2012 [48]	Double-blind reference-controlled study	iCR	70	40	30	12 weeks	There were no adverse effects during treatment
Hong et al., 2012 [49]	Double-blind placebo-controlled study	eCR	100	50	50	12 weeks	No significant change in weight between both groups
Li et al., 2011 [50]	Double-blind placebo-controlled study	iCR	89	45	44	12 weeks	None reported
Bebenek et al., 2010 [51]	Reference-controlled study	eCR	128	42	86	10 weeks	Total and abdominal body fat did not significantly change in the exercise groups. Accordingly, no differences concerning changes in these parameters were observed between the groups. Lean body mass significantly increased in the exercise groups (1.2%) whereas only slightly positive changes were determined in the exercise and CR supplementation. However, no between-group differences were assessed for lean body mass
Geller et al., 2009 [52]	Double-blind placebo-controlled study	eCR	89	21	68	12 months	There were no significant differences between groups reported for any other side-effects
Amsterdam et al., 2009 [53]	Double-blind placebo-controlled study	Unknown	28	15	13	12 weeks	None reported
Oktem et al., 2007 [54]	Reference-controlled study	eCR	120	60	60	6 months	No cases of weight gain were observed in either group
Chung et al., 2007 [27]	Double-blind placebo-controlled study	eCR	77	42	35	12 weeks	One patient reported 2-kg weight gain, but the authors did not specify whether the case occurred in the treatment or placebo group
Wuttke et al., 2006 and 2003 [55,56]	Double-blind placebo-controlled study	eCR	62	20	42	12 weeks	Incidence of non-serious adverse events of mild to moderate severity was comparable in the treatment groups. No cases of weight gain occurred
Newton et al., 2006 [57]	Double-blind placebo-controlled study	eCR	351	80	271	12 months	There were no statistically significant differences among any of the four groups and the placebo group in the number of women with adverse events
Bai et al., 2006 [24]	Double-blind reference-controlled study	iCR	244	122	122	12 weeks	One possible drug-related adverse event, weight increase, occurred in the tibolone group during treatment. The intra-group comparison of mean body weight demonstrates a clinically irrelevant increase at week 12 as compared to baseline and week 4 ($p < 0.01$). The inter-group comparison shows that body weight in the tibolone group at

(*continued*)

Table 2. Continued.

Study	Design	Extract	Total	CR	Control	Duration	Results
							week 12 was significantly higher than in the iCR group ($p = 0.027$)
Uebelhack et al., 2006 [58]	Double-blind placebo-controlled study	iCR	301	151	150	16 weeks	With regard to age, body height, body weight and body mass index, no significant mean group difference was observed
Osmers et al., 2005 [26]	Double-blind placebo-controlled study	iCR	286	153	133	12 weeks	This study found a median increase of the body weight of +0.7 kg in the placebo group during the 3 months, reflecting the spontaneous change of this parameter over time during the menopausal transition. This is in contrast to +0.3 kg in the CR group. Moreover, the change in body weight ranged from −7.1 kg to 12.0 kg with the maximum increase in the placebo group. There was no case of an adverse drug reaction 'weight increase' reported. Thus, in this study CR did not cause an increase in body weight
Frei-Kleiner et al., 2005 [59]	Double-blind placebo-controlled study	eCR	122	81	41	12 weeks	There were no differences between the CR group and the placebo group regarding adverse events or other safety assessments. Intensity and frequency – 17/83 patients (20%) in the CR group and 10/44 patients (23%) in the placebo group – of adverse events were comparable in the two groups
Nappi et al., 2005 [60]	Reference-controlled study	iCR	64	32	32	12 weeks	None reported
Lee et al., 2002 [61]	Double-blind placebo-controlled study	Unknown	74	32	42	12 weeks	None reported
Liske et al., 2002 [62]	Double-blind reference-controlled study	iCR	152	76	76	12–24 weeks	None reported
Lehmann-Willenbrock and Riedel, 1988 [63]	Reference-controlled study	iCR	60	15	45	6 months	None reported
Stoll, 1987 [23]	Double-blind placebo-controlled study	iCR	80	30	50	12 weeks	Two patients from the placebo group terminated the study because of severe headaches and weight gain. One woman in the estrogen group complained about weight gain. In the CR group, three patients experienced minor weight gain. However, they continued the treatment. The causality with CR was assessed as 'unlikely' by the investigator
Warnecke, 1985 [64]	Reference-controlled study	eCR	60	20	40	14 weeks	None reported

CR, *Cimicifuga racemosa*; eCR, ethanolic *Cimicifuga racemosa* extract; iCR, isopropanolic *Cimicifuga racemosa* extract.

were between 40 and 59 years old, and in 16 cases the age was unknown when the adverse event occurred. Treatment duration was between 1 and 24 weeks; in 19 cases, the duration was not reported. For the majority of the cases ($n = 27$), the daily dose was unknown.

In six cases the outcome was reported as resolved. The outcome was not reported or was unknown for the majority of cases ($n = 23$). In 11 cases the drug was withdrawn, and in 17 cases the consequences of the adverse events on drug intake (e.g. dose decrease) were unknown. For 21 cases, no causality assessment was performed by the reporter. In one case the pharmacist regarded the causality as suspected, and in two further cases the causality was assessed as possible (in one case, the patient was a nurse who consumed the preparation herself).

Case reports in scientific literature

Only one case report was found in the literature [22]. A 44-year-old woman presented with a 1-week history of remarkable weight gain of 6.5 kg, headaches and abdominal discomfort. Four weeks before presentation, a gynecologist prescribed a dry extract of CR at a daily dose of 5 mg. The patient took two doses of 1 g acetaminophen because of headaches and reported being a vegetarian and consuming a minimal amount of alcohol.

Because of the difference in leg circumference between the two limbs due to lower leg edema, weight gain and the obvious coagulation activation, further diagnostic procedures were performed. There was remarkable fluid accumulation in the subcutaneous tissue. CR was discontinued. Complete resolution of the symptoms occurred within 1 week. No further case reports about similar reactions during treatment with CR were found in the literature.

Characteristics of the selected studies

Overall, 31 studies with 3827 patients were identified; 1839 patients were in the CR group and 1988 in the control group. In 17 RCTs, patients were randomized to a preparation containing: CR alone ($n = 2223$), CR in combination

with another herbal preparation ($n = 1081$) or placebo ($n = 1142$). In the other five double-blind RCTs, 334 patients were treated with CR and 328 with the reference drug. Furthermore, nine reference-controlled studies with 942 patients were found. In these studies, 424 were allocated to CR and 518 to therapy with other active drugs. An overview of the selected studies is presented in Table 2.

Adverse event reporting in clinical studies

Stoll [23] reported two patients in the placebo group who terminated the study because of strong headaches and weight gain. One woman in the estrogen group and three in the CR group experienced minor weight gain. However, therapy was not terminated and the causality with CR was assessed as unlikely. Bai et al. [24] mentioned one case of weight increase in the tibolone group. The causality was assessed as possibly drug related. No cases of weight increase occurred in the CR group.

Another study [25] noted that weight gain was common in both groups; however, no significant group differences were seen. A causality with the study medication was not reported. Osmers et al. [26] found no case of the ADR 'weight increase' in either trial groups, but they reported an increase in the mean/median body weight, which was higher in the placebo group than in the CR group (Table 2). Chung et al. [27] reported a weight gain of 2 kg in one case but did not specify the treatment group (CR or placebo). In all other studies, no adverse events referring to weight gain occurred or were notified.

Synthesis of results

An overview of the causality assessment for all cases of weight gain from all sources (spontaneous reporting, scientific literature and clinical studies) is presented in Table 3.

Discussion

Weight gain is common among women in perimenopause and postmenopause. Nearly two-thirds of women aged 40–59 years are overweight (BMI >25) [1]. Recently, during the COVID-19 pandemic lockdown, a greater percentage of women gained weight compared to men [28]. Among other factors, weight gain increases the risks for many diseases. A recent study found a positive association between BMI and (estrogen receptor-positive) breast cancer risk [15]. One in 50 women aged 50 years and of average weight using a 5-year continuous combined estrogen plus progestin therapy will be diagnosed with breast cancer within 20 years. During years 5–14 of menopausal hormone therapy use, the risk ratios hardly varied for any personal characteristics except BMI. Risk increased with increasing BMI among never users, but not among current users. On the other hand, many disorders (e.g. sleep disturbances, depressive mood) that are common among perimenopausal and postmenopausal women can lead to weight gain [8,29]. Therefore, in most individual cases it remains unclear whether perimenopausal and postmenopausal weight gain is the result of aging or underlying disorders, or possibly medication-induced.

To assess the latter, we evaluated the scientific evidence regarding any association between the intake of CR and weight gain and did not find any causal relationship. A few cases of weight gain were reported spontaneously, but none of them provided sufficient evidence that CR had had an impact on body weight. For the majority of the cases reported by physicians or pharmacists, no scientific assessment of causality was provided by the reporter. In few cases, the outcome was reported as resolved/resolving, and in the majority of reports the outcome was not reported or known. Using the WHO criteria for causality assessment, no evidence was found that CR induces weight gain. In the same period (2005–2020), about 17.4 million patients were treated with the iCR as a mono preparation worldwide. The literature search revealed only one case report about coagulation activation with subsequent weight gain [22], but the causality was regarded as unlikely, and no further cases regarding coagulation activation under CR therapy were found in the literature. RCTs with black cohosh showed no influence on coagulation parameters [30]. Numerous RCTs were conducted with CR (Table 2), but no evidence regarding weight gain was reported.

Our findings concur with the general development of body weight in women over 50 years of age. About 60% of women in menopause are overweight with a BMI >25 [1]. Weight gain was not related to change in menopausal status or to any lifestyle factors measured [2]. Menopause per se does not result in significant weight gain [9]. A recent review concluded that changes in fat mass quantity between premenopausal and postmenopausal women were mainly attributed to age; menopause had no significant additional

Table 3. Causality assessment regarding weight gain for identified cases (*n*) from different sources of reporting.

	Source and number of cases (n)			
			RCT	
Causality assessment	*Spontaneous reporting*	*Literature case reports*	*CR*	*Control group*
Certain	0	0	0	0
Probable	0	0	0	0
Possible/suspected	3	0	0	1
Unlikely	1	1	3	3
Unrelated	2	0	0	0
Unassessable	3	0	0	0
Not reported/not available	21	0	0	0

CR, *Cimicifuga racemosa*; RCT, randomized controlled trial.

influence [31]. However, an increase in measures of central fat and a decrease in total leg fat percentage indicated a possible change in fat mass distribution after menopause.

The symptoms described in the case report from the literature [22] occurred 3 weeks after starting therapy with CR and resolved 1 week after withdrawal of it. Furthermore, the pathological laboratory values normalized 2–4 weeks after discontinuing treatment. At first glance, a relationship between the intake of CR and the reported side-effects seems to be possible. This assessment, however, has many limitations. The patient had been on a journey abroad shortly before the occurrence of the side-effects. This information was provided in the initial report, but not disclosed in the published case report. Thrombosis after a long flight or driving is a well-known event. Additionally, the patient had been taking pyridostigmine for many years and had been treated with acetaminophen when clinical symptoms occurred. She also sporadically used acetaminophen in a dose of up to 2 g per day; this may explain the slight elevation of transaminases. In summary, a causal relationship between the occurrence of the symptoms and the administration of CR seems to be unlikely. The female patient might have suffered from a thromboembolic event, and the observed weight gain was more likely a symptom of the thromboembolic event and not a change in body composition.

As regards clinical studies, 22 RCTs with a high LoE were included in our analysis. Seventeen studies were with placebo and five studies with other reference drugs. In total, 2885 patients were included. Thereof, 1415 patients were treated with an isopropanolic, an ethanolic or an unspecified CR extract; 1470 patients were allocated to control groups. Only a few single cases of weight gain were reported; however, no significant differences were found between the treatment groups. The causality was regarded as unlikely.

Experimental studies

The results of our analyses of RCTs agree with findings from experimental studies. Sun et al. [32] investigated the long-term effect of iCR on glucose and lipid metabolism in a rat model of menopause. Adult female Sprague-Dawley rats were sham operated (SHAM), ovariectomized (OVX), OVX and treated with estradiol valerate (OVX + E) or OVX and treated with iCR (OVX + iCR). Body weight, body composition and blood glucose levels of the animals were monitored. After 3 months of treatment, OVX + iCR and OVX + E rats exhibited a significant decrease in body weight gain, body and abdominal fat mass, serum triglyceride levels, hepatic fat accumulation and adipocyte hypertrophy compared with OVX rats.

In a further study [33], CR and some of its constituents were investigated in vitro for their effects on AMP-activated protein kinase (AMPK) compared to metformin in HepaRG cells. CR and its constituents activated AMPK to the same extent as metformin. In mice, CR significantly decreased the average daily and cumulative weight gain [33]. The results of this study demonstrate instead that CR may reduce body weight.

A recent study showed that an active ingredient of CR (23-epi-26-deoxyactein) effectively ameliorated obesity in high-fat, diet-fed mice. It is suggested that this compound may have substantial anti-obesity properties and may also improve menopausal and genetic obesity as well as associated metabolic syndrome [34].

Rachoń et al. [35] evaluated the effects of CR consumption on body weight gain, intra-abdominal fat accumulation, plasma leptin, lipids and glucose tolerance and compared them with the effects of 17β-estradiol in vivo. Female Sprague-Dawley rats were ovariectomized and fed soy-free chow with the addition of estradiol-3 benzoate (E2B) or CR. In OVX rats, CR consumption not only decreased enhanced pituitary LH secretion but also attenuated body weight gain and intra-abdominal fat accumulation.

From the clinical perspective, a review of the potential effects of traditional Chinese medicine reported that CR may be beneficial for weight loss [36].

Our results are also in agreement with findings from a retrospective cohort study. In this observational study, women over the age of 40 years were treated with either menopausal hormone therapy ($n = 142$) or CR ($n = 32$). In both groups, metabolic serum parameters (lipids, glucose, insulin) and body weight did not change over the follow-up period of 12 months [37].

Limitations

This systematic review has limitations related to the articles from which data were extracted. We included data from different sources and quality of data. Particularly, cases from spontaneous reporting with low quality (LoE 5) can be seen critically. However, such limitations are a general problem and are well known for spontaneous adverse event reporting in pharmacovigilance.

The variety of designs and methodologies used in the studies is another limitation. While it may have been tempting to include only RCTs in the analysis, such an approach would have been critically incomplete from the perspective of good pharmacovigilance practice. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects, particularly for the signal detection of rare adverse reactions.

Furthermore, details about safety data from clinical study reports were only available for those studies that were conducted with iCR extract. Other information was limited to the available data that had been published.

Another limitation was the variety of doses and extraction procedures used for the products in the studies included in this analysis. For these studies, a second analysis that addresses the doses and extracts most regularly used in clinical practice is needed to minimize the possible effect of the dosage and extract differences. Due to the limited information available in this scientific area, we forwent this analysis. Based on our data, however, we can state that the different doses/extraction procedures for the products analyzed in the present systematic review do not appear to influence the findings.

Conclusion

Our study provides no scientific evidence from spontaneous reporting, case reports in the literature or randomized controlled clinical trials that black cohosh therapy in perimenopausal and postmenopausal women causes weight gain.

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ORCID

B. Naser http://orcid.org/0000-0003-0216-8395
C. Castelo-Branco http://orcid.org/0000-0002-9860-8318
M. J. Minkin http://orcid.org/0000-0001-9594-0182
D. Rachoń http://orcid.org/0000-0002-8300-7026
S. Pickartz http://orcid.org/0000-0002-6850-2491

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