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Black cohosh improves objective sleep in postmenopausal women with sleep disturbance

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Key words: BLACK COHOSH, POSTMENOPAUSAL, POLYSOMNOGRAPHY, SLEEP

ABSTRACT

Objective Sleep problems are prominent after menopause. The aim of our study was to look into the effect of black cohosh on both objective and subjective sleep in early postmenopausal women with sleep complaints.

Methods We performed a randomized, double-blind and placebo-controlled research during a 6-month period. Forty-eight postmenopausal women aged 45–60 years with sleep disturbance were enrolled and received daily administration of either black cohosh or placebo. Polysomnography and the Pittsburg Sleep Quality Index (PSQI) were performed at the initiation and termination of the study, as well as the Menopause-specific Quality of Life questionnaire and estradiol and follicle stimulating hormone tests. Liver and renal functions and breast and pelvic ultrasound were set as safety measures, carried out every 3 months.

Results Seventy-six women were interviewed, of whom 42 women completed the whole trial. Compared with placebo, black cohosh treatment led to significant polysomnographic changes, including increased sleep efficiency and decreased wake after sleep onset (WASO) duration, and tended to improve PSQI with a medium effect size. On average, 15.8% of WASO duration was reduced in the black cohosh group. Vasomotor and physical domains of life quality were improved compared with placebo. Safety measures did not yield any adverse event assigned to black cohosh.

Conclusions In early postmenopausal women with a major sleep complaint, black cohosh effectively improved sleep and might be a safe measure in managing menopausal sleep disturbance.

INTRODUCTION

Menopause is associated with a series of psycho-physiological changes, which persist from the menopausal transition for years in different severities. Besides vasomotor symptoms (VMS), sleep disturbance is another marker of menopause. Sleep is more likely to be disturbed in women than men at all ages and menopause brings about 3.4 times the risk of sleep disorders in postmenopausal women compared with premenopausal women1. A large-scale study proved that sleep problems afflicted 2.5% of midlife women aged 50–64 years, 15% of which were suffering from even severe sleep disturbance2. Sleep problems can vary with menopausal status. Early postmenopausal women experience lower sleep efficiency (SE) and spend more time awake in bed than perimenopausal women3. Compared to early postmenopausal women, late postmenopausal women have a decreased proportion of slow-wave sleep (SWS) and increased arousals4. It is noteworthy that age-related sleep changes become prominent in late postmenopause, when physical aging is the principal concern5,6. As sleep disturbance at menopause is multifactorial, primary menopausal insomnia should be defined as insomnia associated with menopause and cannot be explained by primary sleep disorders or other determinants7,8. Along with other climacteric symptoms, self-reported sleep quality could be improved by hormone therapy, although its effects on objectively measured sleep are not always consistent9–12. However, the duration, dose and indication of hormone
therapy have been strictly limited by its potential risks for future heart attack, stroke and breast cancer. The demand for safe therapies to alleviate climacteric symptoms is increasing, leading gynecologists and researchers to focus on alternative medications for menopausal sleep problems.

Black cohosh (Cimicifuga racemosa, BC) is the most prevalent alternative herbal remedy to hormone therapy in Europe for climacteric complaints that benefit from its non-estrogenic behavior, and its effect on overall climacteric symptoms has been confirmed for decades. More than 50 components have been derived from the crude drug and the key constituents of BC are triterpene glycosides, phenolic acids and N-o-methylserotonin. The active compounds of BC mostly behave as neurotransmitters like 5-hydroxytryptamine (5-HT) and γ-aminobutyric acid (GABA). Serotoninergic and GABAergic activities in relevant brain regions including the hypothalamus are essential in regulation of the normal sleep architecture, which is disrupted by the ovarian insufficiency in menopausal women. Three-month administration of BC could improve self-reported sleep quality in postmenopausal women with or without menopausal complaints, measured by daily diary and the subscore of the Menopause Rating Scale (MRS) or the Kupperman Menopause Index (KMI). To date, however, its effect on sleep architecture and nocturnal awakenings is still not known because of a lack of data on objective sleep measurement. Moreover, menopausal sleep disturbance is not the central issue of these studies.

An objective technique is provided by polysomnography (PSG), which is of great significance to both clinical examination and laboratory research, to capture features of sleep architecture dynamically and non-intrusively. Menopausal insomnia correlates with reduced rapid eye movement (REM) sleep, increasing arousals, low SE but long duration of SWS (stages 3 and 4) in PSG recordings. Very recently, PSG has been effectively applied to estimate the effects of acupuncture, therapeutic massage, yoga, physical therapy and phytoestrogen on menopausal women’s sleep problems. Here we aim to investigate the effect of BC in the management of menopausal sleep disturbance through PSG as well as a sleep questionnaire.

BC has the superiority of safety to other hormonal therapies and has no clear contraindication in the current literature. There is still controversy regarding liver metabolism, and the administration of BC should be given cautiously with regard to potential hepatotoxicity. In our study, liver and renal functions were monitored for vital effects of drug metabolism. In regard to gynecologic organs, a 6-month treatment period of BC did not affect mammographic density in postmenopausal women, nor was there any increase in endometrial thickness during a 1-year treatment. In Chinese menopausal women, a recent controlled trial for tolerability showed that 20.7% of the participants experienced breast pain or enlargement during a 3-month administration of BC. Although this could not be causally interpreted, we examined the major target organs of estrogen as cautionary measures in the present study to further explore BC’s safety.

METHODS

Participants

Seventy-six postmenopausal women with a chief complaint of sleep disturbance for at least 1 month were interviewed for further evaluation (Figure 1). All participants were collected in the 1st Affiliated Hospital of Harbin Medical University. Sleep disturbance in this study was defined as follows: having difficulty in initiating or maintaining sleep or experiencing non-restorative sleep for at least 1 month, without a history of insomnia prior to the menopausal transition (STRAW + stages -2 and -1).

The inclusion criteria were as follows: age between 45 and 60 years old; body mass index (BMI) ≤ 30 kg/m²; 1 year ≤ final menstrual period (FMP) ≤ 5 years (STRAW: stages +1b and +1c); serum follicle stimulating hormone (FSH) > 30.0 IU/L. The exclusion criteria consisted of the following conditions: induced menopause, i.e. bilateral oophorectomy and/or hysterectomy, artificial termination of ovarian function by chemotherapy and/or radiotherapy; poorly controlled clinical diseases, i.e. diabetes, systemic arterial hypertension, hepatic and/or nephritic dysfunction; history of thromboembolic events; historic and/or present clear psychiatric disorders such as schizophrenia, depression and anxiety according to DSM-IV-TR; self-reported and/or PSG-confirmed sleep-related respiratory disorders (i.e. sleep apnea, obstructive snoring) and movement disorders (i.e. restless leg syndrome); night shift work or irregular sleeping habit; systemic use of medications containing opioids, antiepileptics, anxiolytics, hypnotics and sedatives, antidepressants, and antihistamines within 3 months; use of estrogen, progestogen, androgen, or any other therapy against menopausal syndrome such as plant estrogen and Chinese medicine within 3 months; participation in another clinical trial within 3 months; alcohol consumption exceeding seven drinks per week or three per day (containing 14 g alcohol per drink); history of drug or substance abuse.

Forty-eight women who met the criteria agreed to participate after informed consent was obtained. The research protocol had received the approval of the Medical Ethics Committee of Harbin Medical University (HMU Res./Art. Ethics No. 201449) before the first participant was recruited.

Study design

This study was designed as a double-blind, randomized, placebo-controlled clinical trial (Figure 1). The candidates received: clinical interview; physical, medical and socioeconomic data, i.e. age, BMI, FMP, blood pressure, medical history, medication use, educational attainment (junior high school or less, senior high school, college or beyond), financial strain (difficulty in paying for living basics: not very, somewhat, very difficult); indispensable laboratory tests: fasting blood glucose, serum FSH and estradiol levels, blood coagulation function, blood tests of liver and renal function; breast
and pelvic ultrasound. Then, the eligible candidates received the baseline PSG, after which those having sleep-related respiratory disorders and/or movement disorders were excluded. PSG was performed on two consecutive nights, of which the first night was for adaptation and the second night for data analysis. Women were asked to keep a healthy and regular sleep hygiene for at least 1 week before the baseline recording nights and to maintain the sleep schedule throughout the whole trial. PSG was recorded from lights off to lights on. After breakfast, women completed the Pittsburgh Sleep Quality Index (PSQI) questionnaire, as well as the Menopause-specific Quality of Life (MENQOL) questionnaire.

Participants randomly received a standardized isopropanolic BC extract, containing extract of 20 mg crude drug per tablet (about 2.5 mg extract), or placebo. The randomization was conducted by a third party who was not involved in the rest of the study. BC tablets and placebo were prepared in uniform bottles with unique numbers. Both the researchers and the participants were blind to the intervention until the statistical analysis was finished. The intervention lasted for 6 months, when both BC and placebo were orally administrated twice a day at fixed times after meals, one tablet each time. Adverse events were reported. The medication was supplied at the end of each month when the remaining tablets were returned to the researcher. Medication compliance was estimated at the end of the whole trial, by counting returned tablets at each visit. Tablet count was expressed as the percentage of taken tablets over total tablets and 100% represents perfect compliance. Participants who completed the whole trial were re-examined as follows: (1) PSG; (2) questionnaires: MENQOL, PSQI; (3) laboratory tests: serum FSH and estradiol levels, blood tests of liver and renal function; (4) breast and pelvic ultrasound. Examinations (2), (3) and (4) were performed in the morning after the second PSG recording night. Liver and renal function tests and ultrasound were also performed in the middle of the intervention for safety concerns.

Sleep was objectively assessed by PSG (Stellate Harmonie, Natus Medical Incorporated) and subjectively by PSQI. Sleep
Electroencephalography (EEG) recordings were performed by a trained technician and analyzed by two EEG specialists, who were unaware of the intervention of individuals. Sleep stages were visually scored as wakefulness, stage 1, stage 2, stages 3 and 4 (SWS), and REM sleep. Polysomnographic parameters of total sleep time (TST), sleep stage percentages, sleep latency (SL), SE, REM sleep latency (RSL), duration of wake time after sleep onset (WASO), and arousals (alpha activity, 8–13 Hz, for at least 15 s per epoch) were also obtained. PSQI is a self-assessed questionnaire and consists of 24 items, evaluating sleep quality and disturbance. The total score ranges from 0 to 21 and higher scores indicate worse subjective sleep quality and disturbance. The total score ranges from 0 to 21 and higher scores indicate worse subjective sleep quality and disturbance.

Statistical analysis

SPSS v19.0 was used for data analysis. The χ² test, Fisher’s exact test, unpaired Student’s t test and Mann–Whitney U test were used for inter-group comparison while Fisher’s exact test, paired Student’s t test and Wilcoxon rank test were adopted for intra-group comparison. In addition, analysis of covariance (ANCOVA) was also used for the analysis of MENQOL scores. For categorical data analysis, Cramer’s V was measured for effect size. Pearson’s correlation coefficient, r, was chosen to measure the effect size in the means comparisons and non-parameter tests according to Field. When r is 0.10, 0.30 or 0.50, it is equivalent to a small, medium or large experimental effect, respectively. The correlation between estradiol and sleep measures was assessed by the means of linear correlation or Spearman’s rank correlation. Spearman’s rank correlation was also performed to confirm whether MENQOL vasomotor correlated with WASO or arousals. A value of p < 0.05 was considered to be statistically significant.

RESULTS

Twenty women in the BC group and 22 in the placebo group completed the whole trial and were included in the final statistical analysis (Figure 1). No one dropped out for the emergence of adverse events, disease onset or aggravation or sleep respiratory and movement disorders. The treatment compliance in this trial was good (BC group 99.0%, placebo group 98.2%).

Demographic and clinical data at baseline

The demographic and clinical characteristics are presented in Table 1. There was no significant difference between the two groups at baseline in age, BMI, FSH and estradiol levels, PSQI, MENQOL scores and polysomnographic parameters. The two groups were also similar in educational attainment (p = 0.375) and financial strain (p = 0.737). According to MENQOL, 59.5% of the women had VMS (MENQOL vasomotor > 1) and their prevalence was similar in the two groups at baseline (60.0% and 59.1%, p = 0.601). PSG data showed that 76.2% of the women had low SE (< 85%). The percentages of women with low SE were similar in the two groups (70.0% and 81.0%, p = 0.477, Figure 2). Estradiol level did not significantly correlate with PSQI or any polysomnographic parameters. Nor was any correlation found between MENQOL vasomotor and WASO or arousals.

Clinical and polysomnographic assessment after treatment

It seemed that BC could not improve VMS (p = 0.267, Table 2). Concerning the women having VMS at baseline, however, the MENQOL vasomotor score was significantly lower in the BC group than that in the placebo group (p = 0.480, p = 0.015). In spite of a decline of MENQOL psychosocial score in both groups at baseline in age, BMI, FSH and estradiol levels, PSQI, MENQOL scores and polysomnographic parameters. The two groups were also similar in educational attainment (p = 0.375) and financial strain (p = 0.737). According to MENQOL, 59.5% of the women had VMS (MENQOL vasomotor > 1) and their prevalence was similar in the two groups at baseline (60.0% and 59.1%, p = 0.601). PSG data showed that 76.2% of the women had low SE (< 85%). The percentages of women with low SE were similar in the two groups (70.0% and 81.0%, p = 0.477, Figure 2). Estradiol level did not significantly correlate with PSQI or any polysomnographic parameters. Nor was any correlation found between MENQOL vasomotor and WASO or arousals.

Table 1 Baseline characteristics of demographic and clinical data expressed as mean (standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>Black cohosh (n = 20)</th>
<th>Placebo (n = 22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.2 (5.5)</td>
<td>51.6 (4.9)</td>
<td>0.706</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.7 (3.7)</td>
<td>25.0 (3.0)</td>
<td>0.217</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>65.7 (10.9)</td>
<td>69.4 (13.7)</td>
<td>0.668</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>14.9 (2.9)</td>
<td>14.0 (3.9)</td>
<td>0.268</td>
</tr>
<tr>
<td>MENQOL vasomotor (1–8)</td>
<td>3.5 (2.4)</td>
<td>3.7 (2.6)</td>
<td>0.754</td>
</tr>
<tr>
<td>MENQOL psychosocial (1–8)</td>
<td>4.8 (1.9)</td>
<td>4.7 (2.0)</td>
<td>0.574</td>
</tr>
<tr>
<td>MENQOL physical (1–8)</td>
<td>3.9 (0.9)</td>
<td>4.5 (1.17)</td>
<td>0.064</td>
</tr>
<tr>
<td>MENQOL sexual (1–8)</td>
<td>4.9 (2.2)</td>
<td>4.8 (1.9)</td>
<td>0.846</td>
</tr>
<tr>
<td>PSQI (0–21)</td>
<td>12.0 (3.6)</td>
<td>11.9 (3.2)</td>
<td>0.939</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>330.1 (39.8)</td>
<td>323.0 (49.9)</td>
<td>0.716</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>26.45 (17.2)</td>
<td>33.7 (20.5)</td>
<td>0.226</td>
</tr>
<tr>
<td>REM sleep latency (min)</td>
<td>131.4 (51.8)</td>
<td>137.5 (46.3)</td>
<td>0.689</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>78.8 (8.4)</td>
<td>76.6 (8.2)</td>
<td>0.402</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>15.9 (6.5)</td>
<td>19.1 (6.4)</td>
<td>0.124</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>49.3 (9.1)</td>
<td>45.8 (8.0)</td>
<td>0.187</td>
</tr>
<tr>
<td>Stages 3 and 4 (%)</td>
<td>18.5 (6.3)</td>
<td>20.8 (5.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>16.3 (5.1)</td>
<td>14.4 (4.2)</td>
<td>0.199</td>
</tr>
<tr>
<td>Wake after sleep onset (min)</td>
<td>60.6 (30.0)</td>
<td>70.1 (33.1)</td>
<td>0.335</td>
</tr>
<tr>
<td>Arousals (times)</td>
<td>121.6 (38.5)</td>
<td>113.5 (44.1)</td>
<td>0.529</td>
</tr>
</tbody>
</table>

FSH, follicle stimulating hormone; MENQOL, Menopause-specific Quality of Life; PSQI, Pittsburg Sleep Quality Index; REM, rapid eye movement.
Figure 2  Percentage of participants with sleep efficiency (SE) < 85% before and after intervention in the two groups. **, *p = 0.003 compared with baseline; *, p = 0.011 compared with placebo group. BC, black cohosh

the BC group (p = 0.015) and the placebo group (p = 0.019), no difference between groups was observed (p = 0.487, Table 2). For the physical symptom evaluation, the MENQOL physical score decreased in both groups (p = 0.004, 0.023) and it remained significant in the inter-group analysis (r = 0.316, p = 0.041, Table 2). Considering the p value of the MENQOL physical score at baseline (p = 0.064, Table 1), ANCOVA was performed to adjust for the baseline scores of this domain, whereas a small effect size was observed (r = 0.161). No change of MENQOL sexual score was detected in any analysis intra- or inter-group.

Table 2  Clinical data after intervention expressed as mean (standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>Black cohosh (n = 20)</th>
<th>Placebo (n = 22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (IU/l)</td>
<td>66.5 (10.5)</td>
<td>69.4 (14.4)</td>
<td>0.451</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>13.9 (3.1)</td>
<td>14.1 (2.6)</td>
<td>0.881</td>
</tr>
<tr>
<td>MENQOL vasomotor (1–8)</td>
<td>2.9 (1.9)</td>
<td>3.6 (2.5)</td>
<td>0.267</td>
</tr>
<tr>
<td>MENQOL psychosocial (1–8)</td>
<td>4.2 (1.6)</td>
<td>3.9 (1.5)</td>
<td>0.487</td>
</tr>
<tr>
<td>MENQOL physical (1–8)</td>
<td>3.4 (0.9)</td>
<td>4.0 (0.9)</td>
<td>0.041 *</td>
</tr>
<tr>
<td>MENQOL sexual (1–8)</td>
<td>4.7 (1.9)</td>
<td>4.7 (1.4)</td>
<td>0.951</td>
</tr>
<tr>
<td>PSQI (0–21)</td>
<td>10.6 (2.9)</td>
<td>12.2 (3.0)</td>
<td>0.051</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>341.6 (38.9)</td>
<td>332.1 (34.2)</td>
<td>0.403</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>21.5 (12.4)</td>
<td>31.8 (22.2)</td>
<td>0.069</td>
</tr>
<tr>
<td>REM sleep latency (min)</td>
<td>137.8 (42.0)</td>
<td>136.7 (53.6)</td>
<td>0.922</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>81.8 (6.5)</td>
<td>75.7 (8.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>17.7 (8.8)</td>
<td>18.1 (7.3)</td>
<td>0.888</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>47.2 (11.2)</td>
<td>47.4 (9.5)</td>
<td>0.963</td>
</tr>
<tr>
<td>Stages 3 and 4 (%)</td>
<td>19.4 (5.7)</td>
<td>19.9 (6.5)</td>
<td>0.814</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>15.7 (4.6)</td>
<td>14.7 (3.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Wake after sleep onset (min)</td>
<td>48.7 (24.1)</td>
<td>73.6 (31.7)</td>
<td>0.009 **</td>
</tr>
<tr>
<td>Arousals (times)</td>
<td>101.5 (34.5)</td>
<td>120.9 (52.6)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

MENQOL, Menopause-specific Quality of Life; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement

PSQI was the subjective measure of perceived sleep quality in this trial and a reduction of PSQI score indicated an improvement. A decrease of PSQI was found in the BC group (r = 0.601, p = 0.001). Although the decrease vanished when compared with the placebo group (r = 0.301, p = 0.051, Table 2), there was a medium effect in this situation. For the objective measure of sleep, intra-group analysis of polysomnographic parameters showed that no change was observed in the placebo group, while in the BC group, SE (r = 0.559, p = 0.008) was higher and WASO (r = 0.585, p = 0.005) and arousals (r = 0.517, p = 0.016) were lower than those at baseline. When compared with the placebo group, the difference in SE (r = 0.391, p = 0.010) and WASO (r = 0.404, p = 0.009) remained significant (Table 2). Considering the proportion of low SE, the percentage of women with low SE in the BC group decreased from 70% to 50% (Cramer’s V = 0.655, p = 0.003) and was significantly lower than that in placebo group (Cramer’s V = 0.393, p = 0.011, Figure 2). In addition, we calculated the reduction of WASO duration in both groups, expressed as percentage of WASO reduction over WASO at baseline. BC reduced 15.8% of WASO duration at baseline on average (r = 0.427, p = 0.005, Figure 3). Significant changes in other polysomnographic parameters were not observed.

Safety evaluation

Blood tests of liver and renal functions and ultrasound examinations of breast and pelvic cavity were major measures for safety. Only one woman in the BC group was reported to have an increased aspartate aminotransferase (AST) level in the middle of the trial (AST = 48.6 U/l). She was asked to improve dietary hygiene and her AST returned to normal when re-examined 1 month later. For the others, no clinically significant abnormality was found in the tests of liver and renal functions, ultrasound of mammary gland, uterus and bilateral ovaries and no adverse event was reported. No difference in

Figure 3  Reduction in wake after sleep onset (WASO) over WASO at baseline illustrated as mean and standard deviation in the two groups. *, p = 0.005 compared with placebo group. BC, black cohosh
FSG or estradiol level was observed in the comparisons intra-
and inter-group, suggesting that BC did not affect the level of serum estrogen.

DISCUSSION

The present study demonstrated that the 6-month daily oral
administration of a standardized isopropanolic preparation of
BC improved objective sleep quality through increasing SE
and decreasing WASO duration. It tended to ameliorate the
subjective sleep complaints indicated by reducing PSQI in
postmenopausal women with sleep disturbances. Life quality
was also improved in the vasomotor and physical domains.

The prevalence of insomnia in Chinese menopausal women
aged 40–65 years is increasing from 37.2% to 67.65%; insomnia
is one of the most prevalent climacteric symptoms.40–45
Increasing numbers of menopausal women troubled with
new-onset or aggravating sleep disturbances have been seek-
ing safe medication other than hormone therapy in our clinics.
By the very nature of estrogen, hormone therapy has invari-
ably been associated with limited clinical indication and poor
medical compliance. Despite the popularity of alternative
therapies during these years, only a few studies have focused
on menopausal sleep disturbance. Thus, PSG was first chosen
as the principal assessment of sleep in the present study.
Here we addressed the sleep issues related to menopause itself
beyond the whole climacterium, while the primary sleep dis-
orders and the definite psychological and psychiatric disorders
were excluded. The age span and the menopausal stage were
defined as early postmenopause following the menopausal
transition. We also tried to control other confounding fac-
tors having the potential to affect sleep parameters such as
BMI, sex hormone levels, systemic medication use, physical
condition, financial and educational status, according to the
SWAN (Study of Women’s Health Across the Nation) sleep
study.35 The randomization of our study was well performed
as there was no significant difference in baseline data between
the two groups.

The mechanisms of BC underlying sleep changes in vivo
have not been well understood in the literature. The objective
sleep improvement might be mostly attributed to the activities
of 5-HT and GABA in the central nervous system. Bolton and
her colleagues previously identified the serotoninergic behav-
iors of BC compounds in their earlier in vitro studies; these
behaviors were mostly attributed to N-α-methylserotonin.13,42
It competitively binds to the 5-HT₁₃, 5-HT₁D and 5-HT₇
subtypes of serotonin receptors and functions as a partial
agonist.13,42,43 In mammals, 5-HT is involved essentially in
various functions including the sleep–wake transition, cogni-
tion, sexual function, thermoregulation and food ingestion.16
5-HT plays a key role in the normal regulation of sleep initia-
tion, duration and stage transformation. BC might alleviate the
neuroendocrinal fluctuation of serotonin caused by meno-
pause, resulting in reduced duration of WASO. GABA also
participates in sleep regulation and GABA type A (GABAₐ)
receptor agonist can promote SWS and suppress wakefulness
with no influence on REM sleep. Some of the isolated triter-
pene glycosides have been proven positively to modulate the
GABAₐ receptor in vitro.44 It appears that BC acts as an
atypical GABAₐ receptor agonist as it decreases wake time
without affecting REM sleep, but a typical improvement of
SWS was not observed in our study. Besides, Mimaka and
colleagues found earlier that two types of triterpene glycoside
were capable of promoting ACTH secretion of mouse pituitary
tumor cell line. They also revealed that BC interacted with
the hypothalamo–pituitary–adrenal axis and the sympathetic
adrenomedullary system to buffer the systemic responses to
stress events in vivo, probably through its neurotransmitter-
mimetic activities in brain. Moreover, a recent in vitro
study showed that a novel triterpene glycoside reduced the
amyloid beta deposits, well known as the major pathological
change in Alzheimer’s disease, implying its protection of the
central nervous system.47

Postmenopausal women with sleep complaints often expe-
rience poor SE and, as we expected, 76.2% of the partici-
pants exhibited low SE at baseline in our study. BC could
reduce the percentage of women suffering from low SE and
induce a significant improvement of SE compared with pla-
cebo, suggesting its role in the maintenance of sleep. In addi-
tion to poor SE, postmenopausal women tend to spend more
time awake at night, which is another marker of impaired
sleep associated with menopause. Wuttke and colleagues
examined whether BC impacted on sleeping behavior and
showed that the average frequency of self-reported waking
up per night was lower in the BC group than in the group
receiving estrogen. In our PSG analysis, similar results were
achieved: 6-month administration of BC could significantly
reduce WASO duration on the recording nights while no
increase in stages 1 and 2 of non-REM sleep or REM sleep
was observed, indicating that BC provided an amelioration
of the impaired sleep continuity. However, BC failed to ac-
celerate the initiation of sleep since no difference in SL was
observed. Thus, we assume that BC might improve sleep
continuity mainly through attenuating certain nocturnal
arousals that are strong enough to cause total wakefulness,
rather than shortening the latency to the onset of another
sleep stage right after the arousal.

The beneficial effect of BC on perceived sleep quality during
the menopausal transition and postmenopause has been con-
firmed. BC is equivalent to conjugated estrogen and
tibolone in the improvement of subjective sleep, as indicated
by the sleep diary and KMI insomnia subscore. Geller and
colleagues applied PSQI to measure the perceived sleep
quality and showed, however, that 12-month administration
of BC failed to be superior to placebo. It is worth noting
that participants were primarily selected based on moderate
to severe VMS in the previous study. Besides, the previous
PSQI research administrated up to 128 mg crude drug per day,
namely about three times the dose in our study, as well as in
the studies of positive findings by sleep diary and KMI insom-
nia subscore. In our study, although we also failed to observe
a remarkable difference between groups concerning PSQI, a
medium effect was achieved. In addition, serum estradiol did

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not correlate with subjective or objective sleep parameters, consistent with a recent SWAN sleep study\textsuperscript{49}.

In our study, an isopropanolic extract of BC was used, which has been introduced since 2009. Before the formal introduction, Bai and colleagues performed a large-scale clinical trial in 2006 to prove its equivalent efficacy and superior safety to tibolone in managing menopausal complaints in Chinese peri- and postmenopausal women\textsuperscript{19}. Our study again confirmed its effect on VMS. Although there is always a strong link between VMS and sleep disruptions\textsuperscript{50}, no correlation between VMS and nocturnal wake periods or arousals was found in our study. VMS and menopausal sleep complaints might be isolated entities\textsuperscript{8,51,52}. It is well accepted that VMS are caused by a falsely reduced set point of body core temperature and the dysfunction of the hypothalamic thermoregulatory center results from estrogen deficiency and opioid withdrawal\textsuperscript{53}. BC might work through interaction with the endogenous opioid system and acting as a partial agonist\textsuperscript{54,55}. Another connection between BC and VMS is that BC modulates the activities of 5-HT\textsubscript{1A} and 5-HT\textsubscript{7} receptors, which are mainly distributed in the hypothalamus. Although BC failed to be superior to placebo when dealing with the psychosocial domain, both groups reached a significant reduction of MENQOL psychosocial score. Recently, an in vivo study showed that certain hypothalamic nuclei, involved in the physical and psychological changes in menopause, might be the targets of BC. For instance, the suprachiasmatic nucleus (SCN) generates a mammalian circadian rhythm and is vital for maintaining the sleep–wake pattern, the endocrine system, metabolism and physiological rhythm\textsuperscript{56}. BC could up-regulate the neuron density of the impaired neurons of SCN in ovariectomized rats\textsuperscript{57}. The excitatory activities in SCN could be enhanced by estrogen as well, but their responses to various external environments were different from those treated with BC\textsuperscript{57}. The negative result in the sex domain in the present study was supported by another herbal therapy study. It was shown that systemic use of BC did not impact vaginal cytology and vaginal dryness score\textsuperscript{32}. BC might not keep the same advantage of ameliorating menopausal sexual symptoms as in the other domains. Local use of estrogen is recommended for vaginal dryness in menopausal women\textsuperscript{58}.

In our study, a placebo effect was observed. A placebo effect is a neurobiological phenomenon associated with the central nervous system. Its mechanism has been widely studied in somatic pain, as well as depression, anxiety and Parkinson’s disease\textsuperscript{59}. This effect might be remarkable in alleviating subjective symptoms rather than pathological disease, which is mainly due to strong expectations of certain therapies\textsuperscript{60}. In our study, the scores in the psychosocial and physical domains of MENQOL were reduced in the placebo group. The latest research in the literature also show that placebo could decrease the scores of MENQOL in postmenopausal women\textsuperscript{61,62}. In terms of objective symptoms, however, placebo did not impact any polysomnographic parameters.

One participant in the BC group in our study was found to have an abnormal liver enzyme and it could not be assigned to BC since the abnormality was slight and transient and was rectified with diet adjustment. A recent meta-analysis assessed five clinical trials of isopropanolic BC extract and showed that 3–6-month treatment did not cause liver impairment\textsuperscript{63}. Concerning the target organs of estrogen, BC was reported to present a protective effect against breast cancer and this anti-carcinogenic property might be mainly assigned to triterpenes\textsuperscript{64}. Another protective effect of triterpenes is that endometrial proliferation could be suppressed without any stimulation of estrogen receptor α\textsuperscript{65}. Moreover, BC reduces 30% of the ultrasonic volume of uterine fibroids in midlife women\textsuperscript{66}. The circulating levels of estradiol and FSH did not change significantly in our study, supporting the non-estrogenic property of BC in treating estrogen-insufficient symptoms.

There are certain limitations to the present study. As we were limited by the small scale, we did not enroll women of different menopausal status and a wide age span. A larger sample size is needed to involve more covariate and subgroup analysis concerning menopausal status, age and the severity of climacteric symptoms. Also, the dynamic changes of clinical symptoms and polysomnographic parameters during the process of treatment were not evaluated. By conducting repeated measures for the next step, we will be able to investigate the effective treatment duration of BC.

CONCLUSION

We first investigated the effect of black cohosh on sleep disturbance related to menopause. Our study provided, for the first time, the profiles of black cohosh’s effect on sleep architecture and process. In summary, PSG analysis revealed that 6-month daily oral administration of black cohosh is effective in the maintenance of objective sleep by increasing sleep efficiency and reducing time of being awake in early postmenopausal women with the major complaint of impaired sleep. Black cohosh also had the potential to ameliorate perceived sleep quality. Regarding menopausal quality of life, black cohosh could improve the vasomotor and physical domains in this population. The present study opens the possibility that black cohosh might be useful in menopause-related sleep disturbance. Future research is expected to reach a comprehensive understanding of its mechanisms in dealing with impaired sleep in menopausal women.

**Conflict of interest**  The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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