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Original Study

Black cohosh extracts in women with menopausal symptoms: an updated pairwise meta-analysis

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Abstract

Objective: Menopausal symptoms are common in midlife women and have broad impacts on their daily functioning and quality of life. Black cohosh extracts have been widely used to relieve menopausal symptoms. However, the comparative benefits of different combined black cohosh regimens remain inconclusive. The aim of the current updated meta-analysis is to address the comparative efficacies of different black cohosh regimens in improving menopausal symptoms.

Methods: Random-effect model pairwise meta-analysis of randomized controlled trials was conducted to investigate the treatment effect on menopausal symptoms by the black cohosh extract both alone or combined with other related active ingredients. The outcomes studied were changes in menopausal symptoms after treatment with black cohosh extracts in menopausal women.

Results: Twenty-two articles including information on 2,310 menopausal women were included in the analyses. Black cohosh extracts were associated with significant improvements in overall menopausal symptoms (Hedges' $g = 0.575$, 95% CI = 0.283 to 0.867, $P < 0.001$), as well as in hot flashes (Hedges' $g = 0.315$, 95% CIs = 0.107 to 0.524, $P = 0.003$), and somatic symptoms (Hedges' $g = 0.418$, 95% CI = 0.165 to 0.670, $P = 0.001$), compared with placebo. However, black cohosh did not significantly improve anxiety (Hedges' $g = 0.194$, 95% CI = −0.296 to 0.684, $P = 0.438$) or depressive symptoms (Hedges' $g = 0.406$, 95% CI = −0.121 to 0.932, $P = 0.131$). The dropout rate for black cohosh products was similar to that for placebo (odds ratio = 0.911, 95% CI = 0.660 to 1.256, $P = 0.568$).

Conclusions: This study provides updated evidence regarding the potentially beneficial effects of black cohosh extracts for relieving menopausal symptoms in menopausal women.

Key Words: Black cohosh – Hot flash – Menopause – Meta-analysis – Vasomotor symptom.

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For women approaching their midlife years, the menopausal transition has potential impacts on quality of life and the ability to carry out daily functions. Women often seek medical treatment for various menopause-related concerns, particularly severe vasomotor and genitourinary symptoms.[1] Menopausal symptoms occur in women with diverse backgrounds including geographical location, ethnicity, comorbidities, and socioeconomic status. This may mean that social change–induced stress and aging may also contribute to worsening of the symptoms.[1,2] Substantial pathophysiology based on the loss of ovarian function and specifically reduction in estrogen can cause hot flashes, sexual dysfunction, mood disorders, and osteoporosis, along with metabolic changes that might increase the incidence of cardiovascular disease.[3] There is thus a need to understand this pathophysiology and how to manage its effects.

The efficacy of black cohosh (*Actaea racemosa, Cimicifuga racemosa*) has recently been examined for this indication in several randomized controlled trials (RCTs). One double-blind RCT involving 84 postmenopausal women found that administration of 6.5 mg of black cohosh dry root extract once daily after dinner for 8 weeks significantly reduced the severity of vasomotor symptoms and the number of hot flashes compared with placebo.[4] In another RCT involving 120 menopausal women, black cohosh alleviated hot flashes and night sweats to a greater extent than fluoxetine, potentially via dopaminergic and serotonergic modulation.[5] However, a recent meta-analysis of RCTs reported that black cohosh was ineffective for vasomotor symptoms.[6] Beer and Neff[7] conducted a systematic review of 18 clinical trials implemented between 2000 and 2012 including 10,284 women and found that the efficacy of black cohosh seemed to depend on the specific extract or medicinal formulation used. Because of the easy availability of the over the counter products for menopausal symptoms, the menopausal woman has the opportunity to choose combination therapies, including black cohosh. Some of these have also been examined in RCTs.[8-10] However, there is a lack of meta-analyses to elucidate the clinical utility of these combination therapies. In addition, although the safety of black cohosh has been acceptable in many studies,[6,7] clinical uncertainty remains regarding the risk of adverse effects.[11] Furthermore, since the previous meta-analyses were done, several new RCTs had been published. More conclusive evidence relating to the role of black cohosh in the management of menopausal symptoms is therefore needed.

We conducted an updated pairwise meta-analysis to evaluate the efficacy of black cohosh alone and in combination with other herbal medicines in reducing the overall menopausal experience and the severity of individual symptoms. The definition of menopause could be accepted by the clinical relevant operation criteria among the included studies, including but not limit to "no menstruation during a specific time period." By integrating recent evidence from clinical trials, the current results provide an expanded view of the data and a better understanding of the appropriate clinical use of black cohosh during menopause.

METHODS

General guidelines applied in the current study

The current updated meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guidelines (Supplemental Table 1, http://links.lww.com/MENO/B136)[12] and the AMSTAR 2 appraisal tool.[13] The study was approved by the institutional review board of the Tri-Service General Hospital (TSGHIRB: B-109-29). The study protocol is registered in PROSPERO (CRD42021285072).

Search strategy and selection criteria

We conducted a comprehensive, online publication search of the PubMed, Embase, ScienceDirect, ClinicalKey, Cochrane CENTRAL, ProQuest, Web of Science, and ClinicalTrials.gov databases from their inception to November 27, 2022, using the key words ("black cohosh" OR Cimicifuga OR Avlimil OR actaealactone OR Remifemin) AND (placebo) AND (random OR randomized OR randomised). The detailed search strategy

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and results are presented in Supplemental Table 2, http://links.lww.com/MENO/B136. There was no language restriction on the selected articles. We also conducted manual searches to identify potentially eligible articles from the reference lists of review articles or pairwise meta-analyses (Fig. 1).[14-33]

Inclusion criteria and exclusion criteria

The PICO (population, intervention, comparison, outcome) setting of the current meta-analysis included the following: (1) P: menopausal participants, (2) I: black cohosh extract or other related active ingredients (ie, combination therapy including black cohosh extract), (3) C: placebo control, and (4) O: change in severity of overall menopausal symptoms. To eliminate a potential placebo effect, we only included trials with a placebo control in at least one arm (ie, trials with multiple arms could include different active-controlled arms but needed to have at least one placebo arm). The inclusion criteria were as follows: (1) RCT with at least one placebo-controlled arm; (2) human clinical trials; (3) articles published in a peer-reviewed journal; (4) trials providing information on changes in menopausal symptoms after treatment with black cohosh extracts, either alone or in combination with other herbal medicines, in menopausal women; and (5) the severity of menopausal symptoms was only included in the analysis when rated using validated rating scales. Because of the widespread availability of products combining black cohosh with other active ingredients, we did not set any limitations to the RCTs strictly excluding concomitant medication.

The exclusion criteria were as follows: (1) not clinical trials, (2) studies that did not report changes in menopausal symptoms, (3) studies not related to black cohosh extracts, (4) trials without a placebo-controlled arm, (5) meeting abstracts or posters, and (6) trials evaluating menopausal symptoms without validated rating scales. In the event of duplicated usage of data (ie, different articles based on the same sample sources), we only included the report with the most informative and largest sample source.

Data extraction

Two authors independently screened the studies in a two-step process. To be specific, initially, we screened the title and abstract to select the relevant articles into our next screen. Later, we screened the selected articles through a full-text selection. The relevant articles in the full-text selection were included in the current meta-analysis. We extracted the relevant data from the manuscripts and assessed the risk of bias among the included studies. In the event of a discrepancy, a third author was involved. If there was a lack of available data from the articles, we contacted the corresponding authors or coauthors to obtain the original data.

Outcomes

The primary outcome was changes in overall menopausal symptoms after treatment with black cohosh extracts in menopausal women. The defined "overall menopausal symptoms" indicated the overall scores of a menopause symptom rating scale applied in the recruited RCT. The secondary outcomes were changes in specific menopausal symptoms, including hot flashes

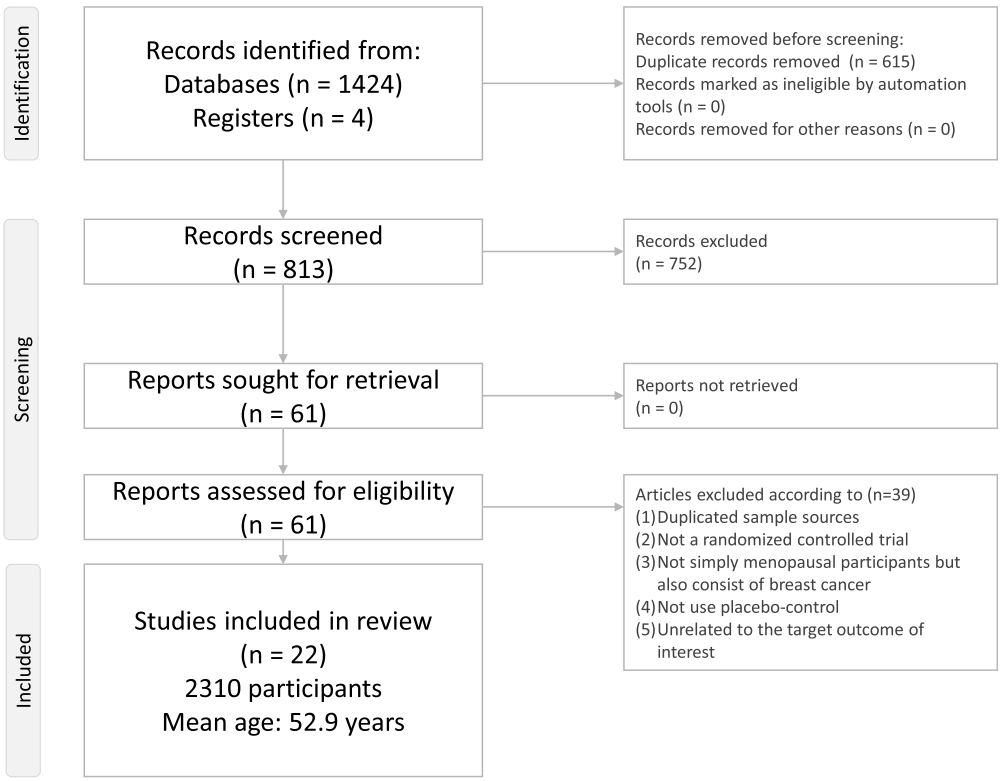

FIG. 1. Flowchart of the meta-analysis procedure.

(ie, vasomotor symptoms), anxiety, vaginal atrophy, depression, and somatic symptoms. The severity of menopausal symptoms was only included in the analysis when rated using validated rating scales. The severity of other specific menopausal symptoms (eg, anxiety, depression, somatic symptoms) were measured with the validated rating scales. The dropout rate was defined as leaving a study early for any reason. In the current study, the value of comparative "dropout rate" was calculated in comparison with that of placebo/control groups but not a "rate/percentage" format. To further analyze the potentially beneficial effect of black cohosh extracts on menopausal symptoms, we carried out subgroup analyses based on trials using "black cohosh extracts alone" versus trials using "combined black cohosh extracts and other herbal medicines." We assessed the significance of the difference between the estimated effect size of these two subgroup.[34] If there was no statistically significant difference, there was no evidence to support the superiority of one subgroup to another (ie, additional ingredients did not enhance black cohosh efficacy). Furthermore, to increase the reliability of the results, we only analyzed subgroups, which included at least three different studies.[35]

Cochrane risk of bias tool

Two independent authors evaluated the risk of bias (interrater reliability, 0.85) for each domain, as described in the Cochrane risk of bias tool.[36]

Statistical analysis

Because of the anticipated high heterogeneity across studies, we used a random-effects model to synthesize evidence from the included studies.[37] The effect sizes of continuous outcomes were estimated as Hedges' *g* with 95% CI, while the effect size of dichotomous outcomes were estimated with odds ratios (OR) and 95% CI. In the forest plot of efficacy, we defined the direction of the effect size to indicate "more improvement with black cohosh extract than placebo" when the value of Hedges' *g* was more than 0 (Fig. 2). In contrast, in the forest plot of dropout rate, we defined the effect size to indicate "a higher dropout rate in participants treated with black cohosh extract than placebo" when the OR was more than 1. The current meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ). The threshold for statistical significance was set at a two-tailed *P* value less than 0.05.

Sensitivity analysis was performed using the "leave-one-out" technique to determine whether a potential outlier among the included studies could have influenced the results of the meta-analysis.[38] Heterogeneity was assessed using the Cochran *Q* test and its corresponding *P* values.[39] Publication bias was assessed by inspecting the funnel plots if fewer than 10 data sets were available,[40] and with Egger regression test if more than one data sets were available.[41] If evidence of publication bias was found, Duval and Tweedie's trim-and-fill procedure was used, as a validated model to estimate an effect size in the context of publication bias.[42] We performed meta-regression analyses with unrestricted maximum likelihood random effects when data for each potential moderator were provided in at least 10 different studies. To be specific, we arranged meta-regression to investigate the potential effect on the treatment efficacy by mean age, body mass index, or treatment duration.

RESULTS

The initial screening procedure identified 61 articles for full-text review (Fig. 1), of which 39 were subsequently excluded for various reasons (Fig. 1 and Supplemental Table 3, http://links.lww.com/MENO/B136). Twenty-two articles were finally included

Study name	Regimen	Statistics for each study					Hedges' *g* and 95% CI
		Hedges' *g*	Lower limit	Upper limit	*p* value	Relative weight	
Amsterdam, J.D. (2009)	Simple	-0.818	-1.571	-0.066	0.033	5.11	
Geller, S.E. (2009)	Simple	-0.053	-0.640	0.534	0.859	5.89	
Tanmahasamut, P. (2015)	Simple	0.061	-0.490	0.612	0.829	6.06	
Jiang, K. (2015)	Simple	0.140	-0.454	0.735	0.644	5.85	
Osmers, R. (2005)	Simple	0.269	0.031	0.507	0.027	7.34	
Frei-Kleiner, S. (2005)	Simple	0.408	0.003	0.813	0.048	6.72	
Pkhaladze, L. (2020)	Simple	0.776	0.443	1.109	<0.001	7.02	
Shahnazi, M. (2013)	Simple	0.967	0.518	1.415	<0.001	6.53	
Wuttke, W. (2003)	Simple	1.123	0.467	1.778	0.001	5.56	
Mohammad-Alizadeh-Charandabi, S. (2013)	Simple	1.310	0.842	1.778	<0.001	6.44	
Schellenberg, R. (2012)	Simple	1.388	1.032	1.744	<0.001	6.93	
van der Sluijs, C.P. (2009)	Combined	-0.153	-0.600	0.293	0.501	6.54	
Verhoeven, M.O. (2005)	Combined	0.057	-0.293	0.407	0.749	6.95	
Uebelhack, R. (2006)	Combined	1.115	0.869	1.361	<0.001	7.32	
Sammartino, A. (2006)	Combined	1.193	0.009	2.376	0.048	3.41	
Chung, D.J. (2007)	Combined	1.329	0.838	1.820	<0.001	6.34	
Overall		**0.575**	**0.283**	**0.867**	**<0.001**	**100.00**	

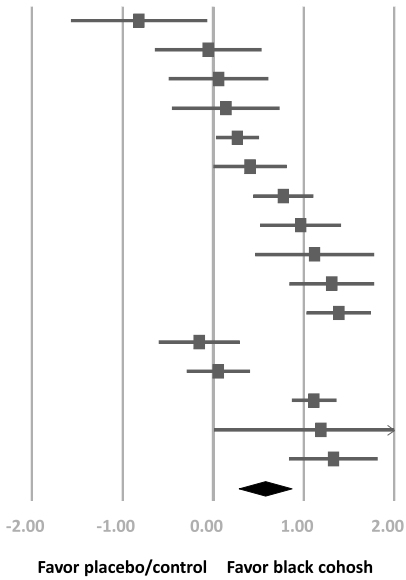

FIG. 2. Forest plot of pair-wise meta-analysis of primary outcome: changes in overall severity.

in the current study (Supplemental Table 4, http://links.lww.com/MENO/B136).

Characteristics of the included studies

The included studies reported data for 2,310 women with menopausal symptoms (mean age = 52.9 y [range = 50.3-59.0 y], mean body mass index = 25.6 [range = 22.4-30.1]). The mean treatment duration was 15.3 weeks (range = 4-52 wk) and the mean overall study duration (ie, treatment + posttreatment follow-up) was 16.7 weeks (range = 4-52 wk). None of the participants were on hormone therapy when recruited with the possible exception of one trial that did not state this.[43] Therefore, there would be no risk of confounding effect from the concomitant medication. None of the recruited menopausal women had any significant physical illness at baseline. Some of the included RCTs consisted of multiple herbal extracts, such as *C. racemosa*, *A. racemosa*, *Angelica sinensis*, and St John's wort (the detailed compounds used in each study were listed in Supplemental Table 4, http://links.lww.com/MENO/B136).

Primary outcome: changes in overall menopausal symptoms

The overall meta-analytic results are listed in Table 1. In brief, the current meta-analysis revealed that black cohosh extracts were associated with significant improvements in overall menopausal symptoms compared with placebo (k = 16, Hedges' g = 0.575, 95% CI = 0.283 to 0.867, P < 0.001) (Fig. 2) with significant heterogeneity (Q = 112.461, df = 15, I^2 = 86.662%, P < 0.001) but no significant publication bias according to Egger regression (t = 0.570, df = 14, P = 0.578). The significant meta-analysis results were unaffected by removal of each included study, indicating that the significant results were unlikely to be due to a single study. Hedges' g was significantly and inversely associated with mean age (k = 16, r = −0.273, P < 0.001), but not body mass index (k = 13, P = 0.945) or treatment duration (k = 16, P = 0.141). Subgroup analysis based on a simple or combined regimen revealed similar results without significant difference between these two subgroups (P = 0.734). To be specific, black cohosh extracts significantly improved overall menopausal symptoms compared with placebo when administered alone or in combination with other herbal medicines (Supplemental Fig. 1A, http://links.lww.com/MENO/B131).

Secondary outcome: changes in hot flashes

Pairwise meta-analysis revealed that black cohosh extracts overall significantly improved hot flash symptoms compared with placebo (Supplemental Fig. 2A, http://links.lww.com/MENO/B131). Subgroup analysis of simple regimens revealed similar results without significant difference between these two subgroups (P = 0.548). However, the black cohosh extracts alone significantly improved hot flash symptoms compared with placebo; in contrast, the subgroup results for combined regimens were not significant (Supplemental Fig. 1B, http://links.lww.com/MENO/B131).

Secondary outcome: changes in somatic symptoms, which were defined according to the rating scales applied in the recruited RCTs

Pairwise meta-analysis revealed that black cohosh extracts overall significantly improved somatic symptoms compared with placebo (k = 7, Hedges' g = 0.418, 95% CI = 0.165 to 0.670, P = 0.001) (Supplemental Fig. 2B, http://links.lww.com/MENO/B131). Subgroup analysis of black cohort extract alone revealed similar results, with significant improvements in somatic symptoms compared with placebo, whereas the subgroup for combined regimens were not calculated because of less than three trials (Supplemental Fig. 1C, http://links.lww.com/MENO/B131).

Secondary outcome: changes in anxiety symptoms

Pairwise meta-analysis revealed that black cohosh extracts overall had no significant effect on anxiety symptoms compared with placebo (k = 5, Hedges' g = 0.194, 95% CI = −0.296 to 0.684, P = 0.438) (Supplemental Fig. 2C, http://links.lww.com/MENO/B131). Subgroup analysis similarly showed that black cohosh extracts alone had no significant effect on anxiety symptoms compared with placebo, whereas the subgroup for combined regimens were not calculated due to less than three trials (Supplemental Fig. 1D, http://links.lww.com/MENO/B131).

Secondary outcome: changes in depressive symptoms

Pairwise meta-analysis revealed that black cohosh extracts overall had no significant effect on depressive symptoms compared with placebo (k = 6, Hedges' g = 0.406, 95% CI = −0.121 to 0.932, P = 0.131) (Supplemental Fig. 2D, http://links.lww.com/MENO/B131). These findings were similar in subgroup analysis without significant difference between these two

TABLE 1. *Summary of the meta-analytic result*

	Overall analysis				Subgroup analysis								
	The whole studies				Subgroup of compound black cohosh				Subgroup of black cohosh alone				Difference between subgroups
Outcome	k	Hedges' g	95% CI	P	k	Hedges' g	95% CI	P	k	Hedges' g	95% CI	P	P
Overall severity	16	0.575	0.283 to 0.867	<0.001	5	0.667	0.026 to 1.308	0.042	11	0.541	0.199 to 0.883	0.002	0.734
Hot flash	17	0.315	0.107 to 0.524	0.003	8	0.240	−0.010 to 0.491	0.060	10	0.368	0.036 to 0.700	0.030	0.548
Somatic symptoms	7	0.418	0.165 to 0.670	0.001	NA	NA	NA	NA	5	0.535	0.209 to 0.860	0.001	NA
Anxiety symptoms	5	0.194	−0.296 to 0.684	0.438	NA	NA	NA	NA	3	0.111	−0.689 to 0.910	0.786	NA
Depressive symptoms	6	0.406	−0.121 to 0.932	0.131	3	0.673	−0.107 to 1.454	0.091	3	0.103	−0.649 to 0.855	0.789	0.302
Drop-out[a]	16	0.911	0.660 to 1.256	0.568	8	0.959	0.530 to 1.736	0.889	8	0.872	0.579 to 1.311	0.509	0.797

95%CIs, 95% confidence intervals; NA, not applicable.
[a]The effect size was present with OR and 95% CI.

subgroups ($P = 0.302$) (Supplemental Fig. 1E, http://links.lww.com/MENO/B131).

Dropout rate

Pairwise meta-analysis revealed that black cohosh extracts overall had no significant effect on the dropout rate compared with placebo ($k = 16$, OR = 0.911, 95% CI = 0.660 to 1.256, $P = 0.568$) (Supplemental Fig. 2E, http://links.lww.com/MENO/B131). Subgroup analysis similarly revealed no association with dropout rates compared with placebo for black cohosh extracts alone or in combination with other herbal medicines without significant difference between these two subgroups ($P = 0.797$) (Supplemental Fig. 1F, http://links.lww.com/MENO/B131).

Risk of bias and publication bias

We found that 72.1% (111/154 items), 27.3% (42/154 items), and 0.6% (1/154 items) of the included studies had overall low, unclear, and high risks of bias, respectively. The source of unclear risk of bias was in the vague reporting of randomization allocation concealment (Supplemental Figs. 3, http://links.lww.com/MENO/B131).

DISCUSSION

The major finding of the current meta-analysis was that black cohosh extracts, either alone or combined with other herbal medicines, improved menopausal symptoms, specifically somatic/vasomotor-associated symptoms, but not mood symptoms (ie, anxiety or depressive symptoms), significantly better than placebo. This finding was consistent with previous meta-analyses, which also demonstrated a significant benefit of black cohosh in relieving overall menopausal symptoms.[17,18,28] In addition to overall menopausal symptoms, as addressed by previous meta-analyses, the current meta-analysis also analyzed the effects on specific menopausal symptoms, such as hot flashes, somatic symptoms, and mood symptoms (ie, anxiety/depressive symptoms), which are the major menopause-related concerns in clinical practice.[44] In contrast to the previous meta-analyses,[17,18,28] we also carried out a subgroup meta-analysis to clarify potential differences in the efficacies of different black cohosh–related combination treatments on menopausal symptoms.

Subgroup meta-analysis demonstrated that there was no significantly different efficacy on the primary outcome and secondary outcomes between those regimens of black cohosh combined with other herbal medicines and those with black cohosh alone. This finding is of clinical importance because of the concerns of adverse effect related to the combination of multiple phytoestrogenic regimens. To be specific, the potential risk of hepatotoxicity[32] is one major concern related to the use of black cohosh extracts and some other phytoestrogenic regimens. In some case reports, the issue of hepatotoxicity was raised related to black cohosh use.[11,45] Although a previous meta-analysis found no conclusive evidence for an association between black cohosh extract use and hepatotoxicity,[32] the potential risk related to combination of phytoestrogenic regimens was mentioned in several review articles.[14,15] The current meta-analysis demonstrates that adding some additional components to black cohosh does not enhance its effectiveness in relieving menopause symptoms.

In addition to hepatotoxicity, there have been concerns about the potential relationship of black cohosh to breast cancer due to its possible action as a selective estrogen receptor modulator-like agent.[30] However, the mechanism of action of black cohosh is uncertain.[46] Similarly, although there had been no RCT addressing black cohosh in menopausal women with concomitant breast cancers, the currently recruited RCTs reported no serious adverse events related to the incidence/recurrence of breast cancer.

Limitations

The current study had some limitations. First, the numbers of RCTs and participants (22 RCTs and 2,310 participants) were relatively small. Second, the treatment duration (mean = 15.3 wk, range = 4-52 wk) and overall study duration (mean = 16.7 wk, range = 4-52 wk) were short, and some potential adverse effects (such as breast cancer) and some secondary outcomes (ie, anxiety or depressive symptoms) might not have been demonstrated with a short study duration. Third, because of the wide variety of menopausal symptoms and investigated outcomes among the recruited RCTs, we focused on the most frequently mentioned outcomes in those recruited RCTs. In addition, to provide a direct measurement regarding a specific outcome would be clinically relevant to the clinicians. However, the most RCTs used a wide variety of scales to evaluate the primary (overall menopausal symptoms) and secondary outcomes (somatic symptoms). Therefore, because of the necessity of statistical process, we had to standardize the effect size and calculate with the Hedges' g. Fourth, few RCTs addressed combination regimens including black cohosh extracts,[8-10,43,47] and the contents of the combinations varied widely among studies, meaning that the comparative different efficacy was mainly based on only a few RCTs. This limitation should be taken into account by clinicians in clinical practice. In addition, in this study, we did not do any subgroup analysis regarding the dosage/preparations because the units and compounds of the black cohosh extracts varied largely among the included RCTs. Therefore, to provide a direction guiding future research, we recommended the researchers try to unify the units/weights of the black cohosh extracts in their future research in this field so that it would provide more information to clinicians. Fifth, unclear risk of bias in the vague reporting of randomization allocation concealment might also contribute potential bias in the current study. Finally, we did not apply a cost-effectiveness analysis in our study, which might limit the clinical application of the current study. In addition, we could not make a quality control analysis for each black cohosh product. In the report by Jiang et al[48] (2006), the quality control of different black cohosh products ranged widely. Furthermore, the definition of the perimenopause transition or menopausal stage varied widely among the included studies, which was important because the outcomes were considered to be stage-specific.

CONCLUSIONS

The current study provided evidence indicating that black cohosh extracts significantly improved overall menopausal

symptoms, as well as hot flashes, and somatic symptoms compared with placebo. Furthermore, the combination of black cohosh extracts with other herbal medicines did not provide statistically superior benefit in comparison with black cohosh alone. Further RCTs with larger sample sizes and longer study durations are needed to investigate the potential benefit of black cohosh extracts for relieving menopausal symptoms. Furthermore, to understand the mechanism of action, the difference between extract compounds, and the safety concerns with respect to this herbal medicine are important.

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REFERENCES

1. Nelson HD. Menopause. *Lancet* 2008;371:760-770. doi: 10.1016/S0140-6736(08)60346-3
2. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015;175:531-539. doi: 10.1001/jamainternmed.2014.8063
3. Davis SR, Lambrinoudaki I, Lumsden M, et al. Menopause. *Nat Rev Dis Primers* 2015;1:15004. doi: 10.1038/nrdp.2015.4
4. Shahnazi M, Nahaee J, Mohammad-Alizadeh-Charandabi S, Bayatipayan S. Effect of black cohosh (cimicifuga racemosa) on vasomotor symptoms in postmenopausal women: a randomized clinical trial. *J Caring Sci* 2013;2:105-113. doi: 10.5681/jcs.2013.013
5. Oktem M, Eroglu D, Karahan HB, Taskintuna N, Kuscu E, Zeyneloglu HB. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. *Adv Ther* 2007;24:448-461. doi: 10.1007/BF02849914
6. Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. *JAMA* 2016;315:2554-2563. doi: 10.1001/jama.2016.8012
7. Beer AM, Neff A. Differentiated evaluation of extract-specific evidence on *Cimicifuga racemosa*'s efficacy and safety for climacteric complaints. *Evid Based Complement Alternat Med* 2013;2013:860602. doi: 10.1155/2013/860602
8. Chung DJ, Kim HY, Park KH, et al. Black cohosh and St. John's wort (GYNO-Plus) for climacteric symptoms. *Yonsei Med J* 2007;48:289-294. doi: 10.3349/ymj.2007.48.2.289
9. Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med* 2006;145:869-879. doi: 10.7326/0003-4819-145-12-200612190-00003
10. Uebelhack R, Blohmer JU, Graubaum HJ, Busch R, Gruenwald J, Wernecke KD. Black cohosh and St. John's wort for climacteric complaints: a randomized trial. *Obstet Gynecol* 2006;107(2 Pt 1):247-255. doi: 10.1097/01.AOG.0000196504.49378.83
11. Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. *Med J Aust* 2003;179:390-391.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
13. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008. doi: 10.1136/bmj.j4008
14. Henneicke-von Zepelin HH. 60 years of *Cimicifuga racemosa* medicinal products: clinical research milestones, current study findings and current development. *Wien Med Wochenschr* 2017;167(7-8):147-159. doi: 10.1007/s10354-016-0537-z
15. Drewe J, Bucher KA, Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. *SpringerPlus* 2015;4:65. doi: 10.1186/s40064-015-0808-y
16. Ulbricht C, Windsor RC. An evidence-based systematic review of black cohosh (*Cimicifuga racemosa*, *Actaea racemosa*) by the Natural Standard Research Collaboration. *J Diet Suppl* 2015;12:265-358. doi: 10.3109/19390211.2014.946731
17. Leach MJ, Moore V. Black cohosh (*Cimicifuga* spp.) for menopausal symptoms. *Cochrane Database Syst Rev* 2012;2012:CD007244. doi: 10.1002/14651858.CD007244.pub2
18. Shams T, Setia MS, Hemmings R, McCusker J, Sewitch M, Ciampi A. Efficacy of black cohosh–containing preparations on menopausal symptoms: a meta-analysis. *Altern Ther Health Med* 2010;16:36-44.
19. Palacio C, Masri G, Mooradian AD. Black cohosh for the management of menopausal symptoms : a systematic review of clinical trials. *Drugs Aging* 2009;26:23-36. doi: 10.2165/0002512-200926010-00002
20. Roozbeh N, Kashef R, Ghazanfarpour M, et al. Overview of the effect of herbal medicines and isoflavones on the treatment of cognitive function. *J Menopausal Med* 2018;24:113-118. doi: 10.6118/jmm.2018.24.2.113
21. Moore TR, Franks RB, Fox C. Review of efficacy of complementary and alternative medicine treatments for menopausal symptoms. *J Midwifery Womens Health* 2017;62:286-297. doi: 10.1111/jmwh.12628
22. Hill DA, Crider M, Hill SR. Hormone therapy and other treatments for symptoms of menopause. *Am Fam Physician* 2016;94:884-889.
23. Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*): a systematic review of adverse events. *Am J Obstet Gynecol* 2008;199:455-466. doi: 10.1016/j.ajog.2008.05.007
24. Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*) for menopausal symptoms: a systematic review of its efficacy. *Pharmacol Res* 2008;58:8-14. doi: 10.1016/j.phrs.2008.05.008
25. The use of black cohosh to treat symptoms of menopause. *Fertil Steril* 2004;81(Suppl 2):27-34; quiz 57-60. doi: 10.1016/S0015-0282(03)01187-7
26. Guo Y, Yin T, Wang X, et al. Traditional uses, phytochemistry, pharmacology and toxicology of the genus *Cimicifuga*: a review. *J Ethnopharmacol* 2017;209:264-282. doi: 10.1016/j.jep.2017.07.040
27. Ross SM. Menopause: a standardized isopropanolic black cohosh extract (remifemin) is found to be safe and effective for menopausal symptoms. *Holist Nurs Pract* 2012;26:58-61. doi: 10.1097/HNP.0b013e31823d1f67
28. Castelo-Branco C, Gambacciani M, Cano A, et al. Review & meta-analysis: isopropanolic black cohosh extract iCR for menopausal symptoms - an update on the evidence. *Climacteric* 2021;24:109-119. doi: 10.1080/13697137.2020.1820477
29. Sarri G, Pedder H, Dias S, Guo Y, Lumsden MA. Vasomotor symptoms resulting from natural menopause: a systematic review and network meta-analysis of treatment effects from the National Institute for Health and Care Excellence guideline on menopause. *BJOG* 2017;124:1514-1523. doi: 10.1111/1471-0528.14619
30. Fritz H, Seely D, McGowan J, et al. Black cohosh and breast cancer: a systematic review. *Integr Cancer Ther* 2014;13:12-29. doi: 10.1177/1534735413477191
31. Guttuso T Jr. Effective and clinically meaningful non-hormonal hot flash therapies. *Maturitas* 2012;72:6-12. doi: 10.1016/j.maturitas.2012.01.023
32. Naser B, Schnitker J, Minkin MJ, de Arriba SG, Nolte KU, Osmers R. Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract. *Menopause* 2011;18:366-375. doi: 10.1097/gme.0b013e3181fcb2a6
33. Shulman LP, Banuvar S, Fong HH, Farnsworth NR. Discussion of a well-designed clinical trial which did not demonstrate effectiveness: UIC center for botanical dietary supplements research study of black cohosh and red clover. *Fitoterapia* 2011;82:88-91. doi: 10.1016/j.fitote.2010.10.013
34. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;326:219. doi: 10.1136/bmj.326.7382.219
35. Davey J, Turner RM, Clarke MJ, Higgins JP. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. *BMC Med Res Methodol* 2011;11:160. doi: 10.1186/1471-2288-11-160
36. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2*. The Cochrane Collaboration. Chichester (UK): John Wiley & Sons; 2009.
37. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1:97-111. doi: 10.1002/jrsm.12
38. Tobias A. Assessing the influence of a single study in meta-analysis. *Stata Tech Bull* 1999;47:15-17.
39. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-1558. doi: 10.1002/sim.1186
40. Higgins JP, Green S. 10.4.3.1 Recommendations on testing for funnel plot asymmetry. In: Higgins JP, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. 5.1.0 ed,. Cochrane Library. Chichester (UK): John Wiley & Sons; 2011.

41. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634. doi: 10.1136/bmj.315.7109.629
42. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455-463. doi: 10.1111/j.0006-341x.2000.00455.x
43. Shayan A, Masoumi SZ, Kazemi F, Oshvandi K. Effect of combined herbal capsule menohelp on hot flashes and night sweats in postmenopausal women: a single-blind randomized controlled trial. *J Menopausal Med* 2020;26:135-142. doi: 10.6118/jmm.20002
44. Academic Committee of the Korean Society of Menopause, Lee SR, Cho MK, et al. The 2020 Menopausal Hormone Therapy Guidelines. *J Menopausal Med* 2020;26:69-98. doi: 10.6118/jmm.20000
45. Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. *Menopause* 2004;11:575-577. doi: 10.1097/01.gme.0000142914.55849.6a
46. Wobser RW, Takov V. Black cohosh. *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2022.
47. Pkhaladze L, Davidova N, Khomasuridze A, Shengelia R, Panossian AG. *Actaea racemosa* L. is more effective in combination with *Rhodiola rosea* L. for relief of menopausal symptoms: a randomized, double-blind, placebo-controlled study. *Pharmaceuticals (Basel)* 2020;13:102. doi: 10.3390/ph13050102
48. Jiang B, Kronenberg F, Nuntanakorn P, Qiu MH, Kennelly EJ. Evaluation of the botanical authenticity and phytochemical profile of black cohosh products by high-performance liquid chromatography with selected ion monitoring liquid chromatography-mass spectrometry. *J Agric Food Chem* 2006;54:3242-3253. doi: 10.1021/jf0606149