



Efficacy of the Complementary and Alternative Therapies for the Management of Psychological Symptoms of Menopause: A Systematic Review of Randomized Controlled Trials

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Menopause is not a high-risk period for psychiatric illness but can cause psychological issues; the most common of which are anxiety and depression, which can impair coping and reduce women's quality of life. Thus, many women have leaned toward complementary and alternative medicine (CAM) for the relief of menopause-related symptoms. No rigorous study exists in the literature on the effects of CAMs on the psychological symptoms of menopause despite this growing patient interest. This systematic review aimed to assess the efficacy of CAM interventions on psychological symptoms of menopause. Databases (PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar) were searched from January 2000 to May 2021 using the keywords: menopause, menopausal symptoms, psychological symptoms, and complementary and alternative medicine. The quality of the included studies was assessed using the Mixed Methods Appraisal Tool (MMAT) for randomized clinical trials. Of the 704 articles found, 33 articles with 3,092 participants entered the final review. Aromatherapy, massage, yoga, and acupuncture, as well as some dietary and herbal supplements improved psychological symptoms during menopause based on the findings of the current study. However, the effectiveness of reflexology and exercise was debatable. However, necessary precautions should be taken when using them in clinical settings despite the positive effect of various CAM interventions on reducing psychological symptoms. More studies with a higher methodology quality are required to make better decisions about the effect of various CAM interventions on the psychological symptoms of menopause.

Key Words: Alternative medicine, Complementary medicine, Menopause, Psychology, Systematic review

INTRODUCTION

The menopausal period is a time in women's life characterized by decreased biological and physiological functioning, which can lead to several physical, sexual, vasomotor, and psychological symptoms [1]. Menopause is not a high-risk period for psychiatric illness, but it can cause psychological issues such as poor memory and concentration, depression, anxiety, irritability, and a high level of distress, with anxiety and depression being the two most common problems that can impair

copied and reduce women's quality of life [2].

Hormone therapy has been considered as a first-line treatment for menopause-related psychological symptoms. According to a meta-analysis, estrogen and androgen alone or in combination are more effective in improving psychological symptoms in menopausal women [3]. However, due to the health risks associated with hormone therapy, many women are unable or unwilling to use it [4,5]. As a result, many women have leaned toward complementary and alternative medicine (CAM) for relief of menopause-related symptoms [6,7].

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The two major categories of CAM interventions for menopause are: 1) natural products such as herbal and supplementary products; and 2) mind-body practices such as aromatherapy, massage, relaxation, hypnosis, cognitive behavioral therapy, reflexology, acupuncture, and meditation [6].

Despite this growing patient interest, there is no rigorous research in the literature on the effects of CAMs on menopausal psychological symptoms. This study aims to review all the randomized controlled trials (RCTs) that investigated the effect of CAM on the psychological symptoms of menopause.

MATERIALS AND METHODS

Two researchers (F.D. and V.M.) developed a method for searching for relevant studies published in electronic databases including PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar. To ensure a comprehensive search, the reference lists of the retrieved studies, especially the systematic reviews, were manually screened. The search terms included menopause, menopausal symptoms, psychological symptoms, mental health, depression, anxiety, mood, and CAM. In addition, different types of CAM inter-

ventions were investigated. To improve results, search terms were tailored to each database.

RCTs with any type of CAM as an intervention and psychological symptoms (e.g., anxiety, depression, mental exhaustion) during menopause as a primary or secondary outcome published between January 2000 and May 2021 were included. Non-English publications and trials with an active control group were excluded, as were studies on participants with surgically induced menopause and those with breast cancer.

The screening process for the studies was performed by two reviewers (F.D. and V.M.). The titles, abstracts, and keywords were all reviewed. Full-text papers were retrieved based on eligible abstracts. Trials that met the inclusion criteria were considered for review.

The quality assessment of the studies in the present systematic review was performed by two reviewers (N.R. and A.Z.) using the Mixed Methods Appraisal Tool (MMAT). This tool contains five items for each group, each of which is scored with a Y (Yes: score 1), N (No: score 0), or C (Cannot tell: score 0). In other words, the total response score is determined by the number of positive responses [8]. Any disagreements were settled by a third party (F.D.).

Participants' characteristics, the type of CAM (inter-

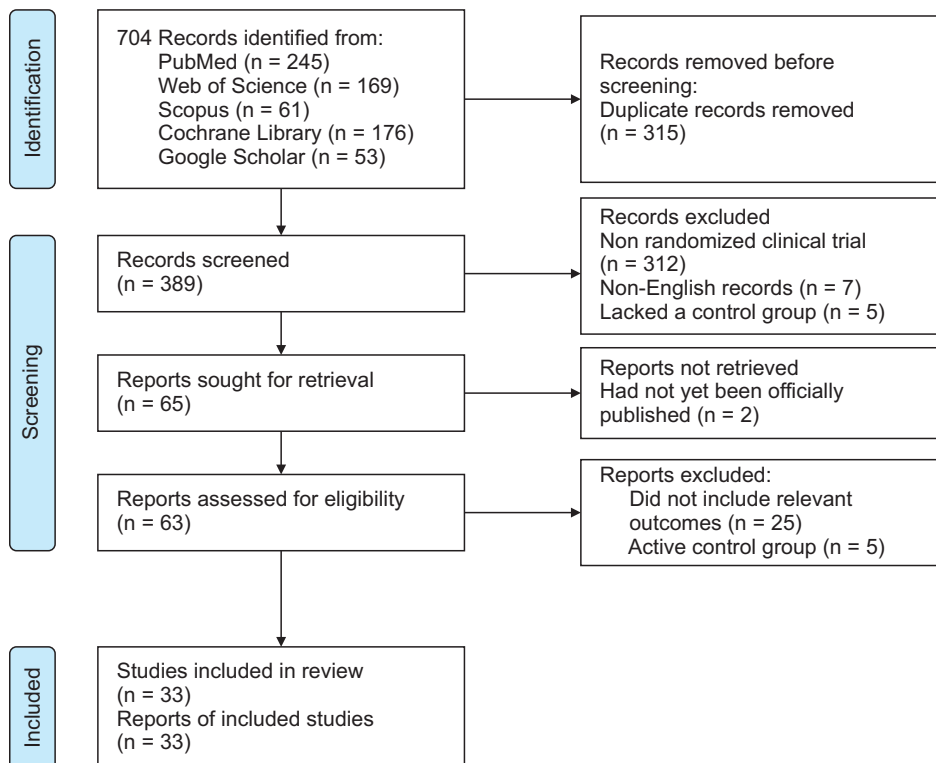


Fig. 1. Study selection process.

vention), the study period, the country, the characteristics of the intervention and control groups, the outcome measure questionnaire, and key relevant findings such as the effectiveness of the intervention on psychological symptoms and any adverse events reported were extracted from each study.

RESULTS

Figure 1 illustrates the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the study selection process. The search strategy yielded 704 research articles. After removing 315 duplicates, 389 publications were eligible for title and abstract review. Based on the selection criteria, 326 studies were excluded. Then, 63 full-text articles were evaluated for eligibility, and 30 records were excluded due to unrelated outcomes or active control group design. Any disagreements among the reviewers were settled through discussion. Finally, 33 studies were included in the qualitative synthesis. The quality assessment is presented in Table 1. The final score for high quality studies is above half (more than 50%).

The characteristics of the 33 relevant studies used for qualitative analyses are described in Table 2. The sample sizes in the studies ranged from 34 to 301 menopausal women. The total number of participants in the included studies' intervention and control groups was 3,092 women with menopausal symptoms. Thirty two studies (97%) had response rates greater than 70% (range, 66.7%–100%). Most of these studies were conducted in Iran (n = 10), followed by the United States (n = 5), Hong Kong (n = 3), Japan (n = 3), Brazil (n = 2), Germany (n = 2), Australia (n = 1), India (n = 1), South Korea (n = 1), China (n = 1), Spain (n = 1), Austria (n = 1), and the United Kingdom (n = 1). Of the trials included in this review, one was a cross over trial and eight had two interventional groups (different types of CAM or different doses of the same type of CAM) and one control group. As a result, there were 41 intervention groups and 33 control groups. The Menopausal Rating Scale, Menopause-Specific Quality of Life Questionnaire, Kupperman Menopause Index, Greene Climacteric Scale, and Women's Health Questionnaire were among the most frequently used questionnaires to assess psychological symptoms in these studies. Herbal and dietary supplements were the most commonly used CAM.

Table 1. Mixed Methods Appraisal Tool (MMAT)

Design	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
Methodological quality criteria/ study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
Quantitative RCT	Y	Y	Y	Y	Y	Y	Y	C	N	N	C	Y	N	Y	Y	C	Y	N	N	Y	Y	N	Y	Y	Y	Y	C	Y	N	Y	Y	Y	Y
1. Is randomization appropriately performed?	Y	Y	Y	Y	Y	Y	Y	C	N	N	C	Y	N	Y	Y	C	Y	N	N	Y	Y	N	Y	Y	Y	Y	C	Y	N	Y	Y	Y	Y
2. Are the groups comparable at baseline?	Y	Y	Y	Y	Y	Y	Y	C	N	N	C	Y	N	Y	Y	C	Y	N	N	Y	Y	C	Y	Y	Y	Y	C	Y	N	Y	Y	Y	Y
3. Are there complete outcome data?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	C	Y	Y	Y	Y	C	Y	N	N	Y	Y	C	Y	Y	Y	Y	C	Y	N	Y	Y	Y	Y
4. Are outcome assessors blinded to the intervention provided?	Y	N	C	Y	N	C	C	N	C	N	Y	Y	N	Y	Y	C	Y	N	N	Y	Y	Y	N	N	N	N	N	N	C	N	Y	N	N
5. Did the participants adhere to the assigned intervention?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	C	Y	Y	Y	Y	Y	C	Y	C	Y	Y	Y	Y	Y	Y	Y	Y	C	Y	Y	Y	Y	Y

RCT: randomized controlled trial, Y: yes, N: no, C: cannot tell.

Table 2. Summary of trials

Study ID	Study	Type of CAM	Participant's characteristics	Drop out (%)	Location	Description of intervention and control	Psychological questionnaire	Key findings
1	Sharif et al. [9] (2020)	Herbal supplement	200 postmenopausal women, aged 45 to 60 years	5.5	Iran	Subjects were randomized to therapy with either daily 1,000 mg of evening primrose oil capsules (n = 100), or matching placebo (n = 100) for 8 weeks.	Menopausal Rating Scale	Evening primrose oil treatment resulted in significant improvements in menopausal psychological symptoms. Upset stomach was reported by one person who used evening primrose oil.
2	Eatemadnia et al. [16] (2019)	Herbal supplement	80 postmenopausal women aged 45–60 years old (70 completed the study)	12.5	Iran	Subjects were randomized to therapy with either a 270–330 µg of St. John's wort (n = 40), or placebo (n = 40) three times a day for two months.	Kupperman Index, Hamilton Depression Rating Scale	The intensity of depression significantly decreased in the St. John's wort group compared to the control group.
3	Ataei-Almanghadim et al. [21] (2020)	Herbal and dietary supplement	93 postmenopausal women aged 40–60 years old (89 completed the study)	4.3	Iran	Subjects were randomized to therapy with either an oral capsule of curcumin (500 mg) (n = 31), or oral tablets of vitamin E (200 IU/day) (n = 31), or placebo (n = 31) twice a day for eight weeks.	Spielberger State-Trait Anxiety Inventory	Curcumin and vitamin E supplementation had no effect on anxiety. Vaginal bleeding, gastric pain, headache and diarrhea were observed in those who used curcumin or vitamin E.
4	Farshbaf-Khalili et al. [23] (2018)	Herbal and dietary supplement	156 postmenopausal women aged 45–60 years old (145 completed the study)	7	Iran	Subjects were randomized to therapy with either 500 mg of the powder of bitter orange (n = 52), or lavender flower (n = 52), or placebo capsules contained 500 mg of starch (n = 52) twice daily for eight weeks.	Spielberger State-Trait Anxiety Inventory	Bitter orange and lavender significantly reduced the mean state-anxiety scores compared with the control. Side effects including nausea, palpitations, and headache in the bitter orange group and in the lavender group was observed.
5	Hirose et al. [49] (2018)	Dietary supplement	96 menopausal women aged 40–59 years who complained of fatigue (89 completed the study)	7.3	Japan	Subjects were randomized to therapy with either active tablets containing high-dose (1,200 mg/day) of soy lecithin (n = 32), or low-dose (600 mg/day) soy lecithin (n = 32), or placebo (n = 32) for 8 weeks.	Menopausal Health-Related Quality of Life, Profile of Mood States	Soy lecithin at a high dose (1,200 mg/day) increased vigor and improved mood in menopausal women. No adverse events were observed.
6	Steels et al. [50] (2017)	Herbal supplement	115 women aged 40 to 65 years (104 completed the study)	9.6	Australia	Subjects were randomized to therapy with either <i>Trigonella foenum-graecum</i> de-husked seed extract, 600 mg per day (n = 59) or placebo (n = 56) for 12 weeks.	Menopause-Specific Quality of Life Questionnaire	600 mg of <i>T. foenum-graecum</i> de-husked seed extract per day reduced psychological symptoms of menopause compared to placebo. No adverse events were reported.

Table 2. Continued

Study ID	Study	Type of CAM	Participant's characteristics	Drop out (%)	Location	Description of intervention and control	Psychological questionnaire	Key findings
7	Hirose et al. [51] (2016)	Dietary supplement	90 healthy women aged 40–60 years who had at least one menopausal symptom on the Menopausal Symptom Scale (87 completed the study)	3.3	Japan	Subjects were randomized to therapy with either active tablets containing ultralow-dose (12.5 mg/day) (n = 30), or low-dose (25 mg/day) isoflavone aglycone (n = 30), or placebo (n = 30), for 8 weeks.	Menopausal Rating Scale, Hospital Anxiety and Depression Scale	A low-dose (25 mg/day) of isoflavone aglycone significantly alleviated symptoms of depression in Japanese middle-aged women.
8	Park and Kim [30] (2016)	Dietary supplement	41 menopausal women between the ages of 40 and 70 years (36 completed the study)	12.2	South Korea	Subjects were randomized to therapy with either 784 mg of natural extract of <i>Schisandra chinensis</i> (n = 20), or placebo (n = 21) for 12 weeks.	Kupperman Index, Menopausal Rating Scale	<i>Schisandra chinensis</i> did not significantly alleviate menopausal psychological symptoms such as nervousness and depression. No adverse event were observed.
9	Shakeri et al. [52] (2015)	Herbal supplement	72 postmenopausal women aged 50–59 years old (71 completed the study)	1.4	Iran	The subjects were randomized to therapy with either two capsules containing 40 mg dried leaves of red clover (n = 36), or matching placebo (n = 36) daily for 12 weeks.	Menopausal Rating Scale	Consumption of dried leaves of red clover reduced the psychological symptoms of menopause.
10	Terauchi et al. [31] (2014)	Dietary supplement	96 women aged 40–60 years who had at least one menopausal symptom (91 completed the study)	5.2	Japan	Subjects were randomized to therapy with either grape seed extract tablets containing either low-dose (100 mg/d) (n = 33), or high-dose (200 mg/d) (n = 32), or placebo (n = 31) for 8 weeks.	Menopausal Health Related Quality of Life Questionnaire, Hospital Anxiety and Depression Scale	Grape seed proanthocyanidin extract decreased psychological symptoms of menopause, including anxiety and depression.
11	Stojanovska et al. [34] (2015)	Herbal supplement	34 postmenopausal Hong Kong Chinese women (29 completed the study)	14.7	Hong Kong	Subjects received 3.3 g/day of Maca or placebo for 6 weeks each, in either order, over 12 weeks. (cross over)	Greene Climacteric Scale, Women's Health Questionnaire (WHQ)	Significant reductions in depression were observed following Maca treatment.
12	Zhong et al. [37] (2013)	Herbal supplement	108 perimenopausal women who reported Menopause Rating Scale (MRS) total scores of 28 or higher (101 completed the study)	6.5	Hong Kong	Subjects were randomized to therapy with either Er-Xian decoction (contained 15 g of six herbs) (n = 54) or placebo sachet (contained 15 g of granules and consisted of dextrin, tea essence, gardenin, and caramel) (n = 54) for 4 weeks.	Menopause Rating Scale, Menopause-Specific Quality of Life Questionnaire	Er-Xian decoction significantly reduced the psychological symptoms of menopause. No serious adverse event was reported.

Table 2. Continued

Study ID	Study	Type of CAM	Participant's characteristics	Drop out (%)	Location	Description of intervention and control	Psychological questionnaire	Key findings
13	Auerbach et al. [54] (2012)	Dietary supplement	100 healthy postmenopausal women aged 45–60 years old (81 completed the study)	19	Austria	Subjects were randomized to therapy with either two daily doses of 30 mg pomegranate seed oil containing 127 kg of steroidal phytoestrogens per dose (n = 50) or placebo (n = 50) for 12 weeks.	Menopausal Rating Scale	When compared to a placebo, pomegranate seed oil had no effect on menopausal psychological symptoms. No adverse effect were reported.
14	Chang et al. [47] (2012)	Dietary supplement	64 menopausal woman with moderate or severe menopausal symptoms (score greater than or equal to 20) (61 completed the study)	4.7	USA	The subjects were randomized to therapy with either Estrog-100 tablets (n = 31), or the placebo tablet (n = 33) twice a day orally for 12 weeks.	Kupperman menopause index	The Estrog-100 group showed statistically significant improvement in psychological symptoms of menopause such as nervousness and feeling blue or depressed. No adverse events were observed.
15	Carmignani et al. [53] (2010)	Dietary supplement	60 healthy, symptomatic, postmenopausal women of 40–60 years of age (all completed the study)	0	Brazil	The subjects were randomized to therapy with either dietary soy supplementation containing 90 mg of isoflavone (n = 20), or HT containing 1 mg estradiol and 0.5 mg norethisterone acetate (n = 20), or placebo (n = 20) for 16 weeks.	Menopausal Rating Scale	There was no difference between the study groups with respect to psychological symptoms or total MRS score, all three groups showing a similar improvement. No adverse events were observed.
16	Hsu et al. [40] (2011)	Herbal supplement	50 menopausal women aged 45–60 years old (all completed the study)	0	China	Women were randomized to receive either two sachets daily of <i>Dioscorea</i> extracts containing 12 mg/sachet (n = 25), or placebo (n = 25) for 12 months.	Greene Climacteric Scale	<i>Dioscorea alata</i> alleviated menopausal symptoms, particularly psychological parameters. No adverse events were reported.
17	Amsterdam et al. [42] (2009)	Herbal supplement	34 postmenopausal women aged 40 and above (28 completed the study)	17.6	USA	Subjects were randomized to therapy with either 2 pharmaceutical-grade of black cohosh extract (n = 15) or placebo (n = 13) for up to 12 weeks.	Hamilton Anxiety Rating Scale, Beck Anxiety Inventory, Green Climacteric Scale, Psychological General Well-Being Index	No statistically significant effect of black cohosh on anxiety compared to placebo. Arthralgia and edema in one person in intervention group was reported.
18	Haines et al. [44] (2008)	Herbal supplement	100 symptomatic menopausal women aged 45–55 years old (84 completed the study)	16	Hong Kong	Subjects were randomized to therapy with either a combination of Danggui (<i>Angelicae sinensis</i>) and Huang Qi (<i>Astragalus membranaceus</i>) in a total dose of 3 g per day (n = 45) or placebo (n = 39) for six months.	Menopause Specific Quality of Life	There were no significant changes in the psychological domain of the Menopause Specific Quality of Life in those who received Danggui Buxue Tang. No serious adverse events were observed.

Table 2. Continued

Study ID	Study	Type of CAM	Participant's characteristics	Drop out (%)	Location	Description of intervention and control	Psychological questionnaire	Key findings
19	Brooks et al. [35] (2008)	Herbal supplement	60 healthy postmenopausal women ages 50 to 60 years who were currently experiencing symptoms of menopause (40 completed the study)	33	Australia	Women were randomized to receive either 3.5 g/day of powdered Maca (n = 30), or matching placebo (n = 30) for 6 weeks, in either order, over a total of 12 weeks.	Greene Climacteric Scale	A significant reduction in scores in the areas of psychological symptoms, including the subscales for anxiety and depression after Maca consumption compared with both baseline and placebo.
20	Heger et al. [48] (2006)	Herbal supplement	110 (109 completed the study)	0.9	Germany	Subjects were randomized to therapy with either one enteric-coated tablet of <i>Rheum rhabarbarum</i> (ERr 731) (n = 55) or placebo (n = 55) daily for 12 weeks.	Menopausal Rating Scale	Psychological symptoms of menopause were significantly reduced in the ERr 731 group compared to the placebo group. No adverse events were reported.
21	Uebelhack et al. [17] (2006)	Herbal supplement	301 women aged 45–60 years experiencing climacteric complaints with psychological symptoms (294 completed the study)	2.3	Germany	The subjects were randomized to therapy with either ethanolic St. John's wort extract and isopropanolic black cohosh extract (n = 151), or a matched placebo (n = 150) for 16 weeks.	Hamilton Depression Rating Scale	The treatment with ethanolic St. John's wort extract and isopropanolic black cohosh extract was significantly superior to placebo in alleviating the related psychological component.
22	Jorge et al. [59] (2016)	Yoga and exercise	117 menopausal women 45–65 years old (88 completed the study)	24.8	Brazil	Subjects were randomized to receive either 75 minutes of supervised practices yoga (n = 47), or exercises (n = 38) twice a week, for 12 weeks. Control consisted of a 12-week waiting period, without any intervention (n = 32).	Lipp Stress Symptom Inventory, Beck Depression Inventory, Brief World Health Organization Quality of Life Questionnaire, State/Trait Anxiety Inventories, Menopausal Rating Scale	Psychological symptoms of menopause, stress levels and depression decreased in yoga practitioners compared to control and exercise groups. No impact on the level of anxiety was observed.
23	Joshi et al. [60] (2011)	Yoga	200 menopausal women between 40 and 55 years of age (180 completed the study)	10	India	The subjects were randomized to receive daily yoga practices including physical postures (asana), breathing technique (pranayama) and meditation under supervision of an expert yoga trainer (n = 100). Control consisted of a 90 days waiting period, without any intervention (n = 100).	Menopausal Rating Scale	Yoga therapy was effective to decrease psychological symptom of menopause.

Table 2. Continued

Study ID	Study	Type of CAM	Participant's characteristics	Drop out (%)	Location	Description of intervention and control	Psychological questionnaire	Key findings
24	Elavsky and McAuley [1] (2007)	Yoga and exercise	164 low active, middle-aged women (42–58 years) experiencing menopausal symptoms (163 completed the study)	0.6	USA	Subjects were randomized to therapy with either 90-minute Yoga session twice a week (n = 63) or walking program met 3 times per week for 1 hour in a large gymnasium for 4 months (n = 62). Control group (n = 39) received no intervention.	Greene Climacteric Scale, Beck Depression Inventory	Walking and yoga were effective in enhancing mental health and reducing psychological symptoms.
25	Abedi et al. [62] (2015)	Exercise	106 postmenopausal women aged 45–60 years (97 completed the study)	8.5	Iran	Subjects were randomized to receive either a pedometer with instruction to increase their steps by 500 per week and wearing the pedometer all times, except when bathing and sleeping (n = 53) or no intervention (n = 53).	General Health Questionnaire (GHQ-28), Beck Depression	Pedometer-based walking decreased the level of anxiety and depression in postmenopausal women.
26	Sternfeld et al. [63] (2014)	Exercise	248 late perimenopausal and postmenopausal sedentary women with frequent vasomotor symptoms (241 completed the study)	2.8	USA	Subjects were randomized to therapy with either exercise intervention consisted of 12 weeks of three individualized cardiovascular conditioning training sessions per week conducted at local fitness facilities and supervised by a trained certified exercise trainer (n = 106), or usual activity (n = 142).	Patient Health Questionnaire-8, Generalized Anxiety Disorder-7 Questionnaire	12 weeks of moderate-intensity aerobic exercise resulted in small improvements in depressive symptoms but not statistically significant when <i>P</i> values were adjusted for multiple comparisons.
27	Bakhtari et al. [56] (2019)	Aromatherapy	70 postmenopausal women aged 45 years and above (62 completed the study)	11.4	Iran	The subjects were randomized to therapy with either aromatherapy inhaled 2% lavender essential oil every night before bedtime for 20 minutes during one month (n = 35), or placebo (distilled water) in the same manner as the intervention group (n = 35).	Menopause-Specific Quality of Life Questionnaire	Inhalation aromatherapy using lavender essential oil decreased psychological symptom of menopause.
28	Lotfipour Rafsanjani et al. [57] (2015)	Aromatherapy and massage	120 menopausal women suffering from depression that got a score of 14 or above based on the Beck Depression Inventory (118 completed the study)	1.7	Iran	The subjects were randomized to therapy with either aromatherapy massage with essential oil of geranium 2% in almond oil (n = 40), or massage (n = 40) for 8 weeks, once a week for 30 minutes, or usual care (n = 30).	Beck Depression Inventory	Aromatherapy massage reduced the mean depression score. Massage therapy also reduced depression score. Aromatherapy massage reduced the depression score more than massage therapy.

Table 2. Continued

Study ID	Study	Type of CAM	Participant's characteristics	Drop out (%)	Location	Description of intervention and control	Psychological questionnaire	Key findings
29	Taavoni et al. [58] (2013)	Aromatherapy and massage	90 menopausal women aged 45–60 years old (87 completed the study)	3.3	Iran	The subjects were randomized to therapy with either 30 minutes aromatherapy sessions with aroma oil (n = 30), or massage therapy with odorless oil (n = 30) twice a week, for four weeks; while no treatment was provided to subjects in the control group (n = 30).	Menopausal Rating Scale	Aromatherapy massage decreased the psychological score. Massage therapy also decreased the psychological score. Aromatherapy massage decreased the psychological score more than massage therapy.
30	Espí-López et al. [65] (2020)	Massage	50 participants with menopause, aged 45–65 years (50 completed the study)	0	Spain	Subjects were randomized to receive either a 30 minutes craniofacial massage sessions using an average degree of pressure consisted of synchronized kneading and sliding movements for three consecutive weeks (one session a week) with a follow-up at one month (n = 25), or no treatment (n = 25).	Menopausal Rating Scale, SF-36 Quality of Life Questionnaire	The treatment improved participants' mental health, partially ameliorated the decrease in scores on the Menopause Rating Scale.
31	Mahdavi pour et al. [66] (2019)	Reflexology	100 women with age of 40–61 years old with depression during their menopausal period, 1–4 years after 12 missed menstrual cycles for 12 consecutive months (90 completed the study)	10	Iran	Subjects were randomized to therapy with either 15 minutes of foot reflexology on each foot for a total of 30 minutes in evenings, twice a week for six week (n = 50), or routine care (n = 50).	Beck Depression Questionnaire	The intervention group's depression was significantly decreased after the foot reflexology in 12 sessions.
32	Williamson et al. [67] (2002)	Reflexology	80 women, aged between 45 and 60 years, reporting menopausal symptoms (76 completed the study)	5	UK	Women were randomized to receive nine sessions of either reflexology (n = 42) or non-specific foot massage (control) (n = 38) by four qualified reflexologists given over a period of 19 weeks.	Women's Health Questionnaire	Foot reflexology was not shown to be more effective than non-specific foot massage in the treatment of psychological symptoms occurring during the menopause.
33	Avis et al. [68] (2016)	Acupuncture	209 perimenopausal and postmenopausal women aged 45–60 experiencing an average of ≥ 4 vasomotor symptoms (176 completed the study)	15.8	USA	Subjects were randomized to therapy with either 6-month course of up to 20 acupuncture treatments (n = 170), or usual care for 6 months followed by the same 6-month course of acupuncture treatments administered to study participants in the control group (n = 39).	The Women's Health Questionnaire Center for Epidemiologic Studies, Depression Scale, General Anxiety Disorder, Perceived Stress Scale	Acupuncture had a significant positive effect on memory and anxiety and these benefits were maintained 6 months following the end of treatment.

CAM: complementary and alternative medicine.

DISCUSSION

To the best of our knowledge, this is the first systematic review solely focused on the psychological symptoms of menopause. The current study provides evidence for the beneficial effects of different types of CAM on psychological symptoms during menopause. Each therapy will be discussed in detail below.

Herbal and dietary supplements

Evening primrose oil

A result of a study investigating the effect of 1,000 mg of daily evening primrose oil (EPO) for eight weeks on psychological symptoms of 200 menopausal women found significant improvements in the psychological symptoms after treatment compared to placebo. In terms of safety, only one woman (1.1%) reported stomach upset after using EPO [9]. EPO is a commonly used alternative therapy with a rich source of omega-3 essential fatty acids (linoleic acid and gamma-linolenic acid) [10]. Although there is insufficient evidence to support the use of EPO for somatic symptoms of menopause such as hot flushes [11,12], its effectiveness and safety for mental health have been confirmed in several studies [13,14]. The therapeutic effects of EPO might be attributed to omega-3's direct effects on immune cells and its indirect effects on eicosanoid synthesis, including prostaglandins, cytokines, and cytokine mediators [15]. Longer trials are required to make more reliable decisions about the use and safety of EPO in clinical practice.

*St. John's wort (*Hypericum perforatum*)*

Two studies, one in Iran and the other in Germany, examined the effect of St. John's wort on the psychological symptoms of 381 menopausal women. Both studies found that treatment with St. John's wort for 8–16 weeks significantly reduced the severity of depression [16,17]. St. John's wort extract is approved for the treatment of mild to moderately severe depressive moods and has gained widespread acceptance and popularity in recent years. The efficacy of St. John's wort on psychological symptoms of various target groups has been confirmed in several studies [18,19]. It has been proposed that St. John's wort acts via similar biochemical mechanisms to other antidepressants by inhibiting synaptosomal uptake of serotonin, dopamine, and norepinephrine, as well as down regulating beta-receptors while up-

regulating 5-HT₂ receptors in the frontal cortex [20].

Curcumin

One study investigated the effect of 1,000 mg of daily curcumin for eight weeks on the anxiety of 93 postmenopausal women in Iran. There were no significant changes in anxiety levels after treatment. In terms of side effects, gastric pain was reported in 5 women (16.7%), vaginal bleeding in one woman (3.3%), headache in one woman (3.3%), and diarrhea in one woman (3.3%) after using curcumin [21]. Curcumin, a type of polyphenol found in turmeric, is derived from the powdered roots of the *Curcuma longa* plant. Because of its antioxidant and anti-inflammatory properties, curcumin is being recognized and used in a variety of forms around the world for a variety of potential health benefits [22]. Longer trials are needed, however, to make more reliable decisions about the use and safety of curcumin in clinical practice.

Vitamin E

One study investigated the effect of 400 IU of vitamin E for eight weeks on the anxiety of 93 postmenopausal women in Iran. There were no significant changes in anxiety levels after treatment. In terms of side effects, 5 women (17.2%) reported gastric pain, one woman (3.4%) reported vaginal bleeding, and one woman (3.4%) reported diarrhea after using vitamin [21]. Vitamin E is a fat-soluble vitamin that is thought to function as an antioxidant in the body. Anecdotal evidence suggests that vitamin E can help with menopausal symptoms. However, there is currently insufficient empirical evidence to conclude that vitamin E is effective and safe for psychological symptoms of menopause.

Bitter orange

One study investigated the effect of 1,000 mg of bitter orange for eight weeks on the anxiety of 156 postmenopausal women in Iran. When compared to the control, bitter orange significantly reduced the mean state-anxiety scores. The following side effects were reported: nausea (4.2%), palpitations (4.2%) and headache (2.1%) [23]. There have been no previous studies on the effects of bitter orange consumption in postmenopausal women. However, one study has found that ingested bitter orange can help reduce preoperative anxiety [24]. Bitter orange's anti-anxiety effects are due to linalool, limonene, and flavonoid, which activate the nervous system by entering the brain via peripheral circulation

and binding to the gamma-aminobutyric acid type A receptor [25]. More research is needed in this field to determine the effectiveness and safety of its use.

Lavender

One study investigated the effect of 1,000 mg of lavender for eight weeks on the anxiety of 156 postmenopausal women. Lavender significantly reduced the mean state-anxiety scores compared with the control. The following side effects were reported: nausea (8.2%), palpitations (4.4%) and headache (4.1%) [23]. This is consistent with previous trials that found lavender to be effective in reducing anxiety and well tolerated, with gastrointestinal side effects being the most commonly reported side effect [26-28]. More research is needed to determine the effectiveness and safety of its use.

Schisandra chinensis

Schisandra chinensis, which means “five flavors,” is a type of berry that has been used for thousands of years in the form of tea to improve memory [29]. The effects of *S. chinensis* on 41 women’s menopausal symptoms were studied. A study found a significant reduction in hot flushes and night sweats after using 784 mg of natural *S. chinensis* extract for 6 weeks, but not in psychological symptoms such as nervousness and depression. There were no adverse events observed [30]. More research is needed to determine its efficacy due to the small number of studies and insufficient information.

Grape seed

Grape seed proanthocyanidin (class of polyphenol antioxidants) extract at low (100 mg/day) and high (200 mg/day) doses for 4 weeks reduced psychological symptoms including anxiety and depression of 96 menopausal women in Japan. A more remarkable improvement was observed in the high-dose group compared to low dose and placebo [31]. The effects of proanthocyanidin (which does not bind to estrogen receptors) on menopausal symptoms have been attributed to its antioxidant activity; however, the precise mechanism remains unknown [32]. Because of the small number of studies and insufficient information, more research is required to determine its efficacy and safety.

Maca (Lepidium meyenii)

Maca, an Andean plant of the brassica (mustard) family, has been used for centuries to treat infertility and

female hormone balance [33]. Our systematic review identified 2 RCTs that investigated the effects of maca on psychological symptoms in 94 women at various stages of menopause. Each of these trials found that maca had a positive effect on menopausal symptoms. Significant reductions in depression and anxiety were observed after six weeks of treatment with different doses of 3.3 mg or 3.5 mg maca [34,35]. Despite preliminary evidence for maca’s benefits, findings were limited by a small number of sample sizes and a lack of safety data. More research is needed to determine the efficacy and safety of maca in the treatment of psychological symptoms of menopause.

Er-Xian decoction

Er-Xian decoction is a Chinese herbal composed of different herbs that was initially designed and named by Zhang Bo-na in 1950 [36]. According to the findings of one trial conducted by Zhong et al. [37], using 15 mg Er-Xian decoction daily for six weeks significantly reduced psychological symptoms of menopause. There were no reports of serious adverse events. The efficacy of Er-Xian decoction in the treatment of menopausal symptoms was previously reported in a systematic review. Despite the fact that the results of that study showed that Er-Xian decoction significantly improved at least one menopausal symptom. The reviewers concluded, however, that the findings were limited by the low quality of the investigated studies, the lack of double-blind controlled trials, and the lack of proper randomization procedures [38]. Thus, current research does not provide enough evidence to support the efficacy of Er-Xian decoction in the treatment of menopausal symptoms. More research is needed to determine the efficacy and safety of Er-Xian decoction in the treatment of menopausal symptoms.

Wild yam (Dioscorea)

Wild yam is a tonic nourishment that is high in ascorbic acid and protein; it is a tuber that has traditionally been used in Chinese medicine to treat a variety of symptoms, including menopausal symptoms [39]. However, the evidence for the effects of wild yam on menopausal symptoms is limited. Significant improvement was seen in psychological symptoms of 50 menopausal women following the use of 12 mg wild yam twice a day for 12 months with no adverse events [40]. More research is needed to determine the efficacy of wild yam due to the small number of studies and insuf-

ficient information regarding long-term effects.

Black cohosh (Cimicifuga racemosa)

A previous systematic review of 16 RCTs that assessed the effects of oral black cohosh on somatic symptoms in 2,027 menopausal women found insufficient evidence to support the use of black cohosh for menopausal symptoms [41]. In our review, the results of a study evaluating the effect of black cohosh on psychological symptoms of 34 menopausal women revealed that black cohosh had no statistically significant effect on anxiety. Arthralgia and edema were reported in one person (5.9%) after using black cohosh [42]. In a second RCT comparing black cohosh extract with St John's wort to placebo in 301 menopausal women, the level of depression significantly decreased compared to placebo [17]. It is difficult to draw any conclusions from this study if black cohosh is beneficial on its own or in combination with other herbs.

Combination of Danggui (Angelicae sinensis) and Huang Qi (Astragalus membranaceus)

Danggui, a traditional Chinese herb, is commonly used in conjunction with other herbs to treat menopausal problems [43]. However, in a RCT comparing Danggui combined with Huang Qi to placebo in 100 women, there were no significant differences in the psychological domain of the Menopause Specific Quality of Life in those who received treatment versus those who did not [44].

Phytoestrogens

Phytoestrogens are non-steroidal plant-derived compounds derived from various herbs that may produce estrogen effects [45]. According to the findings of a meta-analysis on the efficacy of phytoestrogens on menopausal symptoms, phytoestrogens appear to reduce the frequency and intensity of hot flushes without causing adverse events [46]. We identified 8 studies on the effect of phytoestrogen-based herbal medicine on psychological symptoms of 707 menopausal women in our review. The effect of a Korean botanical herb called EstroG-100 containing 0.002% cinnamic acid originated from *Cynanchum wilfordii* root, 0.08% shanzhiside methylester from *Phlomis umbrosa* root and 0.57% nodakenin from *Archispirostreptus gigas* root, revealed statistically significant improvement in psychological symptoms of menopause such as nervousness and feeling blue or depressed without any side effects [47]. He-

ger et al. [48] investigated the effect of *Rheum raphaniticum*, referred to as ERr 731 (trade name Phytoestrol N) on menopausal women, and the results revealed that psychological symptoms of menopause were significantly reduced in those who were treated with ERr 731 for 12 weeks compared to the placebo, with no adverse events. The result of a study by Hirose et al. found that soy lecithin at a high dose (1,200 mg/day) for 8 weeks increased vigor and improved mood in menopausal women with no adverse events [49]. The result of another trial conducted by Steels et al. [50] on 115 healthy menopausal women found that 600 mg of *Trigonella foenum-graecum* de-husked seed extract per day for 12 weeks reduced psychological symptoms of menopause with no adverse events. Another findings revealed that a low-dose (25 mg/day) of isoflavone aglycone for 8 weeks significantly reduced depression symptoms in Japanese middle-aged women [51]. Shakeri et al. [52] found that consuming 40 mg of dried red clover leaves for 12 weeks may be beneficial in reducing the psychological symptoms of menopause. However, the findings of a study conducted by Carmignani et al. [53] revealed that the effectiveness of 90 mg isoflavone for 16 weeks was not superior to placebo or hormone replacement therapy in reducing psychological symptoms of menopause. Another study also found that treatment with 30 mg of pomegranate seed oil (containing 127 kg of steroidal phytoestrogens per dose) for six weeks had no effect on menopausal psychological symptoms [54]. While the majority of evidence suggests that phytoestrogens are safe and effective for alleviating psychological symptoms of menopause, more RCTs using standardized methods that allow for study comparison are thus required in order to draw definitive conclusions about their use.

Aromatherapy

Aromatherapy, also known as essential oil therapy, is thought to reduce anxiety and increase relaxation, which may be beneficial in alleviating stressful menopausal symptoms [55]. Three studies examined the effect of aromatherapy on 280 women's menopausal symptoms. Bakhtiari et al. [56] found that using 2% lavender essential oil inhalation aromatherapy every night before bedtime for 20 minutes for one month reduced psychological symptoms of menopause. Aromatherapy combined with other CAM interventions may provide additional symptom relief. A study, for example, found that aromatherapy massage with 2% essential oil of

geranium in almond oil for 8 weeks may be beneficial in reducing depression in menopausal women [57]. Another study by Taavoni et al. [58] showed that 30-min aromatherapy sessions with aroma oil twice a week for 4 weeks decreased the psychological symptoms of menopause. There is, however, insufficient evidence to support aromatherapy as a stand-alone treatment to manage the psychological symptoms of menopause.

Yoga

All three studies that examined the effect of yoga on psychological symptoms in 481 women found it to be beneficial with no negative side effects [1,59,60]. Elavsky and McAuley [1] found that a 90-minute yoga session twice a week for four months reduced psychological symptoms of menopause. Another study found that 75 minutes of supervised yoga practice twice a week for 12 weeks reduced stress levels and depression of menopausal women [59]. Joshi et al. [60] also found that daily yoga therapy was effective at decreasing psychological symptoms of menopause. This is consistent with a systematic review and meta-analysis that concluded that there was moderate evidence for the short-term effects of yoga on psychological symptoms in menopause [61]. Yoga appears to be safe and may be effective for psychological symptoms, according to a review of research.

Exercise

Four studies evaluated the effect of exercise and physical activity on different psychological symptoms of 635 menopausal women. A walking program three times a week for one hour in a large gymnasium on menopausal symptoms over a four-month period was found to be effective in improving mental health and reducing psychological symptoms in participants [1]. Another study examined the effect of a 12-week training program that included 75 minutes of supervised stretching (for the shoulder girdle, cervical muscles, and lower legs) twice a week. The result showed no significant effect on the level of anxiety and depression of participants compared to the control group. No adverse events were reported during the protocol [59]. Another study examined the effect of pedometer-based walking on depression and anxiety in 106 postmenopausal women. The intervention group's anxiety and depression levels were found to be lower [62]. Sternfeld et al. [63] investigated the effect of a 12-week training program that included three individualized cardiovascular

conditioning training sessions per week on menopausal symptoms in late perimenopausal and postmenopausal women. The findings revealed small but not statistically significant improvements in depressive symptoms [63]. Although a systematic review and meta-analysis found that exercise programs are a viable treatment option for anxiety [64], the inconsistent findings of trials in this review necessitate further research to determine the efficacy of exercise for psychological symptoms of menopause.

Massage

Three studies evaluated the effect of massage therapy on psychological symptoms of 260 menopausal women. Espí-López et al. [65] reported that 30 minute craniofacial massage sessions using an average degree of pressure consisting of synchronized kneading and sliding movements for three consecutive weeks improved the mental health of menopausal women. Lotfipour Rafsanjani et al. [57] found that 30-minute massage therapy with essential oil of geranium 2% in almond oil for 8 weeks reduced depression in menopausal women. Another study by Taavoni et al. [58] also revealed that 30-minute massage therapy with odorless oil twice a week for four weeks decreased the psychological score of menopausal women. There is debate about whether there are true predictors of positive outcomes in clinical trial interventions. One of the predictors that may taint the outcomes of massage therapy, for example, is communication between the therapist and the participants, which may bias the results.

Reflexology

Two studies investigated the effect of 15–30 min foot reflexology for 12–19 sessions on 180 menopausal women. According to a recent study conducted by Mahdavi-pour et al. [66], the level of depression decreased significantly after 12 sessions of foot reflexology. Another study, however, found no statistically significant differences in anxiety and depression symptoms between nonspecific foot massage and reflexology [67]. Because of inconsistent findings, more research is needed to determine the efficacy of reflexology for psychological symptoms of menopause.

Acupuncture

One study investigated the short- and long-term effects of acupuncture on the quality of life-related measures of 209 perimenopausal and postmenopausal

women. The findings revealed that acupuncture had a significant positive effect on memory and anxiety, and these benefits lasted for 6 months after treatment ended [68]. This is consistent with some previous trials that showed the effectiveness of acupuncture for alleviating psychological symptoms including anxiety in different target groups [69,70]. A meta-analysis of the effectiveness of acupuncture in the treatment of anxiety disorder found that acupuncture is safe and effective for the treatment of anxiety disorder [71]. More research using precise methods is needed to determine the true efficacy of acupuncture and the mechanisms underlying the benefit that some participants receive.

Limitation

As with any systematic review, the current study has some limitations. The risk of bias of some of the included RCTs was considerable; additionally, selection biases, which are potential threats to all systematic reviews, may exist. It is nearly impossible to blind participants, intervention providers, and outcome assessors in some studies that use interventions such as yoga, exercise, massage, aromatherapy, reflexology, and acupuncture, which may affect the results. The majority of the studies were constrained by outcome questionnaires and sample size. The majority of study questionnaires were self-reported, and some trials had a small sample size. Because most trials focused on the short-term effects, the long-term effects of such interventions are not well established. Limiting systematic reviews to English-only is also the limitation of our study, which can lead to biased effect estimates and reduce generalizability.

CONCLUSION

Despite the positive effect of various CAM interventions on reducing psychological symptoms, necessary precautions should be taken when using them in the clinical setting. More research with a higher methodology quality is required to make better decisions about the effect of various CAM interventions on psychological symptoms of menopause.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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