Complementary Therapies in Clinical Practice 36 (2019) 181–194

Contents lists available at ScienceDirect

Complementary Therapies in Clinical Practice

journal homepage: www.elsevier.com/locate/ctcp

Complementary and alternative medicine for natural and treatment-induced vasomotor symptoms: An overview of systematic reviews and meta-analyses

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ARTICLE INFO

Keywords:
Complementary and alternative medicine
Hot flashes
Night sweats
Overview
Vasomotor symptoms

ABSTRACT

Background and purpose: Vasomotor symptoms (VMS) are very common in menopausal populations and cancer patients and can cause physical and mental discomfort. We aim to summarize the findings of systematic reviews and meta-analyses (SRs/MAs) that assessed the effectiveness of complementary and alternative medicines (CAMs)on VMS to provide solid evidence for future practice.

Methods: PubMed, Embase, the Cochrane Library, and Web of Science were searched from inception to May 2019 to identify relevant SRs/MAs. The methodological quality of SRs/MAs and evidence levels of the outcomes were assessed.

Results: A total of 29 SRs/MAs were reviewed. Evidence has shown that acupuncture, hypnosis, paced respiration, cognitive behavioural therapy, genistein, soy isoflavones, S-equol, combined preparations of black cohosh, and omega-3 supplements could significantly reduce VMS. The methodological quality of the SRs/MAs was moderate or high.

Conclusion: CAMs might be beneficial for reducing VMS, but the evidence levels were not high. Several priorities for future practice were identified.

1. Introduction

Vasomotor symptoms (VMS) consisting of hot flashes and night sweats are often described as the perception of intense heat on the face, neck and upper chest, then cooling via cutaneous vasodilation, perspiration, and chills [1,2]. These symptoms can either stem from natural causes (such as the menopausal transitions of women and men) or iatrogenic causes (such as cancer endocrine therapies, surgical ovarian removal, androgen deprivation therapy, chemotherapy, or radiotherapy [3–5]). The available evidence indicates that approximately 40–60% of natural perimenopausal women [6] and 40% of middle-aged men [7] worldwide suffered from VMS, and the presence of these symptoms could linger for between 5 months and 10 years [8]. Moreover, VMS induced by diseases or iatrogenic causes may be more common, severe, and long-lasting. It was estimated that two-thirds of breast cancer survivors experience hot flashes, and 60% described these symptoms as moderate or extremely severe [9]. In addition, 58–80% of castrated prostate cancer patients reported hot flashes [10,11], which could last for eight years [12]. What is even more bothersome is that VMS often coexist and interact with other symptoms such as sleep disruption, fatigue, mood disturbances, and social embarrassment, which can disturb daily life and work, impact overall quality of life [13–16], and decrease long-term compliance with cancer treatment [3]. In addition, women with persistent VMS may have a higher risk of breast cancer [17]. Consequently, it is necessary to identify valid and protracted approaches to help individuals improve VMS.

However, the pathogenesis of VMS has not been fully elucidated. Among the existing theories of the aetiology, the most plausible interpretation is a reduction in ovarian/testicular activity that leads to hormonal fluctuations, which results in instability of the hypothalamic thermoregulatory setpoint and finally causes VMS [18]. Thus, hormone therapy (HT), which can stabilize hormone levels in patients, has been widely used for many years to alleviate VMS and remains the most effective treatment available [19,20]. However, the use of HT has fallen dramatically [21] since the Women's Health Initiative first reported negative effects of HT in 2002 [22]. Many studies successively found that long-term use of HT increased the risk of cardiovascular disease, endometrial hyperplasia, stroke, venous thromboembolism, and

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https://doi.org/10.1016/j.ctcp.2019.07.007
Received 5 April 2019; Received in revised form 18 July 2019; Accepted 18 July 2019

gallbladder disease [20,23–25]. Moreover, HT is contraindicated in breast cancer patients [22] and prostate cancer patients [26,27] due to cancer recurrence risks. In addition to the safety concerns, nearly 18% of users did not benefit from HT in the aspect of hot flash reduction [28]. In addition, prescribed medications (e.g. antidepressants and gabapentin) have also been proven effective in improving VMS but have low patient acceptance due to their moderate efficacy and the variety of associated side effects such as gastrointestinal symptoms, constipation, mouth dryness, depressed mood, dizziness, muscle and joint pain, and leukocytopenia [19,29,30]. With the increasing concerns about the risks of HT and prescribed medications, both physicians and patients with VMS have increased interest in complementary and alternative medicines (CAMs) [31] that are considered relatively non-toxic [32].

Existing evidence has shown that the popularity of CAMs is high internationally and herbal medicine, phytoestrogens, and mind-body therapies (e.g. relaxation, yoga) seem to be the most popular [33,34]. According to a survey, approximately 50.5% of menopausal women worldwide used CAMs to reduce VMS and other menopausal symptoms and 32.9% of them were regular users. Additionally, the average prevalence of CAM use during a year was 47.7% [33]. In particular, menopausal women in Australia were the largest users of CAMs (67.9%), compared to other countries in the world, UK(57.25%), USA(34.8%), and Finland (11%) [34]. In addition, CAMs were also used frequently to relieve VMS induced by cancer treatment and other iatrogenic causes [35,36]. Some evidence [37–40] showed that CAMs could significantly reduce the frequency and severity of VMS and shorten the duration of these symptoms, thereby relieving the suffering of these patients.

However, the results from primary trials regarding the efficacy of CAMs on VMS have been controversial and the existing systematic reviews and meta-analyses (SRs/MAs) also did not reach a consensus on this issue. Goldstein et al. [41] conducted an umbrella systematic review based on 14 randomized controlled trials (RCTs) and 10 SRs/MAs to explore the effects of nonpharmacological interventions on VMS in peri- or post-menopausal women. The results showed that acupuncture, yoga, and hypnosis could significantly reduce VMS when compared with inactive controls; the effectiveness of mindfulness and relaxation was mixed; while no benefit was found in regard to exercise or paced respiration. However, they did not assess the effectiveness of other types of CAMs, such as herbal medicines and phytoestrogens, and male patients who can also suffer from VMS were excluded from their study. In addition, a narrative review by Moore et al. [42] reported that some CAM treatment modalities, including hypnosis, soy isoflavones, and black cohosh, showed positive effects on ameliorating VMS, while exercise had no benefit. However, their findings were only based on a small number of RCTs and SRs/MAs rather than comprehensive existing evidence. The effectiveness of other CAMs, such as yoga, red clover, phytoestrogens, and St. John's wort on VMS was still unclear according to their study. Furthermore, many new SRs/MAs [39,40,43–45] related to this issue had been published after these two publications, which might provide new evidence. Overall, the existing evidence from SRs/MAs of the efficacy of CAMs on VMS is still inconsistent, and a more comprehensive study of all available evidence is lacking to date.

By synthesizing findings reported in SRs/MAs, an overview of reviews can provide more concentrated, comprehensive and high-quality evidence about the effects of interventions on a specific topic for readers [46]. Hence, we conducted this overview to summarize all existing evidence from the SRs/MAs of RCTs and control clinical trials (CCTs) about the effectiveness of CAMs in improving VMS to provide more solid evidence for future research and practice.

2. Methods

Our overview was exempt from Institutional Review Board approval because no human participants were involved. This overview was performed in accordance with guidelines introduced by the Cochrane Collaboration [46].

Table 1
Search strategy in PubMed.

1	"Hot Flashes"[Mesh]
2	"vasomotor OR vasomotor symptoms OR hot flashes OR hot flushes OR night sweats OR flushes OR flashes, hot OR climacteric OR climacteric symptoms-outcome or climacteric symptoms-vasomotor OR menopausal symptoms" [All Fields]
3	1 or 2
4	"Homeopathy"[Mesh] OR "Acupuncture"[Mesh] OR "Massage"[Mesh] OR "Music Therapy"[Mesh] OR "Dietary Supplements"[Mesh] OR "Drugs, Chinese Herbal"[Mesh] OR "Therapeutic Touch"[Mesh] OR "Complementary Therapies"[Mesh] OR "Phytotherapy"[Mesh] OR "Medicine, Ayurvedic"[Mesh] OR "Acupressure"[Mesh] OR "Aromatherapy"[Mesh] OR "Oils, Volatile"[Mesh] OR "Exercise"[Mesh] OR "Yoga"[Mesh] OR "Tai Ji"[Mesh] OR "Qigong"[Mesh] OR "Mind-Body Therapies"[Mesh] OR "Breathing Exercises"[Mesh] OR "Hypnosis"[Mesh] OR "Mindfulness"[Mesh] OR "Relaxation Therapy"[Mesh] OR "Meditation"[Mesh] OR "Imagery (Psychotherapy)"[Mesh] OR "Disclosure"[Mesh] OR "Psychotherapy"[Mesh] OR "Motivational Interviewing"[Mesh] OR "Self-Help Groups"[Mesh] OR "Health Education"[Mesh] OR "Cognitive Behavioral Therapy"[Mesh]
5	"energy therapies OR shiatsu OR Volatile Oils OR Oils, Essential OR Fragrance OR Fragrant oil OR Exercises OR Physical Activity OR Exercise, Aerobic OR exercise therapy OR resistance training OR running OR walking OR sports OR swimming OR Tai Chi OR Tai Ji Quan OR Qi Gong OR Mind Body Therapies OR Mind-Body Medicine OR Exercise, Breathing OR Respiratory Muscle Training OR Interviewing, Motivational OR Cognitive Behavioral Therapies OR Cognitive Psychotherapy OR Clinical Psychotherapists OR Information Disclosure OR affirmations OR reflections OR cognitive restructuring OR behavioral activation OR supportive counselling OR supportive listening OR interpretation OR confrontation OR self-regulatory techniques OR mindfulness-based cognitive therapy OR sharing information OR expressive writing OR guided Imagery OR relaxation techniques OR alexander technique or paced respiration OR hypnoses OR Reiki OR Magnet OR Energy therapy OR Essiac OR laser therapy"[All Field]
6	4 or 5
7	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
8	"Clinical Trials, Randomized OR Trials, Randomized Clinical OR Controlled Clinical Trials, Randomized or RCT or CCT" [All Fields]
9	7 or 8
10	"Meta-Analysis" [Publication Type] OR "Systematic Review" [Publication Type]
11	"systematic review OR meta-analysis OR Review, Systematic" [All Fields]
12	10 or 11
13	3 and 6 and 9 and 12

2.1. Search strategy

Searches for possible publications were performed using PubMed, Embase, Web of Science, and the Cochrane Library from their inception to May 2019. The search strategy for each database was personalized and included a combination of medical subject heading (MeSH) terms and entry terms to represent the definitions of CAMs, VMS, RCTs/CCTs, and SR/MA. Table 1 shows the queries in PubMed and similar strategies were used with other databases. In addition, we also performed a manual search of the reference lists of all retrieved reviews.

2.2. Eligibility criteria

The eligibility criteria were SRs/MAs 1) of RCTs or CCTs published in English in a peer-reviewed journal, 2) testing the efficacy of ≥1 CAMs as a treatment, 3) with a population of adult participants ≥18 years experiencing VMS (including hot flashes and night sweats) at baseline, either stemming from spontaneous or iatrogenic causes, and 4) reporting findings regarding the frequency or severity of VMS on a subscale of a compendium score (such as the Greene Score, the Kupperman Index, or any other general menopausal symptom score) or providing data of hot flashes, night sweats, or a combination of these two symptoms. However, reviews that only reported the effects of interventions on total menopausal scores, derived from general menopausal symptom questionnaires, were excluded.

If several SRs/MAs fulfilled the eligibility criteria, we included the latest SR/MA with a high-quality score or the largest number of studies.

2.3. Reviews selection

All searched records were exported to Endnote 8.2. After removing duplicates, two authors (PPG, XHZ) screened the retrieved titles and abstracts and then independently screened the full texts for eligibility. Disagreements were resolved by discussion with a third author (WZ).

2.4. Quality and overlap assessment

(a) The methodological quality of all selected SRs/MAs were evaluated by two independent authors (PPG, DDC) using the validated Assessing Methodological Quality of Systematic Reviews (AMSTAR) tool [47]. This instrument is composed of 11 items, and the total AMSTAR score was 11. Each SRs/MAs was classified as low quality (score ≤ 4), moderate quality (score 5–8), or high quality (score ≥ 9). (b) The Grading of Recommendations Assessment Development and Evaluation (GRADE) guidelines were used to evaluate the level of evidence for the outcomes, which was finally sorted as high, moderate, low, or very low [48]. Discussion was used when there were discrepancies between the two authors.

We also calculated the corrected covered area (CCA), a metric recommended by Pieper [49] to measure the degree of overlap within the SRs/MAs that we reviewed. According to Pieper et al., a CCA of 0–5% indicates a slight overlap, 6–10% indicates a moderate overlap, 11–15% indicates a high overlap, and > 15% indicates a very high overlap.

2.5. Data extraction and analysis

Data were extracted independently by two authors (PPG, NL) into a purpose-built, predesigned, structured template by the lead author and were then checked for accuracy by another author (JW). The following information was extracted from the included reviews: (a) review details (e.g. author, year of publication); (b) participants; (c) interventions; (d) controls; (e) outcome measurement tools; and (f) results. Any discrepancies in data extraction were resolved by consensus.

Because of the variety types of interventions and outcomes measured in the included reviews, a narrative approach was applied to synthesize the evidence to avoid increasing heterogeneity.

3. Results

3.1. Study search and selection

The literature search yielded 864 potentially relevant citations. After duplicates were removed, all 652 SRs/MAs were screened based on the title and abstract. Afterwards, 117 potentially relevant full-text citations were reviewed. Ultimately, 48 SRs/MAs met the eligibility criteria. However, we only reviewed 29 SRs/MAs [37–40,43–45,50–71], as 17 out of the 48 overlapped (Table 2) and two had low methodological quality [72,73]. This process and reasons for exclusion are depicted in Fig. 1.

3.2. Description of review characteristics

The characteristics of the 29 reviewed SRs/MAs are presented in Table 3. They were published between 2009 [67–69] and 2019 [70,71], the number of RCTs/CCTs included in each SR/MA ranged from 3 [44,52] to 57 [53], and the sample sizes ranged from 172 [57] to 6055 [53]. Four SRs/MAs focused on natural menopausal women [37,38,64,71], six SRs/MAs focused on cancer patients with VMS [43,45,51,57,65,67], and 19 were about a mixed population [39,40,44,50,52–56,58–63,66,68–70]. Four SRs/MAs evaluated more than two CAMs [51,53,54,65]. The other 25 SRs/MAs were about acupuncture [38,43,45,57,60,67,69], mind-body therapies [39,40,55,56,58,70], phytoestrogens [59,61,66,68,71], black cohosh and other biologically based therapies [37,52,62–64], herbal medicine [50], and omega-3 supplements [44].

The supplementary file details the first author, publication year, the number of participants, and interventions of all unique primary trials that were included in the 29 reviewed SRs/MAs. A total of 204 unique primary RCTs and CCTs published between 1985 and 2016 with 20603 participants were finally included in our overview.

3.3. Review quality and overlap assessment

After excluding two low-quality SRs/MAs [72,73], 13 SRs/MAs were classified as high-quality [38,40,44,50,53,56,58–60,62,65,70,71] and 16 SRs/MAs were classified as moderate-quality [37,39,43,45,51,52,54,55,57,61,63,64,66–69]. The methodological limitations arose from four major items: unpublished literature was not searched, the list of excluded studies was not provided, the likelihood of publication bias was not assessed, and potential conflicts of interest were not listed. Other details can be found in Table 4. Overall, the methodological quality of the reviewed SRs/MAs was moderate (mean AMSTAR score = 8.4).

Regarding the overlap among SRs/MAs, Table 5 shows the number of primary trials on the subject with VMS, which were repeated in each pair of SRs/MAs. The value of the CCA was approximately 2.9, which was considered a slight overlap.

3.4. Effectiveness of the interventions

3.4.1. Acupuncture

Nine SRs/MAs examined the effects of acupuncture on hot flashes [38,43,45,54,57,60,65,67,69]. However, only eight of them [38,43,45,54,57,60,67,69] were reviewed here because the primary studies of acupuncture analyzed in one SRs/MAs [65] were covered by other SRs/MAs. Four SRs/MAs [38,43,54,57] assessed the overall effects of acupuncture. Three of them [38,54,57] concluded that acupuncture had a beneficial effect on hot flashes, while the fourth [43] pooled the data from RCTs that had significant between-study heterogeneity and found no benefits. Five SRs/MAs [38,45,60,67,69] evaluated the impact of the comparator on the outcomes. When compared with an inactive control (wait list or usual care), both SRs/MAs [60,69] reported that the effect of acupuncture on reducing hot flashes was stronger. However, the results were inconsistent when comparing acupuncture with an active control, including hormone therapy [45,60,67,69], relaxation [45,60,67], venlafaxine [45,67], or oryzanol [69]. But the majority of these studies found that acupuncture was no better than active controls in improving hot flashes. Sham acupuncture was different from other types of controls because we could not identify whether it was inert based on available evidence. Four SRs/MAs [45,60,67,69] compared acupuncture with sham acupuncture on the effect of hot flash improvement but found inconsistent results. However, all of the studies mentioned that both interventions could reduce hot flashes compared with baseline. Follow-up effects of acupuncture on improving hot flashes were only evaluated in three reviews [38,45,57], but the results were inconsistent. Hence, based on available evidence, we could conclude that acupuncture could certainly reduce hot flashes, but the effect was no better than that associated with an active control. Whether acupuncture is superior to sham acupuncture in reducing hot flashes is still unclear. Furthermore, the post-intervention effect of acupuncture on hot flashes was certain, while the follow-up effect should be verified.

3.4.2. Mind-body therapies

Mind-body therapies, including yoga, relaxation, exercise, hypnosis, paced respiration, etc., were assessed in seven SRs/MAs [39,40,55,56,58,65,70]. However, we only reviewed six of the SRs/

Table 2
The 17 overlapped SRs/MAs.

First author	Publication year	Title
Wang Y.	2019	Erxian decoction, a Chinese herbal formula, for menopausal syndrome: An updated systematic review
Pan Y.	2018	Clinical Benefits of Acupuncture for the Reduction of Hormone Therapy-Related Side Effects in Breast Cancer Patients: A Systematic Review
Myers SP.	2017	Effects of a standardised extract of *Trifolium pratense* (Promensil) at a dosage of 80 mg in the treatment of menopausal hot flushes: A systematic review and meta-analysis
Tao WW.	2016	Effects of Acupuncture, Tuina, Tai Chi, Qigong, and Traditional Chinese Medicine Five-Element Music Therapy on Symptom Management and Quality of Life for Cancer Patients: A Meta-Analysis
Lopes-Junior LC.	2016	Effectiveness of Traditional Chinese Acupuncture versus Sham Acupuncture: A Systematic Review
Chiu HY.	2016	Effects of acupuncture on menopause-related symptoms in breast cancer survivors: A meta-analysis of randomized controlled trials
Chen YP.	2016	Acupuncture for hot flashes in women with breast cancer: A systematic review
Kim W.	2015	Traditional herbal medicine as adjunctive therapy for breast cancer: A systematic review
Garcia MK.	2015	Systematic review of acupuncture to control hot flashes in cancer patients
Cramer H.	2015	Hypnosis in breast cancer care: A systematic review of randomized controlled trials
Chen MN.	2015	Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review
Gartoulla P.	2014	Red clover extract for alleviating hot flushes in postmenopausal women: A meta-analysis
Kim MS.	2013	Ginseng for managing menopause symptoms: a systematic review of randomized clinical trials
Lee MS.	2009	Acupuncture for treating menopausal hot flushes: A systematic review
Coon JT.	2007	*Trifolium pratense* isoflavones in the treatment of menopausal hot flushes: A systematic review and meta-analysis
Nelson HD.	2006	Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis
Krebs EE.	2004	Phytoestrogens for treatment of menopausal symptoms: A systematic review

SRs/MAs: systematic reviews and meta-analyses.

MAs [39,40,55,56,58,70] because the related primary studies in one SRs/MAs [65] were included in the others. A SR/MA [70] assessed the overall effects of psychological interventions, including mindfulness, cognitive behavioural therapy (CBT) and relaxation, and reported that these interventions were beneficial for ameliorating hot flashes; however, this SR/MA was unable to determine the effectiveness of specific types of psychological interventions. The effect of hypnosis, paced respiration, and CBT on hot flashes were assessed by one SRs/MAs [39] that reported that the effects of these three interventions were notable. The conclusions regarding the benefits of yoga [39,40,55],

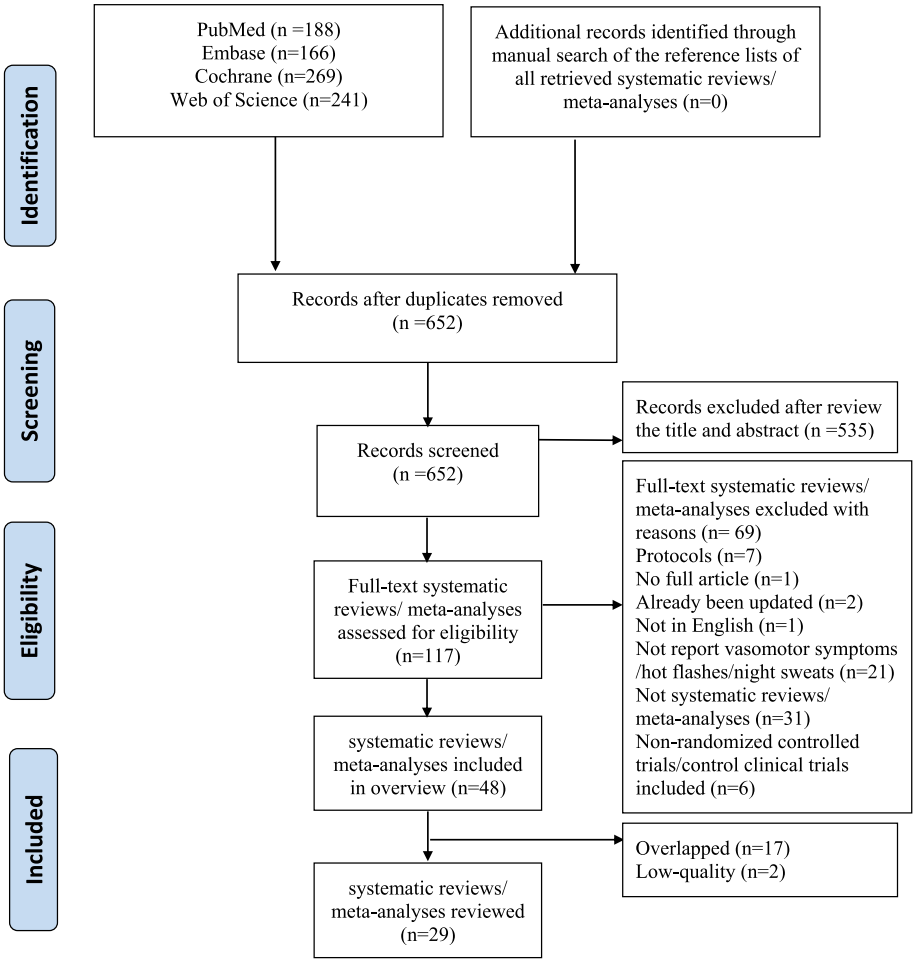

Fig. 1. Flow diagram of article selection process.

Table 3
Summary of characteristics for the 29 selected SRs/MAs.

SR/MA (First author, year)	Participants characteristic	Number of RCT/CCT (sample size)	Interventions	Comparison
Chiu, 2015	Natural menopause women	12 RCT (869)	Acupuncture	Control
Dodin, 2013	Menopause women	16 RCT (1155)	Acupuncture	No treatment/Wait list
				Relaxation
				Sham acupuncture
				HT
Cho, 2009	Menopause women excluded BC	11 RCT (764)	Acupuncture	Wait list
				Sham acupuncture
				HT
				Oryzanol
Wang, 2018	BC patients	10 RCT (554)	Acupuncture	Sham acupuncture
				Relaxation
				HT
				Venlafaxine
Chien, 2017	BC patients	13 RCT (844)	Acupuncture	Control
Frisk, 2014	Cancer patient (BC + PC)	6 RCT (172)	Acupuncture	Control
Lee, 2009	BC patients	6 RCT (281)	Acupuncture	Sham acupuncture
				Relaxation
				Venlafaxine
				HT
Taylor-Swanson, 2015	Menopause women	10 CCT (983)	Acupuncture	Placebo/usual care
		3 CCT (387)	CHM	Placebo/usual care
Rada, 2010	BC patients	2 RCT (168)	Relaxation	Placebo/no treatment
		2 RCT (124)	Homeopathy	Placebo/no treatment
		1 RCT (67)	Acupuncture	Placebo/no treatment
		1 RCT (11)	Magnetic devices	Placebo/no treatment
		1 RCT (105)	Vitamin E	Placebo/no treatment
Crammer, 2018	Menopause women	8 RCT (978)	Yoga	No treatment
				Exercise
Woods, 2014	Menopause women	5 CCT (981)	Exercise	Control
		2 CCT (138)	Relaxation	Control
		1 CCT, 2 publications (120)	Yoga	Exercise
Saensak, 2014	Menopause women excluded BC	4 RCT (281)	Relaxation	Acupuncture
				Paced respiration
				No treatment/placebo
Daley, 2014	Menopause women excluded BC	5 RCT (733)	Exercise	No treatment
				Yoga
				HT
Stefanopoulou, 2017	Menopause women	5 RCT (631)	Yoga	Control
		1 RCT (80)	Reflexology	Control
		7 RCT (391)	Relaxation	Control
		4 RCT (398)	Paced respiration	Control
		2 RCT (171)	Mindfulness-based stress reduction	Control
		3 RCT (262)	Hypnosis	Control
		4 RCT (677)	CBT	Control
van Driel. 2019	Menopause women	12 RCT (1016)	Psychological interventions (including mindfulness, CBT, and relaxation training)	Control
Li, 2016	BC patients	1 RCT (136)	mono-CR	No treatment
		4 RCT (257)	CHM	Control
Lee, 2016	Menopause women excluded BC	3 RCT (459)	Ginseng	Placebo
Zhu, 2016	Menopause women	7 RCT (543)	CHM	Placebo
				HT
Liu, 2014	Natural menopause women	6 RCT (717)	St John's wort	Control
Taku, 2012	Menopause women	19 RCT (1867)	Extracted and synthesized soy isoflavones	Placebo

(*continued on next page*)

Table 3 (*continued*)

SR/MA (First author, year)	Participants characteristic	Number of RCT/CCT (sample size)	Interventions	Comparison
Bolanos, 2010	Menopause women excluded BC	19 RCT (1415)	Overall Soy isoflavone	Control
		10 RCT (650)	Dietary soy isoflavone	Control
		9 RCT (765)	Soy isoflavone extracts and concentrates	Control
Leach, 2012	Menopause women	8 RCT (1202)	mono-CR	Placebo
				HT
				Red clover
				Fluoxetine
Laakmann, 2012	Menopause women	4 RCT (326)	mono-CR	Placebo
		2 RCT (378)	CR + St John's wort	Placebo
		1 RCT (100)	*Agnus castus* + St John's wort	Placebo
Shams, 2010	Natural menopause women	9 RCT (1266)	Complex-CR	Placebo
Daily, 2019	Natural menopause women	6 RCT (779)	S-equol	Control
Lethaby, 2013	Menopause women excluded BC	13 RCT(911)	Dietary soy isoflavone	Control
		11 RCT(1015)	Soy isoflavone extract	Control
		9 RCT(715)	Red clover	Control
		5 RCT(652)	Genistein	Control
		5 RCT(452)	Other phytoestrogens	Control
Jacobs, 2009	Menopause women excluded BC	2 RCT (337)	Genistein	Placebo
		11 RCT (2042)	Soy isoflavone extract	Placebo
		4 RCT (379)	Soy protein powder	Placebo
Franco, 2016	Menopause women	32 RCT(4133)	Overall Phytoestrogens	Placebo/no treatment
			Sub-group: Dietary soy isoflavones	
			Extracts of soy isoflavones	
			Red clover	
		5 RCT(315)	CHM	Placebo/no treatment
		4 RCT(523)	non-CHM	Placebo/no treatment
		7 RCT (449)	mono-CR	Placebo/no treatment
		2 RCT (139)	Complex-CR	Placebo/no treatment
		7 RCT (496)	Other biological therapy	Placebo/no treatment
Mina, 2018	Menopause women excluded BC	3 RCT (483)	Omega-3 supplements	Placebo

SR/MA (First author, year)	Methodological quality assessment tool	Outcomes measurement tools	Adverse effects	Main result	Evidence level
Chiu, 2015	ROB	DD, MRS, Flash log	Not reported in RCT.	HF(+)	Moderate[3]
				3 months follow-up HF (+)	Moderate[3]
Dodin, 2013	ROB	DD, MRS, WHQ, GCS, KI, VAS, HFRDI	Not reported in RCT.	HF (+)	Low[2,3]
				HF (−)	Very Low[1,2,3]
				HF (−)	Very Low[1,2,3]
				HF (−)	Low[1,3]
Cho, 2009	The categories provided by the Menstrual Disorders and Subfertility Review Group	DD, KI, GCS	No serious adverse events.	HF (+)	Moderate[3]
				HF (−)	Low[1,3]
				HF (+)	Moderate[3]
				HF (+)	Moderate[3]
Wang, 2018	ROB	DD, HFRDI, VAS	Not assessed in SR.	HF (+)	Very Low[1,2,3]
				Follow-up HF (−)	Very Low[1,2,3]
				HF (−)	Low[1,3]
				HF (−)	Low[1,3]
				HF (−)	Low[1,3]
Chien, 2017	ROB	DD, HFCS, VAS, KI, MENQOL	Not assessed in SR.	HF(−)	Low[2,3]
Frisk, 2014	Jadad	Subjectively reported HF (more details were not mentioned)	Not assessed in SR.	HF frequency (+)	Low[1,3]
				5.8 months follow-up HF (+)	Low[1,3]

(*continued on next page*)

Table 3 (*continued*)

SR/MA (First author, year)	Methodological quality assessment tool	Outcomes measurement tools	Adverse effects	Main result	Evidence level
Lee, 2009	Jadad	DD, Flash log	No serious adverse events.	HF (+) HF (−) HF (−) HF (−)	Low[2,3] Low[1,3] Low[1,3] Low[1,3]
Taylor-Swanson, 2015	Not mention	DD, MRS, WHQ, GCS, HFRDI, MENQOL, KI, Flash log	No serious adverse events.	HF (+) HF (+)	not available
Rada, 2010	ROB	DD, HF score, HFRDIS, SSC, VAS	No serious adverse events.	HF (+) HF (−) HF (−) HF (−) HF (−)	Low[1,3] Moderate[3] Low[1,3] Low[1,3] Moderate[3]
Crammer, 2018	ROB	NRS, HFRDIS, GCS, MENQOL	No serious adverse events.	VMS (+) VMS (+)	Very Low[1,2,3] Very Low[1,2,3]
Woods, 2014	Not mention	DD, VAS, Flash log, GCS	Not assessed in SR.	HF (−) HF (−) HF (+)	not available
Saensak, 2014	ROB	DD, KI	Not reported in RCT.	HF (−) HF (−) HF (−)	Very Low[1,2,3] Low[1,3] Very Low[1,2,3]
Daley, 2014	ROB	DD, WHQ, GCS, KI	No serious adverse events and no difference between groups.	HF (−) HF (−) HF (−)	Low[2,3] Low[2,3] Low[1,3]
Stefanopoulou, 2017	Standard quality assessment tool	DD, GCS, KI, VAS, SSC	Not assessed in SR.	HF inconsistent HF (−) HF (+) HF (+) HF inconsistent HF (+) HF (+)	Moderate[3] Moderate[3] Low[1,3] Moderate[3] Moderate[3] Low[1,3] Low[1,3]
van Driel. 2019	ROB	HFRS, DD	No adverse events.	HF (+)	Very Low[1,2,3]
Li, 2016	ROB	DD, KI	No serious adverse events and no difference between groups.	HF (+) HF (+)	Moderate[3] Moderate[3]
Lee, 2016	ROB	DD, KI, WHQ	No serious adverse events and no difference between groups.	VMS (−)	Moderate[1]
Zhu, 2016	ROB	DD, MENQOL, KI	No serious adverse events and no difference between groups.	VMS (−) VMS (−)	Very Low[1,2,3] Very Low[1,2,3]
Liu, 2014	ROB	MRS, KI, MENQOL, GCS	No serious adverse events and no difference between groups.	HF (+)	Very Low[1,2,3]
Taku, 2012	Three-category grading system	GCS, KI, Likter scale	Not assessed in SR.	HF (+)	Low[1,3]
Bolanos, 2010	Jadad	DD, GCS, KI	Not assessed in SR.	HF (+) HF (+) HF (+)	Very Low[1,2,3] Very Low[1,2,3] Very Low[1,2,3]
Leach, 2012	ROB	DD, GCS, KI, MRS	No difference between groups.	HF (−) NS (−) HF (−) NS(−) HF (−) - - NS(+)	Moderate[3], Moderate[3] Low[2,3] Low[2,3] Moderate[3] - - Moderate[3]
Laakmann, 2012	Jadad	MRS, KI, GCS HF score	No difference between groups.	VMS (−) VMS (+) VMS (−)	Moderate[1] Moderate[3] Moderate[3]
Shams, 2010	Jadad	DD, MRS, GCS, KI	No difference between groups.	VMS (+)	Low[1,3]
Daily, 2019	ROB	GCS, KI, VAS	No serious adverse events and no difference between groups.	HF (+)	Moderate[1]

(*continued on next page*)

Table 3 (*continued*)

SR/MA (First author, year)	Methodological quality assessment tool	Outcomes measurement tools	Adverse effects	Main result	Evidence level
Lethaby, 2013	ROB	DD, GCS, MRS, KI, VMS score	No serious adverse events.	HF (−) HF inconsistent HF (−) HF (+) HF inconsistent	Very Low[1,2,3] Low[1,3] Low[2,3] Moderate[3] Low[1,3]
Jacobs, 2009	A catalog of quality criteria based on the consolidated standards of reporting trials	KI, Self-rating scale	No serious adverse events.	HF (+) HF inconsistent HF inconsistent	Moderate[3] Low[1,3] Low[1,3]
Franco, 2016	ROB	DD, KI, GCS, HF score, VMS score	Not assessed in SR.	HF (+) NS(−) Sub-group: HF (+) NS (−) HF (+) - HF (+) NS (−) VMS (−) VMS (+) HF (−) HF (+) HF inconsistent	Very Low[1,2,3,] Very Low[1,2,3] Sub-group: Low[2,3,] Moderate[3] Low[2,3] - Very Low[1,2,3,] Moderate[3] Low[1,3] Low[1,3] Low[2,3] Moderate[3] Moderate[3]
Mina, 2018	ROB	DD	No serious adverse events and no difference between groups.	HF (−) NS (+)	Low[2,3,] Low[2,3]

SRs/MAs: systematic reviews and meta-analyses; BC: Breast cancer; PC: Prostate cancer; RCT: randomized controlled trials; CCT: control clinical trials; CHM: Chinese Herb Medicine; CR: Cimicifuga racemosa; CBT: cognitive behavioral therapy; HT: hormone therapy; ROB: The Cochrane Collaboration's tool; SR: systematic review; VMS: Vasomotor symptoms; HF: Hot Flash; NS: Night Sweats; DD: Daily diary; MRS: Menopause Rating Scale; WHQ: The Women's Health Questionnaire; GCS: Greene climateric Scale; KI: Kupperman's Index; VAS: Visual analogue scale; HFRDI: Hot Flash Related Daily Interference Scale; HFCS: Hot Flash Composite Score; MENQOL: Menopause-Specific Quality of life; SSC: Sternal skin conductance; NRS: Numerical Rating Scale; (+): The effect was significant; (−): No significant effect; -: Not reported in primary trial; [1the] total sample size was small; [2there] was a high heterogeneity; [3the] risk of bias was high.

Table 4
Methodological quality of SRs/MAs based on the 11-items AMSTAR Checklist.

SR/MA (First author, year)	1. Was an a priori design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Did the search cover unpublished literature?	5. Was a list of included and excluded studies provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality used appropriately in formulating conclusions?	9. Were the methods used to combine findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Were potential conflicts of interest listed?	Total score
Chiu, 2015	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9
Dodin, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Cho, 2009	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	6
Wang, 2018	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	8
Chien, 2017	Yes	No	Yes	No	No	Yes	Yes	No	Yes	No	No	5
Frisk, 2014	Yes	No	No	No	No	Yes	Yes	Yes	No	Yes	No	5
Lee, 2009	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	7
Taylor-Swanson, 2015	Yes	Yes	Yes	No	No	Yes	No	No	No	No	Yes	5
Rada, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Crammer, 2018	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Woods, 2014	Yes	Yes	Yes	No	No	Yes	No	No	No	No	Yes	5
Saensak, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Daley, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Stefanopoulou, 2018	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8
van Driel, 2019	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Li, 2016	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8
Lee, 2016	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	8
Zhu, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Liu, 2014	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	8
Taku, 2012	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	8
Bolanos, 2010	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Leach, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Laakmann, 2012	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	6
Shams, 2010	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	7
Daily, 2019	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Lethaby, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Jacobs, 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	8
Franco, 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10
Mina, 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	9
Dew, 2013	No	No	No	No	No	Yes	No	No	No	No	No	1
Thomas, 2014	Yes	No	Yes	No	No	Yes	No	No	No	No	Yes	4

SRs/MAs: systematic reviews and meta-analyses; AMSTAR: Assessment of Multiple Systematic Reviews.

Table 5
Overlap of primary trials within the 29 selected SRs/MAs.

First author, year	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
1. Chiu, 2015	**12**	10	4	0	0	0	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2. Dodin., 2013		**16**	4	5	5	3	3	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3. Cho, 2009			**11**	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4. Wang., 2018				**10**	8	4	4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5. Chien, 2017					**13**	5	4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6. Frisk, 2014						**6**	4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7. Lee, 2009							**6**	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8. Taylor-Swanson, 2015								**13**	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	3	0
9. Rada, 2010									**7**	0	0	1	0	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10. Crammer, 2018										**8**	1	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11. Woods, 2014											**10**	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12. Saensak, 2014												**4**	0	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13. Daley, 2014													**5**	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
14. Stefanopoulou, 2018														**26**	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15. van Driel, 2019															**12**	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16. Li, 2016																**5**	0	0	0	0	0	0	0	0	0	0	0	0	0
17. Lee, 2016																	**3**	0	0	0	0	0	0	0	0	0	0	0	0
18. Zhu, 2016																		**7**	0	0	0	0	0	0	0	0	0	3	0
19. Liu, 2014																			**6**	0	0	0	3	2	0	0	0	3	0
20. Taku, 2012																				**19**	8	0	0	0	1	13	10	14	0
21. Bolanos, 2010																					**19**	0	0	0	0	16	13	12	0
22. Leach, 2012																						**8**	2	2	0	1	0	3	0
23. Laakmann, 2012																							**7**	5	0	0	0	4	0
24. Shams, 2010																								**9**	0	0	0	4	0
25. Daily, 2019																									**6**	2	0	2	0
26. Lethaby, 2013																										**43**	14	21	0
27. Jacobs, 2009																											**17**	11	0
28. Franco, 2016																												**57**	0
29. Mina, 2018																													**3**

SRs/MAs: systematic reviews and meta-analyses; The values indicate the number of primary trials that were included in both SR/MA (row and column); Bold characters show the number of primary trials for each SR/MA; Corrected covered area: 2.9 (calculated as recommended by Pieper et al., 2014).

relaxation [39,55], and mindfulness [39] on hot flashes were inconsistent. In addition, the effect of exercise was examined by two SRs/MAs [55,58], and the effect of reflexology [39] was estimated by one SRs/MAs. The results showed no benefit for these two interventions on hot flash reduction. Overall, evidence showed that hypnosis, paced respiration, and CBT could significantly improve hot flashes, while exercise and reflexology had no effect. Yoga, relaxation, and mindfulness might also benefit hot flashes, but their effects should be verified in future trials.

3.4.3. Phytoestrogens

The effect of phytoestrogens (mainly including soy isoflavones, red clover isoflavones, genistein) on hot flashes was considered by six SRs/MAs. The overall effects of phytoestrogens were examined by one SR/MA [53], and the effect of genistein was estimated by two SRs/MAs [59,68]. They found that these two interventions were helpful for managing hot flashes. Moreover, two SRs/MAs [53,59] assessed the effect of red clover isoflavones on hot flashes, but evidence was conflicting. Additionally, the overall effects of soy isoflavones were assessed by one SR/MA [66], which found a small reduction in hot flashes. However, 4 SRs/MAs [53,59,66,68] examined dietary soy isoflavones, and 5 SRs/MAs [53,59,61,66,68] evaluated concentrates and extracts of soy isoflavone, but evidence for both were not consistent. In addition, two SRs/MAs [59,71] evaluated the effects of S-equol and reported a significant benefit of S-equol for reducing hot flashes. Furthermore, one SR/MA [59] assessed the effects of hop extracts and *Rheum rhaponticum* on hot flashes, but the evidence was less consistent. In addition, one SR/MA [53] examined the effects of phytoestrogens on night sweats, but no significant effect was found. In total, we could see that genistein and S-equol could significantly improve hot flashes. Additionally, soy isoflavone might also have beneficial effects on these symptoms. However, the efficacy of other phytoestrogens remains unclear.

3.4.4. Biologically based therapies

The effects of black cohosh (*Cimicifuga racemosa*) on VMS were examined in five SRs/MAs [51,53,62–64]. Four SRs/MAs [51,53,62,63] assessed the effects of a mono-preparation of black cohosh on overall VMS, hot flashes, and night sweats, but only one of them [51] reported significant effects on hot flashes. In contrast, the effectiveness of combined preparations of black cohosh on VMS was assessed by three SRs/MAs [53,63,64], and all of them found significant positive effects. Moreover, St. John's wort (*Hypericum perforatum* L.) was the most commonly used component that was combined with black cohosh. The effects of other biologically based therapies, including St. John's wort, ginseng, chaste tree (*Agnus castus*), evening primrose, and wheat germ, on overall VMS and hot flashes were evaluated by four SRs/MAs [37,52,53,63], but the evidence was less consistent. Briefly, we could see that only combined preparations of black cohosh could significantly improve VMS, while the effectiveness of other biologically based therapies was still unclear.

3.4.5. Herbal medicine

Chinese herbal medicines included *Angelica sinensis*, *Phellodendron amurens*, *Rehmannia glutinosa*, and preparations of formulas such as Kun tai capsules and Shen Qi Wu Wei Zi tablets. Four SRs/MAs [50,51,53,54] evaluated the effects of these interventions on VMS, but only half of them [51,54] found significant effects. A SR/MA [53] reported non-Chinese medicinal herbs, including pollen extract combined with pistil extract, *Pycnogenol*, and plant extract, could ameliorate VMS. However, this conclusion was based on only four RCTs. In total, we could conclude that both Chinese herbal medicine and non-Chinese herbal medicine might have some benefits in managing VMS, but the current evidence was insufficient.

3.4.6. Other CAMs

There was only one SR/MA for each of the other CAMs, including vitamin E [65], magnetic therapy [65], homeopathy [65], and omega-3

supplements [44]. The existing evidence only showed that omega-3 could significantly improve night sweats. However, no evidence has shown that the above interventions help alleviate hot flashes.

3.5. The levels of evidence for the outcomes

We could not acquire the levels of evidence for the outcomes in two SRs/MAs [54,55] because they did not perform an assessment for the methodological quality of the primary studies. Among the other 27 SRs/MAs, 22 had a small sample size [37,39,40,45,50,52,53,56–61,63–71], high heterogeneity existed in 15 SRs/MAs [37,40,43–45,50,53,56,58–60,62,66,67,70], and the risk of bias of 25 SRs/MAs was high [37–40,43–45,50,51,53,56–70]. Therefore, based on the GRADE tool, the evidence levels for paced respiration, reflexology, mindfulness, homeopathy, genistein, vitamin E and *Agnus castus* combined with St John's wort were moderate. The levels of evidence for exercise, hypnosis, omega-3 supplements, magnetic therapy, overall soy isoflavones, concentrates and extracts of soy isoflavone, and other phytoestrogens (flaxseed, hop extracts, and *Rheum rhaponticum*) were low; for overall, phytoestrogens and overall psychological interventions, the evidence levels were very low. However, the evidence levels for other interventions were less consistent, ranging from moderate to very low (Table 3).

4. Discussion

Collectively, the findings of this overview suggested that acupuncture; some types of mind-body therapies such as hypnosis, paced respiration, and CBT; some types of phytoestrogens including genistein, soy isoflavone, and S-equol; combined preparations of black cohosh; and omega-3 supplements could significantly ameliorate VMS, while the effectiveness of other CAMs were either uncertain or nonsignificant.

4.1. Detailed discussion based on the results of the interventions

The findings regarding acupuncture were as follows. First, acupuncture was an efficacious treatment for hot flashes when compared with inactive controls, which was consistent with the results of Goldstein et al. [41] and was also supported by the finding of another narrative review [74] of clinical evidence of acupuncture. However, the mechanism of this technique in relieving VMS has not been completely understood until now. Western explanations were that acupuncture may act in the same way as HT or prescriptions such as antidepressants and gabapentin by increasing hypothalamic-endorphin activity or affecting the nervous system by modulating the levels of some neurotransmitters and neuropeptides [75]. However, the Eastern view attributed the mechanism of diseases to the disruption of the flow of qi, the “body's vital energies”; VMS and other menopausal symptoms are thought to be mainly due to a deficiency in yin qi [76]. Acupuncture that is specifically designed to alleviate menopausal symptoms is performed to stimulate specific acupoints and increase qi flow to subdue kidney yang and balance kidney qi [77]. Second, although the effect of acupuncture on relieving VMS did not seem to be better than that of the active control groups, the safety of acupuncture might be superior to that of HT and prescriptions. Only a few mild adverse effects of acupuncture, such as bleeding, bruising at the insert site, and discomfort, occurred. Third, the efficacy of traditional acupuncture was uncertain when compared with sham acupuncture, which reflected that the latter might also play an active role. This viewpoint was supported by a study [78] that reported that sham acupuncture was not inert and elicited a mild to moderate physiological effect. Therefore, further trials are necessary to set an inactive control group and draw more reliable conclusions on whether sham acupuncture can improve VMS.

The present overview also suggested that to date, hypnosis, paced respiration, and CBT were valid approaches to relieve VMS, and other mind-body therapies such as yoga, relaxation, and mindfulness might also have some benefits but need to be verified; these results were supported by Moore et al.‘s narrative review [42]. These findings were generally in accordance with the results of Goldstein et al. [41]. However, the effectiveness of paced respiration on VMS was inconsistent, and this method was proven to be ineffective in Goldstein et al.'s study. This inconsistency, on the one hand, might have resulted from different primary RCTs being analyzed between reviews. On the other hand, Goldstein's conclusion was based on a meta-analysis of four RCTs with high heterogeneity ($I^2 > 50\%$) of the pooled results, which limited the interpretability of their finding. Nevertheless, the underlying mechanisms of mind-body therapies on alleviating VMS remain unclear, but several ways in which these interventions might act have been suggested. First, Norton et al. [79] and Chilcot et al. [80] reported that beliefs about control/coping with VMS were the strongest mediators of severity rating, and CBT works mainly by changing the cognitive appraisal of VMS and negative beliefs, improving mood and sleep. Second, VMS always coexist and interact with sleep disruption, mood disturbances, and other menopausal symptoms [13–16]; mind-body therapies could significantly improve these troublesome symptoms [40,41,55,56,58], which might, in turn, alleviate VMS. Third, hypnosis, relaxation, and mindfulness might decrease sympathetic activity and improve parasympathetic tone to relieve VMS. In addition, it was encouraging that only mild adverse effects were reported in the implementation of mind-body therapies, so these interventions could be considered relatively risk-free and deserve to be tried in future clinical practice.

As previously demonstrated, for the CAMs provided in the oral form, genistein, soy isoflavones, S-equol, combined preparations of black cohosh, and omega-3 supplements could significantly improve VMS. Evidence has shown that [59,81] genistein, soy isoflavones, and other phytoestrogens with structural resemblance to oestradiol relieve VMS by exerting oestrogen-like effects, but they have 100 to 1000 times less activity than oestrogen and are preferentially expressed in the central nervous system, vascular system, skin and bone without causing unwanted oestrogenic effects on the breasts or uterus. In addition, short-term (within 2 years) use of phytoestrogens was considered safe and was not associated with an increased the risk of breast or endometrial cancers [59]. However, the mechanism of other oral forms of CAMs in reducing VMS has not been fully elucidated, but acting similarly to neurotransmitters has been suggested by some studies as a mean of the activity of black cohosh, St. John's wort, and omega-3 supplementation [62,64]. Moreover, gastrointestinal complaints and taste intolerance were the most common adverse events of the oral form of CAMs but were generally comparable with the effects associated with placebo, and no health-threatening side effects resulting from the use of oral forms of CAMs were found. Therefore, although more studies are needed to unveil their mechanisms and safety, these interventions are promising for managing VMS safely under the appropriate guidance of clinicians.

4.2. Strengths and limitations of this overview

To the best of our knowledge, this overview is the first investigation of the effects of CAMs on VMS based on all existing evidence from the SRs/MAs of RCTs and CCTs, which are high standards of evidence-based clinical research. Moreover, apart from two low-quality SRs/MA, which were excluded from further analysis, the methodological quality of reviewed SRs/MAs was rated as either moderate or high. In addition, the findings of this overview were based on relatively recent evidence because almost 62% of the SRs/MAs reviewed were conducted in the past five years. This is greatly important because trials in related fields have been widely published in recent years. Furthermore, this overview had slight overlap between the included SRs/MAs; therefore, the joint findings were less likely to be biased due to overlap.

Nonetheless, some important limitations existed in our overview. Although we tried our best to retrieve all possible publications, it was

still possible that some relevant SRs/MAs might have been missed because of limiting the search to English-language publications. In addition, we relied on the appropriateness of the SRs/MAs authors' inclusion and exclusion criteria, search strategies, risk of bias judgements for primary studies, and evidence synthesis. Furthermore, only SRs/MAs were taken into consideration, which means that the latest evidence from primary trials could be missed [82,83]. However, this is a common weakness for the overview of SRs/MAs. Additionally, the findings should be interpreted with caution because the small sample size, high heterogeneity across studies, and high risk of bias of primary studies led to the evidence levels of the outcomes were not high. Finally, it was impossible to conclude which intervention is best because no direct comparisons between treatments were performed.

4.3. Gap in the evidence and recommendations for future practice

4.3.1. Assessing patient groups comprehensively

As previously reported, 40% of middle-aged men [7] and 58–80% of prostate cancer patients [10,11] suffered from VMS. However, only one of our reviewed SRs/MAs [57] took male patients into consideration, which reflected a phenomenon that research on the effectiveness of CAMs in relieving VMS in males was insufficient. In view of the reasons above, future studies should pay more attention to this population.

4.3.2. Focusing on the specific aetiology

Evidence showed that VMS stemming from diseases or iatrogenic causes were more frequent and severe [9], so it is reasonable to suppose that the efficacy of CAMs might be influenced by the underlying aetiology of VMS. However, we could not discuss this issue in depth because only limited data from SRs/MAs about this aspect were available. Future research should focus on determining whether VMS originating from different causes can be managed in the same way or require tailored therapies.

4.3.3. Developing optimal outcome measures

The outcome measures of VMS differed substantially in primary studies (see Table 2), which increased the difficulty of comparing findings across studies. Moreover, opposite results might be obtained when different subjective outcome measurement tools were used to evaluate the effect of an intervention on VMS [84,85]. Furthermore, sternal skin conductance, the most commonly used objective outcome measure, can only assess the frequency of VMS while failing to reflect the distress felt by patients [86]; therefore, it cannot replace subjective outcome measures. Hence, recommendations for future practice include identifying an optimal subjective outcome measurement tool for use in clinical trials and developing practical objective measurement tools to help accurately assess the effects of interventions for VMS and to aid comparisons of findings across studies.

4.3.4. Observing the maintenance of improvements

Short-term VMS improvements were generally observed in the SRs/MAs, while only 3 SRs/MAs evaluated the long-term follow-up effects of acupuncture on hot flashes, which revealed that the results were inconsistent. Therefore, long-term effects of CAMs on VMS remain unclear. Longitudinal research should be carried out to examine whether these effects can be maintained.

4.3.5. Unveiling action mechanism

As mentioned above, studies have reported how phytoestrogens and CBT work to reduce VMS, while the mechanisms of other types of CAMs, such as acupuncture, black cohosh, etc., have been studied but not yet clearly elucidated. Therefore, exploring the underlying mechanisms by which these interventions work is recommended as a field for future studies.

4.3.6. Integrating with emerging technology

Mobile health, which makes treatment more accessible and affordable, has become increasingly popular over the last few years [87]. We found that researchers who conducted a recent RCT [88] had committed to using mobile health to implement CAMs and reported that internet-based CBT could significantly improve VMS in breast cancer patients. However, mobile health interventions may lead to a high drop-out rate [89]. Future research and clinical practice should be devoted to decreasing the drop-out rate and combining CAMs with mobile health to obtain the full advantages of mobile health.

5. Conclusion

Our overview was the first to systematically review the available SRs/MAs of CAMs to treat VMS. Evidence has shown that acupuncture, hypnosis, paced respiration, CBT, genistein, soy isoflavones, S-equol, combined preparations of black cohosh, and omega-3 supplements might have beneficial effects on VMS. However, exercise, reflexology, vitamin E, magnetic therapy, and homeopathy had no benefit. The results of other CAMs were inconsistent. Clinicians and policy makers should take our results, patients' specific conditions, and their preferences into consideration when making clinical decisions to provide patients with the best advice to help them improve their VMS. However, what needs to be emphasized is that the methodological quality of RCTs and CCTs was not high and the evidence levels of outcomes ranged from moderate to very low, so firm conclusions were unable to be drawn. Further well-designed and sufficiently powered trials should be carried out to assess the effectiveness of CAMs to treat VMS. In addition, we identified several priorities for future practice.

Disclosure statement

The authors declare no conflicts of interest.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

No potential conflicts of interest are declared.

Acknowledgements

The authors thank the students who took time to become involved in the investigation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.07.007.

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