

Acupuncture for Hot Flashes: A Literature Review of Randomized Controlled Trials Conducted in the Last 10 Years

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Abstract

Objective: To conduct a literature review of randomized controlled trials (RCTs) on the use of acupuncture for hot flashes to analyze the characteristics of each study, draw a conclusion on the advantages and disadvantages of previous studies and provide the suggestions for future studies on the same topic. **Methods:** We searched English and Chinese databases for the literature published from 2009 to 2019 restricted in the English and Chinese language, and we included RCT using acupuncture as the main observational intervention for hot flashes by the criteria. **Results:** Twenty studies met our eligibility criteria. All the studies were of high quality and confirmed the clinical efficacy of acupuncture for hot flashes, although they used different controlled interventions. The acupuncture treatment and theory of acupoints selection were relatively consistent among the studies, and they had close trial designs. **Conclusions:** These RCTs on acupuncture were nonuniform, which made the studies on this topic lack coherence, leading to unsatisfactory research outcomes. Therefore, more professional research teams are needed to perform studies on a definite topic and draw a specific conclusion to previous studies before the next step is taken.

Keywords: Acupuncture, breast cancer survivors, hot flashes, menopausal women, review, vasomotor symptom

INTRODUCTION

Hot flashes, a clinical symptom accompanied by palpitations, anxiety, sleep disturbances, aprosexia, and cognitive disorder, refer to a sudden feeling of fever and sweating in the face, neck, and front chest.^[1-3] Hot flashes are the most representative symptom among pre- and postmenopausal women and breast cancer survivors, with an incidence of 80%–90% and 51%–81%, respectively.^[4,5] Although hot flashes pose no fatal threat to perimenopausal women, the relevant symptoms severely impact the treatment of their sleeping disorders, emotional problems, or protopathy, greatly reducing the quality of daily life because hot flashes can last from 6 months to more than 10 years.^[6,7]

Hormone therapy (HT) is the recommended intervention for hot flashes by the Food and Drug Administration (FDA). However, recent studies have shown that HT had many side effects and could enhance the incidence rate of cardiovascular disease or breast cancer. In recent years, international research on complementary and alternative medicines (CAM) is

increasing. Data show that the American government allocated 339 million every year to fund research on CAM, of which acupuncture was the most significant.^[8] At present, due to its satisfactory clinical curative effect, lower side effects, and nondrug resistance, acupuncture has been widely accepted by global physicians and patients as a promising complementary and alternative therapy.^[9,10] Acupuncture has an acceptable efficacy for hot flashes.

Pathogenesis and therapies of hot flashes

Pathogenesis

As a type of vasomotor symptom, the most generally acceptable pathogenesis hypothesis of hot flashes is the

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Received: 25-04-2020, **Accepted:** 14-12-2020, **Published:** 01-06-2021

How to cite this article: Sheng RY, Yan Y, Linh Dang HH. Acupuncture for hot flashes: A literature review of randomized controlled trials conducted in the last 10 years. World J Tradit Chin Med 2021;7:397-407.

Access this article online

Quick Response Code:



Website:
www.wjtcn.net

DOI:
10.4103/wjtcn.wjtcn_27_21

“withdrawal of sex hormone” theory,^[6] which argues that the decrease in estrogen levels is directly responsible for female hot flashes. An abnormal sex hormone level can cause the dysfunction of the automatic nervous system and peripheral vasculature; therefore, a female with a lower estrogen level is more likely to have hot flashes than one with a higher estrogen level.^[11] Studies have shown that hot flashes can occur in breast cancer survivors after mastectomy and among patients with prostate cancer with an androgen deprivation therapy (ADT), when their androgen levels decrease,^[12,13] verifying this hypothesis.

Therapies

Based on this pathogenesis, hormone replacement therapy (HRT) was recognized as the only intervention for hot flashes by the FDA,^[14] especially due to its reliable effect in treating perimenopausal hot flashes.^[15] However, several studies have demonstrated that HRT enhances the risk of cardiovascular disease or breast cancer.^[16] In addition, because breast cancer survivors have more severe and longer-lasting hot flashes,^[17] it has been suggested that HRT should be used with caution.^[18] Therefore, the requirement for a considerably effective non-HT has garnered extensive attention. Compared with HRT, nonhormonal oral medications such as gabapentin, venlafaxine, or clonidine have lower clinical effects; however, they have fewer and milder side effects, such as inappetence, vomiting, or thirst.^[19] Evidence-based medicine studies have revealed that the side effects of nonhormonal oral medications increased with the increase in dose,^[20] thereby limiting its clinical application. In addition, the stellate ganglion narcotherapy is a new and developing treatment for hot flashes, but the high cost prevents its popularization.^[21] As a result, it is necessary to explore new CAM therapies like acupuncture.

Hot flashes and acupuncture

Hot flashes are an independent and a typical symptom and can be associated with a variety of diseases such as the perimenopause syndrome or post breast cancer, both of which are complicated syndromes accompanied by other symptoms caused by the withdrawal of sex hormones. Differentiation of Traditional Chinese Medicine (TCM) diagnosis is generally driven by the patients’ symptoms. Every patient can manifest different combination of symptoms, even if they all have the perimenopause syndrome. TCM practitioners conclude on a customized differential diagnosis and administer a specific treatment for each patient according their symptoms. It is difficult to separate an independent intervention that only has an effect on hot flashes from the integrated treatment, especially for an acupuncture intervention. However, TCM studies should focus on an independent symptom to prove the advantages of differentiation and treatment, which is also the feature of TCM that needs further study. Based on our previous literature search, we found several randomized controlled trials (RCTs) that studied hot flashes as an individual symptom. Accordingly, we aimed to review such RCTs in this study, and therefore, excluded a mixture of symptoms from the inclusion criteria.

However, from the existing systemic reviews and meta-analysis of acupuncture for hot flashes, a doubtable attitude has been developed toward this topic. Although some articles advocate that acupuncture could lead to “acceptance and encouraging effectiveness,”^[22] most articles hold that there is “insufficient evidence to determine whether acupuncture is effective”^[3] or that it “had no effect on hot flush.”^[23] Based on a quantitative analysis, the effects of acupuncture with sham acupuncture or positive drugs are unexceptional. Articles suggest that “sham-controlled RCTs failed to show the specific effects of acupuncture,”^[24] “HT was more effective than electroacupuncture,” or “acupuncture with venlafaxine reported no significant intergroup difference.”^[25] It can be speculated that “there was insufficient evidence to support the efficacy of acupuncture.”^[26] In addition, nearly all the studies evaluated the previous trials process an unsatisfactory quality. Moreover, it is suggested that future studies should be more precise and of a higher quality. In summary, the science of acupuncture therapies remains inadequate to sufficiently support its benefits.

There is a need to determine how studies can be improved. In general, the development of an intervention for a symptom needs a series of coherent studies including acupoints selection, outcome measures, and controlled interventions. Although the results of trials are important to consider when conducting a meta-analysis, the framework of an independent topic also needs to be defined.

In this literature review, we aimed to provide a relatively valuable overview regarding three aspects: (1) the characteristics of each study in terms of the research design, acupuncture intervention setting, controlled intervention setting, and TCM differentiation and outcomes; (2) the advantages and disadvantages of these studies; and (3) make suggestions for future studies.

METHODS

Search strategy

We searched the following databases for the articles in the English and Chinese language: PubMed, EMBASE, Cochrane Library, and CNKI, and the search strategy was confirmed by our initial search. We also screened the bibliographies of identified trials and reviewed articles for further potentially relevant publications. The details of the search strategy on PubMed are listed in Table 1.

Selection

Inclusion criteria

(1) Clinical studies on hot flashes or clinical studies in which hot flashes were listed separately in the efficacy outcome assessment; (2) clinical studies with acupuncture or electro-acupuncture stipulated as the main observational intervention; and (3) studies with an RCT design.

Exclusion criteria

(1) Studies with nonacupuncture as the main intervention, such as herb decoctions or tuina, or studies with acupuncture as a supplementary therapy; (2) Non-RCT designs, such as a

clinical effect observational study; (3) the study which shared the same RCT with a previous one and published with identical result; (4) the study assessed hot flashes as a secondary outcome, or without an independent assessment for hot flashes.

Based on the criteria listed above, we searched for relevant articles and removed duplicated studies. Two authors (Ruya Sheng and Yan Yan) independently screened the titles and abstracts of the articles during the primary search, included or excluded studies following the criteria, and finally verified the remaining articles with each other. The full texts of the included studies were reviewed by the two authors, and relevant data were extracted. The flow chart of the literature search and screening process is presented in Figure 1.

Table 1: The search strategy of eligible articles in PubMed

<i>n</i>	Search items
1	Randomized controlled trial
2	Controlled clinical trial
3	Randomized
4	Trial
5	OR/1-4
6	Hot flash
7	Hot flashes
8	Vasomotor symptom
9	OR/6-8
10	Acupuncture
11	Acupuncture therapy
12	Electroacupuncture
13	Acupoints
14	OR/10-13
15	5 AND 9 AND 14

Data extraction

We enacted the extraction items by consulting to the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA),^[27] as it was an authoritative guideline to report an acupuncture RCT and to ensure the integrity and accuracy of our review. Details are presented in our following charts.

RESULTS

Characteristics of included studies

Our research finally included 20 studies. Figure 2 shows the number of publications per year and the country of publication in the last 10 years. These studies on acupuncture for hot flashes are divided into two parts: 12 studies about perimenopausal women^[28-39] and 8 studies on breast cancer survivors.^[40-47] These studies were performed in nine countries from Asia, America, and Europe and were mostly published between 2009 and 2016, with a lower number in the recent 3 years. We found a recently published large sample multi-center trials protocol,^[48] signifying that acupuncture treatment for hot flashes had gained wide attention. Our literature search revealed that a few large sample multi-center RCTs on acupuncture for perimenopausal hot flashes had been conducted, and studies on acupuncture for hot flashes among breast cancer survivors still involves small sample RCT or clinical effect observational studies as emphasis. Information about these studies is provided in Tables 2 and 3.

Acupuncture intervention projects

Acupoints selection

The selection of acupoints in these studies was relatively consistent. Among these 20 studies, acupoints selection was conducted according to the TCM physician’s clinical

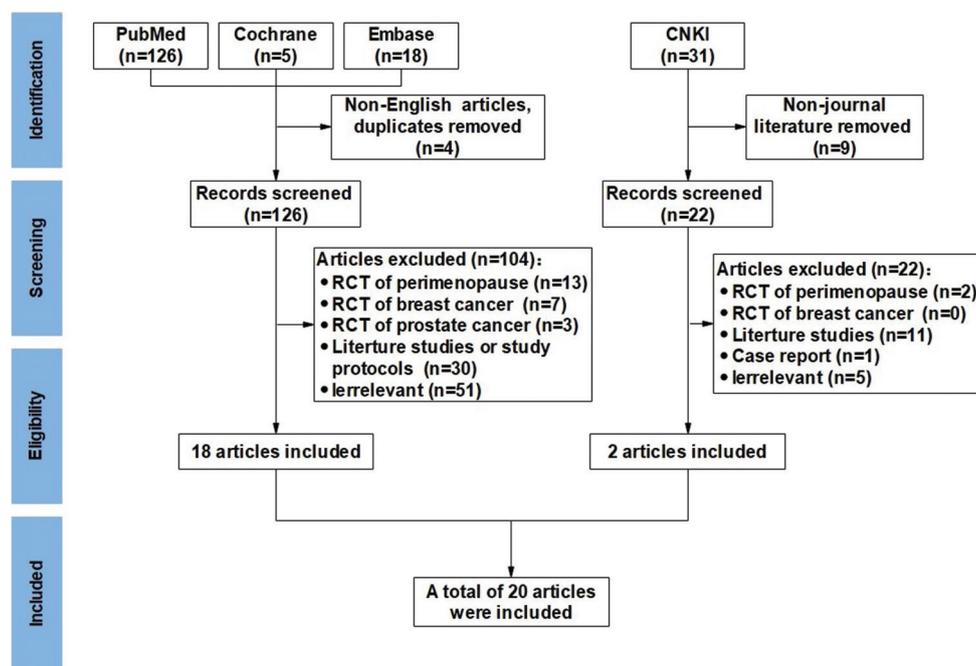


Figure 1: The flowchart of literature search and screening process

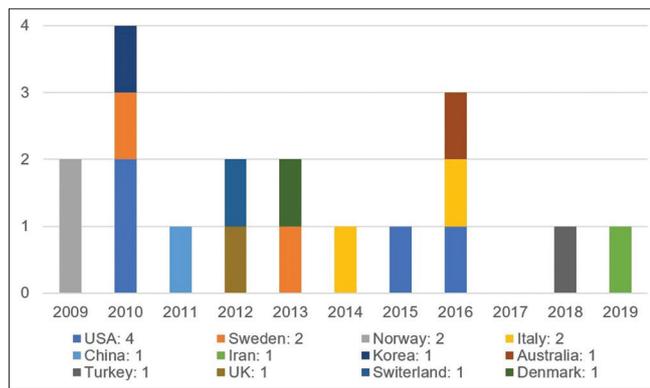


Figure 2: Number and region of RCT publications on acupuncture for hot flashes in last 10 years

experience and TCM differentiation in three studies, but they did not mention acupoint selection.^[30,38,41] The other 17 studies carried out consistent acupoints selection, which concentrated on acupoints of function in tonifying Kidney essence such as CV4 (Guanyuan), ST36 (Zusanli), SP6 (Sanyinjiao), KI3 (Taixi), etc., [Figure 3]. In addition, some acupoints were used only once, including LU9 (Taiyuan), ST37 (Shangjuxu), SP10 (Xuehai), HT8 (Shaofu), LR8 (Ququan), CV22 (Tiantu), GV4 (Mingmen), GV9 (Zhiyang), GV23 (Shangxing), CV17 (Danzhong), GV24 (shenting), GV29 (Yintang), BL15 (Xinshu), BL17 (Geshu), BL18 (Ganshu), BL20 (Pishu), BL32 (Ciliao), and EX-CA1 (Zigong).

Manipulation

In terms of acupuncture manipulation, all were administered by acupuncture physicians with long-term acupuncture clinical experience or those who had received training on acupuncture. Needle sensations called “de qi” in TCM were required during the whole process. It is a very representative feeling, which shows that the needle has reached the right position and is functioning effectively.

Efficacy

By comparing the outcomes of observational groups, the clinical curative effect was satisfactory, and the difference was statistically significant. However, the difference in efficacy caused by various acupoints selection remained unknown.

Acupuncture component therapy

The studies generally applied conventional acupuncture therapy, with the exception of some studies using acupuncture component therapies including electro-acupuncture (4 studies), moxibustion (2 studies), auricular acupuncture (1 study), and plum-blossom needle (1 study). Among the four studies that used an electro-acupuncture, one study did not describe the process of manipulation,^[42] and the other three studies used BL23 (Shenshu), SP6 (Sanyinjiao), SP10 (Xuehai), and BL32 (Ciliao). These studies suggested that the electro-acupuncture possessed tonifying functions. Two studies were performed at a low frequency of 2 Hz,^[35,40] and one in a high frequency of 100 Hz or 40 Hz. In addition, this study used the plum-blossom needle to stimulate

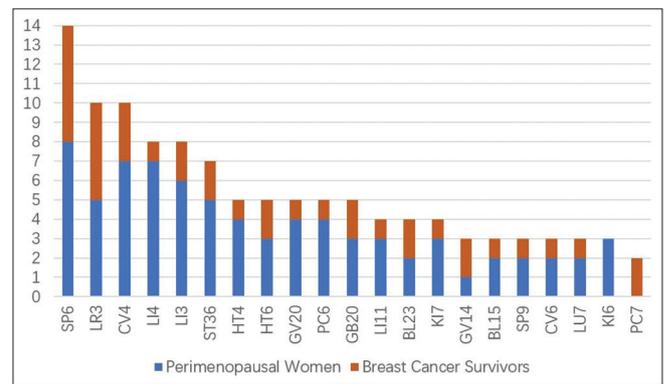


Figure 3: Frequency of acupoints selections in the two kind studies

the dorsal region C7-T5 of the DU and BL meridian for 5 min.^[37] Moxibustion could have been used by physicians as per their consideration in two studies, but they did not list the manipulation.^[30,43] One study designed auricular acupuncture within their observational intervention, with a weekly exchange and daily self-massage.^[28]

Regimen

The needle retention time of the 18 studies was relatively consistent between 20 and 40 min. The administration frequency was mostly set at twice a week, and some studies reduced it to one session per week at the latter stage of treatment. The whole course of treatment was 12 weeks most cases, and in a few cases, it lasted for 4–6 weeks.

Controlled intervention projects

Drugs

In the trials that used HT as the controlled intervention,^[28,40] the efficacy of acupuncture was satisfactory in both groups, but the effective rate of acupuncture group remained lower than the HT group. In the controlled group using gabapentin or venlafaxine, the frequency and severity of hot flashes were significantly relieved according to the follow-up results.^[40,42,46] A study even demonstrated that acupuncture efficacy for reducing the frequency of hot flashes was sustained for a longer period than in the controlled group.^[41]

Self-care

The acupuncture group combined with self-care achieved good results in improving the hot flashes symptom of perimenopausal females and in those with breast cancer.^[29-31,43] However, the self-care intervention designs were different, hence, were unable to determine whether such differences in designs affected the result or not. One study carried out diet and self-tuina under the guidance of the TCM theory.^[29] Three studies reported that the self-care was conducted under the guidance of professionals and it was emphasized that nonhormone and nonprescribed drugs were allowed to be used.

Sham acupuncture and devices

Among the 20 studies reviewed, 12 studies designed a sham acupuncture controlled group against true acupuncture, and

Table 2: Study characteristics of menopausal women

Author, years	Region	Acupuncture group (acupoint, regimen, component)	Controlled group	Placebo needle method	Course	Follow-up	Differentiation of TCM	Outcome measurement
Zhou <i>et al.</i> 2011 ^[28]	China	Acupuncture + auricular acupuncture (<i>n</i> =21) Acupoints: SP6, GB20, LI4, LI11, CV4, GV14, KI7, EX-CA1 Retaining needles for 40 min. 2 sessions a week for the 12 weeks Auricular acupoints: AH6a, TF4, TG2p, AT4, CO18, CO120, CO15, CO12 Self-massaged every day and exchanged 1 time a week for 12 weeks	Tibolone tablet (<i>n</i> =25) 2.5 mg Qd	-	12 weeks	Yes	Deficiency of kidney qi	HF frequency ^{a,c,g} HF severity ^{c,g} FSH ^{a,c} , LH ^{a,c} , E ₂ ^{a,c}
Baccetti <i>et al.</i> , 2014 ^[29]	Italy	Acupuncture + electro-acupuncture + diet and self-massage (<i>n</i> =50) Plum-blossom needle stimulated in the dorsal region C7-T5 for 5 min Acupoints: GV23*, CV22, BG2, LI11, SP10**, SP6**, GV20, CV4, ST37 Stimulated with 100 Hz electro-acupuncture*, stimulated with 40 Hz electro-acupuncture** Retaining needles for 30 min. 2 sessions a week for the 6 weeks	Diet and self-massage (<i>n</i> =50) Guided under TCM theory and professional	-	6 weeks	Yes	Deficiency of kidney yin	HF frequency ^{a,c,e,g} HF severity ^{a,c,e,g} Menopause symptoms questionnaire ^a
Borud <i>et al.</i> , 2009 ^[30]	Norway	Acupuncture + self-care (<i>n</i> =134) Acupoints selected by differentiation of acupuncture physicians but were not given. Moxibustion was allowed 10 sessions acupuncture in 8 weeks, but regimen was not given	Self-care (<i>n</i> =133) Under the professional guide	-	8 weeks	No	Acupoints selected by differentiation of TCM physicians	HF frequency ^{a,c} HF severity ^{a,c} WHQ ^a u-CGRP/ u-creatinine ^b
Kim <i>et al.</i> , 2010 ^[31]	Korea	Acupuncture (<i>n</i> =116) ST36, SP6, LI4, CP6, HT7, HT8, CV4 Retaining needles for 20 min. 3 sessions a week for the 4 weeks	Self-care (<i>n</i> =59) Under the professional guide	-	4 weeks	Yes	Not mentioned	HFS ^a HF frequency ^a HF severity ^a MRS ^a
Kargozar <i>et al.</i> , 2019 ^[32]	Iran	Acupuncture + placebo tables (<i>n</i> =17) CP7, HT6, LI4, LU7, CV4, KI3, KI6, LR3, SP6, ST36, GV20 Retaining needles for 30 min. 2 sessions a week for the first 4 weeks, then 1 session a week for 3 weeks	Urticadioica tablets + sham acupuncture (<i>n</i> =17) 450 mg Qd	Noninserted with shorter needles on skin, at original acupoints	7 weeks	Yes	Acupoints Selected by literatures or expert's experience	HFS ^{b,c,f,g} MenQOL ^{b,c,f,g} FSH ^{b,d} , LH ^{b,d} , E ₂ ^{b,c}
Ee <i>et al.</i> , 2016 ^[33]	Australia	Acupuncture (<i>n</i> =163) KI6, KI7, SP6, HT6, CV4, LR3 Twirling needle 10 min, retaining needles for 20 min. 2 sessions a week for the first 2 weeks, then 1 session a week for 6 weeks	Sham acupuncture (<i>n</i> =164) At bilateral 3 nonacupoints with sham acupuncture device	Park sham acupuncture device, nonacupoint, noninserted acupuncture	8 weeks	Yes	Deficiency of kidney yin	HFS ^{b,f} HF frequency ^{b,f} HF severity ^{b,f}

Contd...

Table 2: Contd....

Author, years	Region	Acupuncture group (acupoint, regimen, component)	Controlled group	Placebo needle method	Course	Follow-up	Differentiation of TCM	Outcome measurement
Sunay et al., 2011 ^[34]	Turkey	Acupuncture (n=27) ST36, LI4, KI3, LR3, GV29 Retaining needles for 20 min. 2 sessions a week for 5 weeks	Sham acupuncture (n=26) At original acupoints with sham acupuncture device	Streitberger sham acupuncture device, nonacupoint, noninserted acupuncture	5 weeks	No	Not mentioned	HF severity ^{a,c} MRS ^{a,c} FSH ^d , LH ^d
Venzke et al., 2010 ^[35]	USA	Acupuncture + electro-acupuncture (n=27) BL23*, BL20, BL15, BL17, GV9, GV4, GB34, SP6*, LU7, KI6, KI3, KI7, HT6, GB20, HT7, LR3, GV24 Stimulated with 2 Hz electro-acupuncture* Retaining needles for 25 min. 2 sessions a week for the first 4 weeks, then 1 session a week for 8 weeks	Sham acupuncture (n=24) At bilateral 6 nonacupoints with sham acupuncture device	Streitberger sham acupuncture device, nonacupoint, noninserted acupuncture	12 weeks	Yes	Deficiency of kidney yin	HFS ^{b,c} BDI ^{b,c} BAI ^{b,c} GCS ^{b,c}
Painovich et al., 2012 ^[36]	UK	Acupuncture (n=12) GV20, PC6, HT6, LR3, LI4, LI11, KI3, SP6, ST36, CV17, CV6, GV14, BL15, BL18, BL20, BL23, GB34 Retaining needles for 30 min. 3 sessions a week for 12 weeks	Sham acupuncture (n=12) At nonacupoints with sham acupuncture device	Sham acupuncture device but not given name, nonacupoint, noninserted acupuncture	12 weeks	No	Not mentioned	HF frequency ^{b,c} HF severity ^{b,c} MenQOL ^d PSQI ^d , BDI ^d , STAI ^d 24 h UCM ^{a,c}
Nedeljkovic et al., 2014 ^[37]	Switzerland	Acupuncture (n=10) CV4, GV20, GV20, PC6, ST36, SP6, LI4, KI3, and additional acupoints with differentiation Retaining needles for 30 min. 1 session a week for 12 weeks	Sham acupuncture (n=10) At bilateral 7 nonacupoints and shallowly inserted with sham acupuncture device	Shallowly inserted, at nonacupoints	12 weeks	Yes	Deficiency of kidney yin	HF frequency ^{a,c,f,g} HF severity ^{a,c,f} MRS ^{a,c,e,g}
Avis et al., 2016 ^[38]	USA	Acupuncture (n=170) Acupoints and treatment frequency are decided by acupuncturist and study participant, 20 sessions totally	Blank control (n=39)	-	6 months	Yes	Not mentioned	HF frequency ^{a,c,f,g} HF severity ^{a,c,f,g} PSQI ^{a,c,f,g} WHQ ^{a,c,f,g} PROMIS short form sleep disturbance measure ^{a,c,f,g}
Xu, 2015 ^[39]	China	Acupuncture (n=11) RN4, EX-CA1, ST36, SP6, and additional acupoints with different symptoms Retaining needles for 30 min. 3 sessions a week first 4 weeks, then 2 sessions a week for 4 weeks	Sham acupuncture (n=10) At point away 0.5 cm from the original acupoint by sham acupuncture	Insert 1-1.5 cun at nonacupoints	8 weeks	No	Not mentioned	MRS ^{a,c} MenQOL ^{a,c} PSQI ^{a,d} E ₂ ^{a,d} FSH ^{a,d} LH ^{a,d}

*and***: means setting electro-acupuncture on acupoints. ^aAfter treatment, difference between groups was statistically significant ($P<0.05$), ^bAfter treatment, difference between groups was not statistically significant ($P>0.05$), ^cAfter treatment, difference inside group was statistically significant ($P<0.05$), ^dAfter treatment, difference inside group was not statistically significant ($P>0.05$), ^eIn the follow-up, difference between groups was statistically significant ($P<0.05$), ^fIn the follow-up, difference between groups was not statistically significant ($P>0.05$), ^gIn the follow-up, difference inside acupuncture group was statistically significant ($P<0.05$). HF: Hot flashes, CGRP: Calcitonin gene-related peptide, u-CGRP/u-creatinine: The ratio of u-CGRP/u-creatinine, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E₂: Estradiol, WHQ: Women's Health Questionnaire, HFS: Hot flash scores, MRS: Menopause Rating Scale, MenQOL: Menopause-specific quality of life questionnaire, BDI: Beck depression inventory, BAI: Beck anxiety inventory, GCS: Greene Climacteric Scales, PSQI: Pittsburgh sleep quality index, STAI: State-trait anxiety inventory, UCM: Urinary cortisol and metabolites, PROMIS: Patient reported outcomes measurement information system, TCM: Traditional Chinese medicine

Table 3: Study characteristics of breast cancer survivors

Author, years	Region	Acupuncture group (acupoint, regimen, component)	Controlled group	Placebo needle method	Course (weeks)	Follow-up	Differentiation of TCM	Outcome measurement
Frisk <i>et al.</i> , 2012 ^[40]	Switzerland	Acupuncture + electro-acupuncture (<i>n</i> =27) BL15, BL23*, BL32*, CV4, HT7, PC6, LR3, SP6, SP9 Stimulated with 2 Hz electro-acupuncture* Retaining needle for 30 min. 2 sessions a week for the first 2 weeks, then 1 session a week for 10 weeks	Estrogen/progestin (<i>n</i> =18) Dosage was not mentioned	-	12	Yes	Not mentioned	HFS ^{c,g} HF frequency ^c WHQ ^{b,c,f,g} PGWB ^{b,c,f,g}
Walker <i>et al.</i> , 2010 ^[41]	USA	Acupuncture (<i>n</i> =25) BL23, SP6, KI3, GV14, GB20, LU9, CV4, GV20, ST36, CV6, PC7 Retaining needle for 30 min. 2 sessions a week for the first 4 weeks, then 1 session a week for 8 weeks	Venlafaxine (<i>n</i> =25) 70 mg Qd	-	12	Yes	Acupoints Selected by differentiation of TCM physicians	HF frequency ^{b,c,e} HF severity ^{b,c} MenQOL ^{b,c,f,g}
Mao <i>et al.</i> , 2015 ^[42]	USA	Acupuncture + electro-acupuncture (<i>n</i> =30) Acupoints selected by differentiation of acupuncture physicians but were not given Electro-acupuncture regimen was not given Retaining needle for 30 min. 2 sessions a week for the first 2 weeks, then 1 session a week for 6 weeks	A: Gabapentin (<i>n</i> =30) 300 mg Tid B: Sham acupuncture (<i>n</i> =32) At the nonacupoint and nonmeridian, number was same with acupuncture group, with sham acupuncture device	- Streitberger sham acupuncture device, nonacupoint, noninserted acupuncture	8	Yes	Acupoints was Selected by differentiation of TCM experts	A: HFCS ^{b,c,e,g} B: HFCS ^{b,c,f,g}
Lesi <i>et al.</i> , 2016 ^[43]	Italy	Acupuncture + self-care (<i>n</i> =85) SP6, LI11, CV4 as the primary acupoints. Moxibustion was allowed Retaining needle for 20 min. 1 session a week for 12 weeks	Self-care (<i>n</i> =105) By professional guide and booklet	-	12	Yes	Acupoints was Selected by differentiation of TCM experts	HFS ^{a,c,e,g} GCS ^{a,c,e,g} MenQOL ^{a,c,e,g}
Liljegren <i>et al.</i> , 2012 ^[44]	Sweden	Acupuncture (<i>n</i> =38) LI4, HT6, LR3, ST36, KI7, SP6 Retaining needle for 20 min. 2 sessions a week for 5 weeks	Sham acupuncture (<i>n</i> =36) At point away 1 cm from the original acupoint by sham acupuncture	Park sham acupuncture device, nonacupoint, noninserted acupuncture	5	No	Acupoints was selected by differentiation of TCM experts	HF frequency ^b HF severity ^{a,c} Sex hormoned (FSH, LH, E ₂ , PRGE, SHBG, PRL, TSTO)
Hervik and Mjåland, 2009 ^[45]	Norway	Acupuncture (<i>n</i> =30) LR3, GB20, LU7, KI3, CV4, SP6, PC7, LR8 Retaining needle for 30 min. 2 sessions a week for the first 5 weeks, then 1 session a week for 5 weeks	Sham acupuncture (<i>n</i> =29) At the nonacupoint and nonmeridian	Nonacupoint, noninserted acupuncture	10	Yes	Selected acupoints of tonifying yin from textbooks	HF frequency ^{a,c,e,g} KI ^{a,c,e,g}
Bokmand and Flyger, 2013 ^[46]	Denmark	Acupuncture (<i>n</i> =31) KI3, SP6, HT6, CV3 Retaining needle for 15-20 min. 1 session a week for 5 weeks	Sham acupuncture (<i>n</i> =29) At the nonacupoint and nonmeridian	Nonacupoint, noninserted acupuncture	5	Yes	Not mentioned.	VAS ^{a,c,e,g} Sleeping condition ^{a,c,e,g} E ₂ ^d

Contd...

Table 3: Contd.....

Author, years	Region	Acupuncture group (acupoint, regimen, component)	Controlled group	Placebo needle method	Course (weeks)	Follow-up	Differentiation of TCM	Outcome measurement
Lin, 2018 ^[46]	China	Drug and acupuncture (n=36) Gabapentin, one tablet 3 times a day SP6, SP9, LI4, RN4 Retaining needle for 30 min. 6 sessions a week for 12 weeks	Drug and sham acupuncture (n=26) Gabapentin, one tablet 3 times a day At the nonacupoint and nonmeridian	Shallowly inserted, at nonacupoints	12	Yes	Not mentioned	KI ^{a,c,e}

*and***: means setting electro-acupuncture on acupoints. ^aAfter treatment, difference between groups was statistically significant ($P<0.05$), ^bAfter treatment, difference between groups was not statistically significant ($P>0.05$), ^cAfter treatment, difference inside group was statistically significant ($P<0.05$), ^dAfter treatment, difference inside group was not statistically significant ($P>0.05$), ^eIn the follow-up, difference between groups was statistically significant ($P<0.05$), ^fIn the follow-up, difference between groups was not statistically significant ($P>0.05$), ^gIn the follow-up, difference inside acupuncture group was statistically significant ($P<0.05$). HF: Hot flashes, WHQ: Women's health questionnaire, MenQOL: Menopause-specific quality of life questionnaire, PGWB: Psychological and general well-being index, HFCS: Hot flash composite score, PRGE: progesterone, SHBG: Sex hormone-binding globulin, PRL: Prolactin, TSTO: Testosterone, KI: Kupperman index, VAS: Visual Analog Scale, GCS: Greene Climacteric Scales, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E₂: Estradiol, TCM: Traditional Chinese medicine, HFS: Hot flash scores

needle sensations should not appear in the controlled groups. Sham acupuncture, as a placebo intervention for acupuncture trials, was not supposed to make the patients have the feeling of "De qi," which was essential in the operation of true acupuncture. However, the difference in outcome after treatment between the true/sham groups was not statistically different; therefore, we could not eliminate the placebo effect of acupuncture according to these studies.

Sham acupuncture devices were used in six studies among which one did not give the definite name,^[36] and all the other five studies used the devices commonly appearing in the international acupuncture RCT. Three of them chose the streitberger sham acupuncture device, among which, one was manipulated at the original acupoints, which was the same as that in the true acupuncture group.^[34] The other two trials manipulated the device at points away from original acupoints or the meridians.^[33,42] The Park sham acupuncture device was used by the other two studies,^[33,44] and both of them chose nonacupoints away from meridians.

Five studies also used other kinds of stimulation as the placebo-controlled intervention. In four of them, the needle was shallowly inserted into the skin for 1–2 mm at nonacupoints.^[37,45–47] However, it was shallowly inserted at the original acupoints in the fifth study.^[32]

Outcome measurement

Scale

At present, there are uniform scales for the measurement of hot flashes symptoms and the treatment accepted by the international community. Such scales offered a standard for the discussion of the efficacy of acupuncture for hot flashes. Relatively united scales of hot flashes frequency, severity, or dedicated scale HFS were employed in the 20 studies to measure the symptom of hot flashes. The quality of the participations' daily life was assessed in most studies by using the scales of WHQ, PGWB, MenQOL, GCS, KI, PSQI, BDI,

or STAI. Some studies adopted the dedicated scales to measure participations' depression, anxiety, or sleeping conditions at the same time to give a comprehensive symptom description under interventions.

Laboratory examination

Part of these studies used laboratory indicators to estimate the efficacy. The most commonly used indicator was the sex hormone test in the peripheral circulation (FSH, LH, E₂, PRL, TSTO, PRGE, and SHBG). Others included the calcitonin gene-related peptide urine test,^[30] urinary cortisol, and metabolites to explore the mechanism of the acupuncture effect, but the results did not show any benefits.^[30,36]

TCM syndrome differentiation

Thirteen of the 20 studies were involved in TCM syndrome differentiation, whereas the other seven studies did not depict their basic theories.^[31,34,36,39,40,46,47] Among these 13 articles, five clearly mentioned the TCM differentiation of the kidney yin deficiency or kidney qi deficiency,^[28,29,33,35,37] which was similar to the TCM theory, and they were all from trials of perimenopausal females. Eight articles showed that the acupuncture prescriptions were chosen according to the differentiation of TCM physicians, although the acupoints were not listed.^[30,32,38–44]

DISCUSSION

Quality of studies

Acupuncture therapy is rooted in Chinese and prospering in Asia. We believe that its retrieval results are complete enough to cover the latest progress in acupuncture for hot flashes at home and abroad. We found that articles published in English were in accordance with the clauses of the CONSORT and STRICTA guidelines.^[27,49] Therefore, they were all of high quality and their results were reliable with the complete description of the trial design and process. The studies also clearly enumerated the criteria and flow diagram, and

illustrated the randomization and blinding method used. For the controlled interventions, the commonly used drugs or therapies recommended by guides were employed, which ensured the reliability of the trials.

From this review, we can conclude that acupuncture has an established efficacy on hot flashes among Americans and Europeans; nevertheless, these included studies from America and Europe. Therefore, similar studies should be carried out in Asia, working as stimuli to enhance local research facilities, and contribute to researches on acupuncture or hot flashes. Finally, a more effective acupuncture therapeutic project should be conducted.

Result of acupuncture efficacy

By horizontal comparison, all the mentioned studies confirmed the therapeutic efficacy of acupuncture on hot flashes. Using different pathogenesis, it lowers the frequency and alleviates the severity of hot flashes. This efficacy was better than that of nonhormone drugs or self-care treatments, and it had a long-term effect after the intervention was stopped. Nevertheless, to some extent acupuncture was not as effective as conventional HT; however, it has some important advantages including that it causes few side effects and could improve concomitant symptoms of depression, anxiety, or insomnia.^[35,36,40,46] Given the several side effects of HT,^[50] we recommend that acupuncture should be considered as a main or supplementary therapy to treat hot flashes.

Study methods

There was no distinct inconformity of acupuncture in our included studies, and acupuncture supplements, like electro or moxibustion, were less used. This was ideal for the popularization of acupuncture. All studies highlighted that their therapies were based on the TCM and they also emphasized the sensation of “de qi” during acupuncture treatment which provided some supports for TCM. Some studies provide unique perspectives on TCM or its benefits for some diseases. However, there are some doubts as well. For instance, the different effects between the different acupoints remained unclear. As a study showed, there was no difference between the personalized and standardized acupoints in the treatment of backache.^[51] There is a need to explore if hot flashes acupuncture therapy should be personalized by differentiation or standardized for acupoints selection. This is also a difficulty that should be overcome in the process of standardization and popularization of TCM or acupuncture, and further research is warranted.

In terms of the controlled intervention for acupuncture RCT, some studies chose universal positive drugs as the controlled intervention, followed by the conventional RCT. Placebo acupuncture controlled intervention gradually became the main intervention used in acupuncture RCT. This type of placebo set could eliminate the placebo effect of acupuncture to some degree. However, the manipulation and designs of placebo acupuncture have been controversial. Some sham

acupuncture adopted a shallow penetration at the original acupoints; however, this kind of stimulation can pass through the skin, stimulate the nerve, and cause an effect.^[52] Some sham acu punctures manipulated shallow penetration at nonacupoint positions or utilized sham acupuncture devices to conduct noninserted acupuncture. These nonacupoints may be located at the meridians, and the noninserted acupuncture was very similar with a classical manipulation called “Di needle” from *miracle pivot*, such that the effect caused by sham acupuncture might be similar to true acupuncture.^[53] Presently, there are several sham acupuncture devices to fulfill the needs of RCT. Such devices simulate acupuncture manipulation and confused the individuals to achieve the effect of placebo.^[54-56] Based on this, the assessment for blinding of placebo was designed.^[57] However, for people who are more familiar with acupuncture, like the Chinese, these sham acupuncture designs may not realize this purpose. The short-term and long-term acupuncture effect assessments may reflect acupuncture’s real efficacy. In Hervik’s study, all the patients were followed-up for 2 years after their treatment with a true/sham acupuncture controlled trial for hot flashes of breast cancer. The results showed that participants in the true acupuncture group generally remained in a good condition, while the condition was opposite in the sham group.^[58] Some imaging studies focusing on different brain area influence screened by fMRI between the true and sham acupuncture also demonstrated the difference between them.^[59] At present, although we cannot totally eliminate the placebo effect of acupuncture, it is arbitrarily necessary and noncommittal to conclude that acupuncture effect is the placebo effect.

To date, the outcomes for measuring hot flashes symptom are unified, and specific scales are mostly used. That avails for the research on the therapies of this disease. The review and analysis in this paper contributes to similar studies in future. Some new kind of laboratory examinations can provide mechanism explanation for treatments. The studies discussed in this article mainly followed the “withdrawal of sex hormone” theory or set the test indicators from the perspective of neuroendocrinology. It can be helpful to explain the mechanism of acupuncture in treating hot flashes.

Present limitations and future expectations

In this research, we found the following limitations of the current studies:

1. The interventions of the acupuncture group were inconsistent, covering the TCM syndrome differentiation, acupoints selection, manipulation of the acupuncture, and the regimen
2. The controlled interventions of these trials were not yet unified. Since the number of trials choosing HT as the positive drug were small, the reliability of the sham acupuncture interventions as well as the placebo control was not discussed
3. The trial that employed a combination of acupuncture and drugs as the observational intervention was rare; therefore, its clinical effect was unclear

4. Due to the different characteristics of the trials, a systematic review or meta-analysis on this topic should have been conducted.

Based on the above-mentioned shortcomings, we put forward the following suggestions for future studies:

1. Based on CONSORT and STRICTA guidelines, a more suitable sham acupuncture should be conducted to further explore the difference between true and sham acuapunctures
2. Studies should be conducted to explore whether a combination of acupuncture and nonhormone drugs can alleviate the side effects and cut down the dose of the only drug used
3. Studies should be conducted to explore a proposal for conducting practicable and effective acupoints selection and formulate a standardized plan for the treatment of hot flashes by applying acupuncture
4. Large sample, multi-center, and high-quality RCT or animal experiments should be conducted to prove the effectiveness of acupuncture for hot flashes caused by menopausal transition, breast cancer, and ADT, and explain its mechanisms.

TCM syndrome differentiation is vital in TCM treatment. When planning, it is necessary to confirm the definite differentiation and make corresponding discussions through the report. In addition, to make the research in a certain topic receive a deep and coherent development, researchers are supposed to better arrange the acupuncture intervention to make it consistent with relevant studies, which is also a beneficial factor for the standardization of acupuncture.

CONCLUSIONS

These RCTs on acupuncture were nonuniform, which made the studies on this topic lack coherence, leading to unsatisfactory research outcomes. It is a necessity to have more professional research teams to conduct studies on a definite topic and draw a precise conclusion to previous studies before the next step is taken.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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