

## Herbal Medicines for Improving Quality of Life in Menopause Women: A Systematic Review

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### Abstract

**Back ground and Objective:** Menopause encompasses 25 million women worldwide each year, and the World Health Organization estimates that 1.2 billion women will be postmenopausal by 2030. Menopause is explained as the transition from the reproductive phase of women to the non-reproductive. Menopausal symptoms are common in menopausal women. These symptoms are not life-threatening, but may reduce especially quality of life.

Our aim in this review is assess the articles that have herbal treatment for quality of life in menopause.

**Method and Material:** We conducted a literature search including published studies from database initiation from their inception through December 2015, using MED LINE Pub Med, Science Direct and Scopus search. The search was limited to published studies in English and studies of humans, clinical trial study and full text and published, by using the following search key words and medical subject heading terms: (menopause OR climacteric) AND ("Herbal medicine" OR "Medicinal Herb" OR "Medicinal Plant"). Furthermore, we then adhered to standard criteria for conducting and reporting systematic review.

**Results:** We conducted a literature search including published studies from database initiation. A total of 371 articles were located, and 361 were excluded for the reasons. The remaining 10 RCTs were included, and their key data are summarized. Of 10 randomized control trials that we assessed, 6 of them showed significant improvement across all domains measured by the MenQoL and Greene climacteric scales and the Menopause-Specific Quality of Life questionnaire.

**Conclusion:** No final statement can be drawn regarding the effectiveness of herbal medicines treatment due to qualitative shortcomings of included studies and a general limited availability of studies in this field. But most of the studies show that herbal medicines can be effective in improving the quality of life in menopause women especially in those who suffers from different disorders with the minimum side effects.

**Keywords:** Menopause, Quality of life, Herbal medicine

### Introduction

Menopause encompasses 25 million women worldwide each year, and the World Health Organization estimates that 1.2 billion women will be postmenopausal by 2030 [1].

Menopause is explained as the transition from the reproductive phase of a woman to the non-reproductive phase. Changes in hormone levels might make complaints and health consequences especially during peri-and post menopause. Menopausal symptoms are common in menopausal women. The main key is the cease of menstruation, which occurs in many industrial countries on average at age 51 years. In Iran according to Rajae fard s study in 1390 the mean age of menopause was 48.18 years [2]. This period starts almost between age of 40 and 50 and is demonstrated by the reduction of estrogen levels [3].

Climacteric disturbances arise in two thirds of women. Hormonal changing, especially the lack of estrogens, leads to menopausal Symptoms. These menopausal symptoms are not life-threatening, but may reduce especially quality of life. Main complaints are vasomotor and vaginal symptoms, aided by cardiovascular complaints,

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depressive episodes and sleep disturbance and a range of symptoms including mood changes and dysphoric mood, hot flashes, night sweats, vaginal dryness, decreasing in libido, and imbalance in cognitive function, osteoporosis, osteoarthritis, depression, dementia, and frailty [1,4,5].

Hot flashes and night sweats are experienced by almost 70% of menopausal women and are serious problems for about 20-25% of women that seeking for treatment [6].

Although many physical and emotional symptoms have been attributed to menopause, but hot flashes and night sweats are the main change, and the main reason that menopausal women seek for medical help [7].

Almost some of these menopausal symptoms can be effectively treated with hormone replacement therapy (HRT). However, possible adverse effects of long-term HRT have made to a high prevalence of use of complementary therapies by menopausal women [8].

Hormone therapy has a potential risk hazards of damaging health and is recommended for temporal limited therapy for sever vasomotor symptoms only [3].

Some of the most common of these treatments include herbal supplements.

Also an increasing interest and need for alternative treatment methods including phytotherapeutics exist. About 15 to 17 % of postmenopausal women with menopausal symptoms - affected by ethnicity, education and medical and herbal consultation - use alternative treatment methods (e. g. natural products, mind-body-therapies, acupuncture) Phytotherapeutics (drugs made out of plants, e. g. red clover, St. John's wort, hop or black cohosh) are most commonly used as tea, through nutrition as food supplements [3].

A large proportion of patients felt that they wanted a good safety profile and strong evidence base for treatment [9].

The value of herbal medicine for improving menopause symptoms is limited and contradictory.

Quality of life has been complained by the World Health Organization (WHO) as the "individual's perceptions of their position in life in the context of the cultural and value systems in which they live and in relation to their goals, expectations, standards and concerns". It is a broad ranging idea incorporating

in a complex way a person's physical health, psychological state, level of independence, social relationships, and personal beliefs, as well as their relationships to relevant features of the environment Quality of life is the major goal of health care, is a significant aspect for individual health, and is used to plan and evaluate health care programs [10,11].

Motivation for health support in menopausal women may be further strengthened if women recognize lifestyle modifications, especially nonpharmacological ways of managing menopausal symptoms, and increasing quality of life is urgently needed.

The objective of this systematic review was to summarize and critically assess the evidence from randomized clinical trials (RCTs) of herbal medicines in menopausal women quality of life.

## Materials and Methods

### Data sources and searches

We conducted a literature search including published studies from database initiation from their inception through October 2015, using MED LINE Pub Med, Science Direct and Scopus search. Because two systematic reviews about this course were reported in November and December 2003, therefore we omitted RCT articles that had been published before 2003. The search was limited to published studies in English and studies of humans by using the following search key words and medical subject heading terms: (menopause OR climacteric) AND( Herbal medicines OR Medicinal Herb OR Medicinal Plant). Furthermore, we adhered to standard criteria for conducting and reporting systematic review [12].

### Study Selection

At least 2 reviewers independently evaluated each study to determine inclusion criteria. We selected randomized control trials studies that evaluate herbal medicines for managing menopausal symptoms.

We restricted the included studies to English-language articles and excluded studies published only as abstracts.

### Data Extraction and Quality Rating

One investigator abstracted details about the sample size / conditions, age range (yr.), intervention, treatment duration (wk), main outcome measures, main results, side effects, author's conclusion and quality (Table1).

First author	Sample size / Conditions	Intervention	Treatment duration (wk)	Main results	AEs	Author's conclusion
Scheid V 2015	117 perimenopausal women between 45 and 55 years of age	using Chinese herbal medicine and/ or acupuncture along with dietary and lifestyle advice	6 months	Significant improvement across all domains measured by the MenQoL and Greene climacteric scales. Reduction on the MenQoL scale between first and last visit was from 4.31 to 3.27 (p<0.001)	No adverse events or abnormal liver or kidney function values were observed during the course of the study.	Further research that seeks to investigate the effects observed in more detail and to evaluate them against other forms of treatment and/or no-treatment controls is warranted
2. Zhong LL 2013	108 Hong Kong perimenopausal women who reported (MRS) total scores of 28 or higher.	a Chinese herbal formula, Er-Xian decoction (EXD)	12 w	Greater improvement in the total scores for the Menopause-Specific Quality of Life questionnaire (P < 0.01).(4.35 via 3.15)	There were no serious adverse events	The Chinese herbal formula EXD is superior to placebo in reducing the frequency and severity of hot flushes and in improving menopausal symptoms in Hong Kong perimenopausal women.

3. Nedeljkovic M. 2014	40 women reporting at least 20 hot flushes per week	They were randomly allocated to receive traditional Chinese medicine (TCM) AP, sham AP, verum CHM, or placebo CHM	12w	MRS QOL in verum 25.7 via 23.11 (baseline) and in verum 5.6 via placebo 4.1 (12w) and in verum 8.9 via 4.6 (24w)	In one participant in the verum CHM group, dysplasia of the squamous epithelium was diagnosed at the final gynecologic examination during follow-up assessment. This serious adverse event, however, is not thought to be related to the trial medication. Only one participant in the sham AP group reported a mild adverse event by stating pain sensation at needle insertion	verum CHM does not differ from placebo CHM
4. Wang CC 2013	60 postmenopausal women	participants were randomized to receive DBT preparations at 1.5, 3.0, or 6.0 g/day	12 w	There were differences between-group in psychological/psychosocial (P = 0.015, GCS; P = 0.013, MENQOL) and somatic/physical (P = 0.019, GCS; P = 0.037, MENQOL) domains, and improvement was significantly greatest (P < 0.05) in the 6.0 g/day dose group.	no serious adverse events	DBT preparations at 6.0 g/day significantly improve physical and psychological scores and significantly reduce vasomotor symptoms from baseline
5. Leung PC 2011	total of 150 women aged 40-60 years, who were after menopause for at least 1 year and (BMD) must be lower than 0.891 g/cm	Randomly divided into the ELP group treated with ELP and the placebo group, with 75 in each group.	12w	Physical function of SF-36 QOL questionnaire was remarkably improved compared with the baseline, but did not show dominance over the placebo group. (58 via 65)	Not reported	QOL did not show dominance over the placebo group.
6. Xia Y 2012	72 perimenopausal women who reported 14 or more hot flashes per week	participants were randomly allocated to receive JQF or placebo	8w	There were differences between-group in vasomotor (P = 0.011) and physical (P = 0.034) domains In vasomotor 3.83 ± 1.24 via 4.40 ± 1.44 (baseline) 2.71 ± .87 via 2.36 ± 1.01 (12w) In psychosocial 3.5 ± 1.25 via 3.56 ± 1.31 (baseline) 3.07 ± 1.14 via 3 ± 1.10 (12w) In physical 3.17 ± 1.02 via 3.29 ± 1.32 (baseline) 2.98 ± 0.82 via 2.85 ± 1.04 (12w) In sexual 3.16 ± 1.79 via 3.21 ± 1.63 (baseline) 3.17 ± 1.55 via 2.88 ± 1.41 (12w)	no serious adverse events	The Chinese herbal medicine preparation JQF was found to be superior to placebo in reducing hot flashes and improving menopausal symptoms in the vasomotor and physical aspects
7. Li WJ 2010	total of 57 cases of early postmenopausal women were randomly divided into two groups	Patients in Kuntai group received 6 g Kuntai capsules three times a day. The patients in CEE group received CEE 0.3 mg and 0.6 mg alternately once a day (average dose of 0.45 mg/d). The patients with intact uterus in CEE group were treated with 2 mg medroxyprogesterone acetate daily.	12m	QOL scores at each time point were improved as compared with those before treatment (P < 0.05), however there were no statistical differences between the two groups (P > 0.05). In CEE, QOL was 12.6 ± 8.14 (baseline) and 7.8 ± 8.99 (12w) and 4.83 ± 7.33 in KNTAI 12.96 ± 11.01 (baseline) and 10.46 ± 10.2 (12w) and 5.46 ± 6.54	No severe adverse effects occurred in the study	Both Kuntai Capsule and CEE may contribute to maintain the cognitive function and ameliorate mental symptoms of early postmenopausal women
8. Haines CJ	103 symptomatic women	50 women Dang Gui Buxue Tang and 50 women received placebo	6m	In the vasomotor domain of the Menopause Specific Quality of Life, there was a significant reduction in scoring in the placebo group (from 2.8 ± 1.6 to 1.7 ± 1.3, p < 0.01) but not in the treatment group (from 2.8 ± 2.1 to 2.3 ± 1.6, p = 0.247)	No serious adverse events attributable to treatment during the study period.	no significant difference between Dang Gui Buxue Tang and placebo in the treatment of vasomotor symptoms in Hong Kong Chinese women

9. Kwee SH 2007	31 peri- and post-menopausal Dutch	CHM formulae (n=10), HRT (n=11) or placebo (n=10)	12w	qualitatively there was no overall improvement sp-36 in HRT in physical health 59.45 and in mental health 59.75, in CHM in physical health 62.37 and in mental health 58.9, in placebo physical health 59.5 and in mental health 70.07	No serious adverse events were reported.	we need to conduct a larger trial with a more menopause specific questioner
10. Lai JN 2005	126 women were included who were between 45 and 55 years of age	Every participant received TMN-1 treatment 4 g, 3 times per day	12w	It improved symptoms of insomnia, nervousness, melancholia, and palpitation in perimenopausal women	Five (5) adverse drug reactions were detected: three single events of nausea, abdominal pain, and abdominal fullness; and two events of diarrhea.	This study provides evidence that 12 weeks of TMN-1 therapy is a viable alternative treatment to consider in perimenopausal women with hot flashes, particularly in those with palpitations, emotional disturbance, and insomnia

Table 1: Summary of randomized clinical trials of herbal medicine for quality of life.

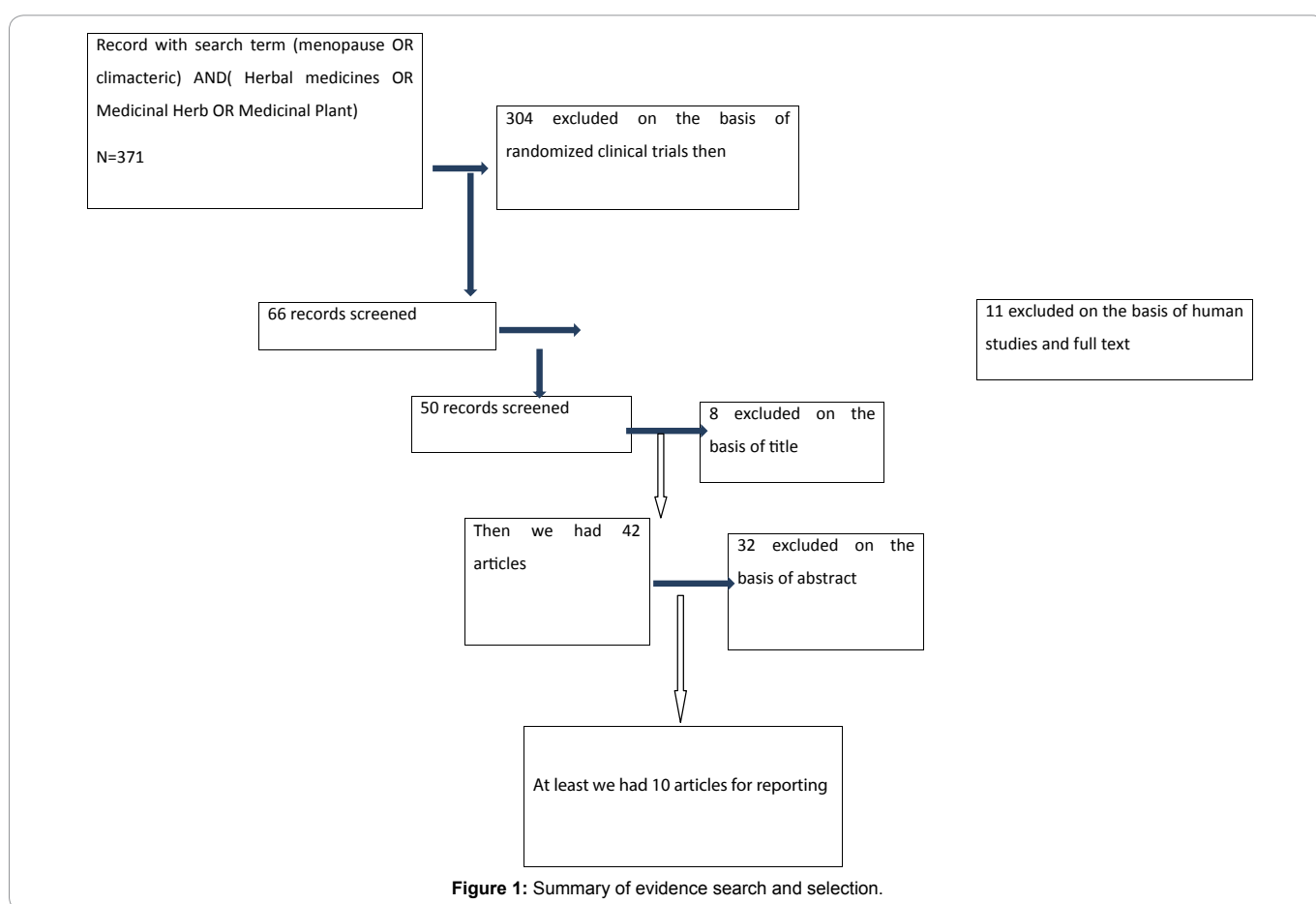


Figure 1: Summary of evidence search and selection.

A second investigator reviewed data for accuracy. Two investigators employed predefined criteria to assess the quality of each study. Risk of bias of Cochrane collaborations was used for the valuation of the involved studies' quality in six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias [12].

Disagreements were discussed and the third author opinion was used for resolving the remaining discrepancies.

## Results

We conducted a literature search including published studies

from database initiation from their inception through October 2015, using MED LINE Pub Med and Science Direct and Scopus search. A total of 371 articles were located, and 361 were excluded for the reasons given in Figure 1.

The remaining 10 RCTs were included, and their key data are summarized in Table 1.

Of 10 articles we assessed, the first article was done by Scheid Vin 2015. He recruited 117 perimenopausal women between 45 and 55 years of age from the general population. They involved using Chinese herbal medicine and/or acupuncture along with dietary and lifestyle advice. A maximum of 12 treatments over 6 months was allowed per patient. Patients showed significant

improvement across all domains measured by the MenQoL. Reduction on the MenQoL scale between first and last visit was from 4.31 to 3.27 ( $p < 0.001$ ). No adverse events or abnormal liver or kidney function values were observed during the course of the study [13].

In the second article, conducted by Zhong LL in 2013, a randomized, double-blind, controlled trial was conducted among 108 Hong Kong perimenopausal women who reported Menopause Rating Scale (MRS) total scores of 28 or higher. They used Er-Xian decoction (EXD) for 12 weeks. He reported greater improvement in the total scores for the Menopause-Specific Quality of Life questionnaire ( $P < 0.01$ ). (4.35 before treatment and 3.15 after treatment).

In conclusion the Chinese herbal formula EXD is superior to placebo in reducing the frequency and severity of hot flushes and in improving menopausal symptoms in Hong Kong perimenopausal women [14].

In 2014, forty postmenopausal women, that reporting at least 20 hot flushes per week were enrolled in a randomized controlled trial by Nedeljkovic M. They were randomly allocated to receive traditional Chinese medicine (TCM) AP, sham AP, verum CHM, or placebo CHM for 12 weeks. Follow-up assessment was conducted 12 weeks after intervention. Results showed that MRS QOL score in verum CHM was 25.7 via 23.11 in placebo CHM at baseline and in verum CHM was 5.6 via 4.1 in placebo CHM at 12w and in verum CHM was 8.9 via 4.6 in placebo CHM at 24w. In conclusion VERUM CHM shows no significant improvement when compared with placebo CHM [15].

In another article that assess the effect of a Chinese herbal medicine (Dang Gui Buxue Tang) for quality of life in postmenopausal women in 2013, 60 postmenopausal women experiencing severe hot flashes and night sweats, were randomized to receive DBT preparations at 1.5, 3.0, or 6.0 g/day for 12 weeks. Results showed that there were significant differences between-group in psychological/psychosocial ( $P = 0.015$ , GCS;  $P = 0.013$ , MENQOL) and somatic/physical ( $P = 0.019$ , GCS;  $P = 0.037$ , MENQOL) domains, and improvement was significantly greatest ( $P < 0.05$ ) in the 6.0 g/day dose group. Thus DBT preparations at 6.0 g/day significantly improve physical and psychological scores [16].

Leung PC in 2011 recruited 150 women aged 40-60 years, who were after menopause for at least 1 year randomly divided into the ELP group treated with ELP and the placebo group, with 75 in each group. In conclusion physical function of SF-36 QOL questionnaire was remarkably improved compared with the baseline, but did not show dominance over the placebo group. (58 via 65) [17].

In a randomized double-blind placebo-controlled trial of a Chinese herbal medicine in 2012, 72 perimenopausal women who reported 14 or more hot flashes per week, were randomly allocated to receive JQF or placebo for 8 weeks. Post treatment follow-up was performed 4 weeks after intervention.

There were between-group differences in vasomotor ( $P = 0.011$ ) and physical ( $P = 0.034$ ) domains. In vasomotor domain, the scores were  $3.83 \pm 1.24$  via  $4.40 \pm 1.44$  at base line and was  $71 \pm 1.87$  via  $2.36 \pm 1.01$  at 12w.

In psychosocial domain, the scores were  $13.5 \pm 1.25$  via  $3.56 \pm 1.31$  at baseline and were  $3.07 \pm 1.14$  via  $3 \pm 1.10$  at 12w.

In physical domain, the scores were  $3.17 \pm 1.02$  via  $3.29 \pm 1.32$  at baseline and were  $2.98 \pm 0.82$  via  $2.85 \pm 1.04$  at 12w.

In sexual domain, the scores were  $3.16 \pm 1.79$  via  $3.21 \pm 1.63$  at baseline and were  $3.17 \pm 1.55$  via  $2.88 \pm 1.41$  at 12w. Then the Chinese herbal medicine preparation JQF was found to be superior to placebo improving menopausal symptoms in the vasomotor and physical aspects [18].

In another study Li in 2010 recruited 57 cases of early postmenopausal women. They were randomly divided into two groups: Kuntai group with 28 cases and CEE group with 29 cases. The patients in Kuntai group received 6 g Kuntai capsules three times a day. The patients in CEE group received CEE 0.3 mg and 0.6 mg alternately once a day (average dose of 0.45 mg/d). The patients with intact uterus in CEE group were treated with 2 mg medroxyprogesterone acetate daily for 12 months. In CEE, score of QOL was  $12.6 +_8.14$  at baseline and  $7.8 +_8.99$  at 12w and  $4.83 +_7.33$  at 12 month. In KNTAI score of QOL was  $12.96 +_11.01$  at baseline and  $10.46 +_10.2$  at 12w) and  $5.46 +_6.54$  at 12 month.

QOL scores at each time point were improved as compared with those before treatment ( $P < 0.05$ ), however there were no statistical differences between the two groups ( $P > 0.05$ ) [19].

Haines did a 6-month randomized, double-blind, placebo-controlled study of the effect of Dang Gui Buxue Tang (a 1: 5 combination of Dang Gui (*Angelicae sinensis*) and Huang Qi (*Astragalus membranaceus*) on acute menopausal symptoms. A total of 103 symptomatic women were enrolled. Three of them failed to meet inclusion criteria, and 50 subjects for inclusion in each group. Results showed that in the vasomotor domain of the Menopause Specific Quality of Life, there was a significant reduction in scoring in the placebo group (from  $2.8 \pm 1.6$  to  $1.7 \pm 1.3$ ,  $p < 0.01$ ) but not in the treatment group (from  $2.8 \pm 2.1$  to  $2.3 \pm 1.6$ ,  $p = 0.247$ ). Thus he resulted that the Dang GUI and Huang Qi did not improve the Menopause Specific Quality of Life [20].

Kwee SH in 2007 evaluate within the Traditional Chinese Medicine (TCM) setting, the effect of CHM-formulae on menopausal symptoms. 31 peri- and postmenopausal Dutch women were recruited to complete 12 weeks of treatment with either CHM formulae ( $n=10$ ), HRT ( $n=11$ ) or placebo ( $n=10$ ) medications plus 4 weeks of non-treatment follow-up observation. Results showed that qualitatively there was no overall improvement sp-36. In HRT group, the score in physical health was 59.45 and score in mental health was 59.75 and in CHM group, the score in physical health was 62.37 and the score in mental health was 58.9 and in placebo group, score in physical health was 59.5 and score in mental health was 70.07. Although quantitatively there was a significant difference in the reduction of hot flushes between groups, qualitatively there was no overall improvement [21].

Lai (2005) evaluated safety and efficacy of the finished herbal product TMN-1 in the treatment of menopausal symptoms in climacteric women. 126 women were included who were between 45 and 55 years of age, were experiencing hot flashes, and were without hormone replacement therapy. Every participant received TMN-1 treatment 4 g, 3 times per day, for 12 weeks. It

first author	random sequence generation	Allocation concealment	blinding Patient and practitioner	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
1. Scheid V	H	U	L	L	L	L
2. Zhong LL	H	U	L	L	L	L
3. Nedeljkovic M	H	L	L	L	L	L
4. Wang CC	H	L	L	L	L	L
5. Leung PC	H	L	L	L	L	L
6. Xia Y	H	L	L	L	L	L
7- Li WJ	H	L	L	L	L	L
8-Haines CJ	H	L	L	L	L	L
9. Kwee SH	H	H	H	L	L	L
10. Lai JN	H	H	H	H	H	H

L, low risk of bias; U, unclear; H, high risk of bias

**Table 2:** Risk of bias in included trials.

improved symptoms of insomnia, nervousness, melancholia, and palpitation in perimenopausal women. He provided that 12 weeks of TMN-1 therapy was a viable alternative treatment to consider in perimenopausal women with hot flashes, particularly in those with palpitations, emotional disturbance and insomnia [22].

### Risk of bias

ALL of RCTs had a high risk of bias in sequence generation method for randomization.

Except one study that a high risk bias in all [22].

Two of them had an unclear allocation concealment [13,14]. Six of studies had a low risk bias in allocation concealment [15-20] and one had a high risk of bias allocation concealment [21].

Eight of studies had a low risk of bias in blinding patient and practitioner, blinding of outcome assessment, incomplete outcome data and selective reporting [13-20].

One study had a high risk bias in blinding patient and practitioner and had a low risk bias in blinding of outcome assessment, incomplete outcome data and selective reporting [21] (Table 2).

### Discussion

Menopausal symptoms are highly customary and due to their potential restriction in the quality of life a relevant healthcare policy and medical area. Considering the fact that hormone preparations are only of restricted temporal use, there is a vast problem among women as well as requirement and growing interest in alternative treatment methods.

All included RCTs show multiple weaknesses in quality with regard to concealment, randomization, sample size calculation and blinding, Incomplete outcome data and selective reporting, which led to the down-grading of the evidence level of some studies by the authors .

This systematic review identified 10 RCTs of herbal medicine as a treatment of menopause symptoms and quality of life.

Some of the RCTs used placebo controls or use group with no intervention and at least reported the Successful of their interventions.

All RCTs report details about ethical approval.

Of 10 randomized control trials that we assessed, 6 of them showed significant improvement across all domains measured by the MenQoL and Greene climacteric scales and the Menopause-Specific Quality of Life questionnaire [13,14,16,18,19,21].

In the study that innovative herbal product for the prevention of osteoporosis and effects of acupuncture and Chinese herbal medicine (Zhi Mu 14) on quality of life, physical function of SF-36 QOL questionnaire was remarkably improved compared with the baseline, but did not show dominance over the placebo group [14,16].

In the randomized, double-blind, placebo-controlled study of the effect of a Chinese herbal medicine preparation (Dang Gui Buxue Tang) on menopausal symptoms, in the vasomotor domain of the Menopause Specific Quality of Life, there was a significant reduction in scoring in the placebo group , but not in the treatment group20 .

To evaluate within the Traditional Chinese Medicine (TCM) setting, the effect of CHM-formulae on menopausal symptoms in 2007, quantitatively there was a significant difference between groups, qualitatively there was no overall improvement [20].

In 8 studies, no serious adverse events attributable to treatment during the study period [12,13,15-20].

In one study, one participant in the verum CHM group, dysplasia of the squamous epithelium was diagnosed at the final gynecologic examination during follow-up assessment. This serious adverse event, however, is not thought to be related to the trial medication.

In another study, five adverse drug reactions were detected: three single events of nausea, abdominal pain, and abdominal fullness; and two events of diarrhea [21].

Our review has a number of vital limitations. Although strong efforts were made to rescue all RCTs on the subject, we cannot be sure that our searches located all relevant RCTs. Moreover, selective publishing and reporting are foremost sources of bias, which must be deliberated. It is possible that several negative RCTs remain unpublished, and their absence could falsify the overall picture. Further limitations include the lack and the often suboptimal methodological quality of the principal data. Some of the RCTs included in the present review were not successful in diminishing bias. These issues limit the determination of this systematic review.

## Conclusion

No final statement can be drawn regarding the effectiveness of herbal medicine treatment due to qualitative shortcomings of included studies and a general limited availability of studies in this field. But most of the studies show that herbal medicine can be effective in improving the quality of life in menopause women especially in those who suffers from different disorders with the minimum side effects.

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