

# A Systematic Review and Meta-analysis on the Effect of Herbal Medicine to Manage Sleep Dysfunction in Peri- and Postmenopause

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**Objectives:** Some conventional medications used to treat insomnia, such as benzodiazepine, non-benzodiazepine, and hormone therapy, are associated with side effects. Therefore, there is a growing interest in the use of herbal medicine. The aim of this systematic review is to assess the effects herbal medicines have on sleep disorders of peri- and postmenopausal women.

**Methods:** Three databases were searched including MEDLINE, Scopus, and the Cochrane Library from inception to March 2018.

**Results:** Six trials assessed the effect of soy on sleep disorders. Forrest plot for 2 studies showed that the standardized mean difference (SMD) of the sleep problems was lower in the soy group than the placebo group (SMD = -0.996;  $P < 0.001$ ; 95% confidence interval, -1.42 to -0.563). Three trials showed soy had no significant effect on sleep disorders and one study showed a positive effect on sleep disorders. Accordingly, it is difficult to reach a definite conclusion regarding the effects of soy on sleep disorders based on these findings. According to a trial, significant beneficial effect associated with taking *Schisandra chinensis*. Findings suggested that some herbal medicines like red clover, lavender combined with bitter orange and pin bark extract had attenuating effects on sleep disorders. After intake of 530 mg of valerian twice a day for one month, statistically significant effects were observed regarding the quality of sleep of postmenopausal women.

**Conclusions:** The present systematic review and meta-analysis found inadequate evidence to draw conclusions regarding the effectiveness of herbal medications, especially soy. (**J Menopausal Med 2018;24:92-99**)

**Key Words:** Herbal medicine · Insomnia · Maintenance disorders · Meta-analysis · Sleep disorders

## Introduction

Sleep is a natural daily routine of mind and body.<sup>1</sup> Accordingly, the sleep disturbance can followed by adverse health problems, such as impaired daytime function, fatigue, reduced quality of life and high healthcare utilization. Ad-

ditionally, insomnia as a key risk factor accounts for major depression disorder. Aging is also an important contributor to high incidence of the sleep-induced concerns.<sup>2</sup> One of the obvious symptoms appeared in menopause is sleep difficulty. Complaint of sleep disturbance can be seen among about 24% to 50% of the menopausal women while 15% of

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the general population.<sup>3</sup>

There are some approaches, including hormone therapy (HT), behavioral therapy, circadian rhythm training and medications and herbal medicine for the management of insomnia.<sup>4</sup>

Cognitive behavioral therapy (CBT) can employ alongside other treatments. According to previous clinical trials, the CBT is equally or more effective compared to the pharmacological therapies. Antidepressants such as trazodone and nefazodone has therapeutic application for insomnia, especially insomnia caused by depression.<sup>4</sup> Some of medications to treat the insomnia include benzodiazepine hypnotics like flurazepam and triazolam and non benzodiazepine hypnotics like zolpidem and zopiclone.<sup>5</sup> Nevertheless, certain complications make them to be recruited in managing the acute sleep problems along with some other interventions such as behavioral therapy, circadian rhythm training and lifestyle modification. Many investigations reported the active and significant impacts of the HT on reducing the sleep disturbance.<sup>4</sup>

Regarding healthcare concerns on HT-induced tumors as well as positive attitudes toward medicinal plants especially phytoestrogens have attracted further attentions of many consumers to complementary and alternative medicine.<sup>6</sup>

Despite existing several systematic reviews and meta-analysis assessing the effect of herbal medicine on reducing the sleep problem, none of them has dealt with the menopause. Therefore, we decide to conduct the present systematic review and meta-analysis to examine the efficacy of herbal medicine on eliminating sleep problems in post- and perimenopausal women.

## Materials and Methods

### 1. Objective

The aim of this systematic review was to assess the effect of herbal medicine on the sleep disorders.

### 2. Inclusion criteria

The current systematic review was conducted on published randomized controlled trials that met the following inclusion criteria: 1) including peri- and postmenopausal women; 2)

being designed as parallel or crossover groups; 3) reporting at least different kinds of sleep problems; and 4) administering herbal medicine; and 5) studies used placebo as control group.

### 3. Search strategy

Three databases including MEDLINE, Scopus and the Cochrane Library (Cochrane Central Register of Controlled Trials) from inception to March 2018 were searched to find those trials examining the effect of herbal medicines on reducing the sleep problem. In addition, the references listed in the articles were included into search to find further studies.

To this end, the search keywords were (sleep or insomnia) AND (complementary therapies or alternative treatments or evening primrose oil or *Oenothera biennis* or *Hypericum perforatum* or herbal treatments, herbs or St. John's wort or phytomedicine or *racemosa rhizome* or *Salvia officinalis* or *Trigonella foenum-graecum* or Avocado plus or Black cohosh or *cimicifuga* or Evening primrose oil or flaxseed or fenugreek or dong quai or Ginseng or red licorice or red clover, *Vitex agnus-castus*, kava, *Piascledine* or yam). The search was performed without any language restriction.

### 4. Data extraction

Both authors separately extracted data, involving name of authors, name of country, design of study, age, status of menopause, level of complaints, type of measurement tool, type of intervention, number of participant in intervention and placebo group, rate of drop out and major relevant finding (Table 1).

### 5. Assessment of study quality using

#### Collaboration's tool for evaluating risk of bias

Two authors using Cochrane Collaboration's tool to study risk of bias independently performed assessment of study quality. This tool assessed seven risks of bias, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias (Table 2).

**Table 1.** Characteristics of 12 randomized placebo-controlled trials included in the systematic review

References	Country	Duration of study	Design	Age	Menopause status	Level of complaints	Measurement tool	Type of interventions/control	No. of participants Intervention/control	Rate of drop out	Major relevant findings
Lipovac et al. <sup>7</sup>	Austria	12 weeks 7-day washout period another 12 weeks	Cross over	≥40	Postmeno-pause	KI ≥ 15	VAS (0-100)	Two capsules red clover (80 mg red clover isoflavones)/placebo	Red clover = 53, placebo = 60	3.5%	Sleep problem decreased significantly in red clover group compared to placebo group
Shamshad Begum et al. <sup>8</sup>	India	13 weeks	Parallel	45-58	Meno-pause	Mean score of GCS ≥ 25, ≥3 hot flash over the previous 3 to 5 week	GCS	Fenugreek husk extract/placebo	44/44	20.0%	Treatment with fenugreek husk cause a statistically significant improvement (75%) in insomnia in compared to placebo
Balk et al. <sup>9</sup>	American	24 weeks	Parallel	57	Postmeno-pause	-	Severity of insomnia ranged from (0-3)	Soy cereal supplementation/wheat	7/12	29.0%	A significant improvement in intervention group compared to placebo
Kotsopoulos et al. <sup>10</sup>	Australia	12 weeks	Parallel	52	Postmeno-pause	-	Four point scale (0-4)	Soy protein 118 mg isoflavones/placebo	34/41	25.0%	Sleepness showed a non-significant decrease in soy group (10%) compared to placebo (5%)
Liu et al. <sup>11</sup>	China	24 weeks	Parallel	Soy = 57, placebo = 58	Postmeno-pause	-	Structured symptom checklist	Whole soy group/40 g of soy flour, daidzein group/40 g of low-fat milk powder + 63 mg of daidzein, placebo group/40 g of low-fat milk powder	Whole soy group = 90, daidzein group = 90, placebo group = 90	6.3%	Covariate showed no significant difference in frequencies of insomnia among three groups (P = 0.199)
Davinelli et al. <sup>12</sup>	Italy	12 weeks	Parallel	52	Recently meno-pause	Moderate insomnia	Sleep domain of sleep problem of MRS	200 mg of fermented soy (including 80 mg of isoflavone aglycones + 10 mg of equol) + 25 mg of resveratrol from Vitis vinifera	Intervention = equol and resveratrol supplementation (n = 30), control = placebo (n = 30)	0.0%	No. of women affected by sexual problems was declined by 36% at 1 month and 53.3% at months 6 in group treatment with soy containing equol and resveratrol. Comparison of two group were significant in 6 months but not at 1 month

**Table 1.** Continued

References	Country	Duration of study	Design	Age	Menopause status	Level of complaints	Measurement tool	Type of interventions/control	No. of participants Intervention/control	Rate of drop out	Major relevant findings
Carmignani et al. <sup>13</sup>	Brazil	16 weeks	Parallel	Soy = 49, co = 48	Postmeno-pause	-	Urogenital sub-scale of the MRS	90 mg/day of isoflavone, 1 mg of estradiol + 0.5 mg of norethisterone	Soy supplement group (n = 20), low-dose hormone therapy group (n = 20), placebo (n = 20)	0.0%	Any significant change in score of urogenital symptoms among three groups (P = 0.42)
Hanachi and Golkho <sup>14</sup>	Iran	12 weeks	Parallel	52	Postmeno-pause	-	KI	Soy protein dietary supplements/casein placebo	Soy protein dietary supplements = 34, casein placebo = 41	0.0%	The improvement rate was 25% for soymilk plus exercise and 30% for soymilk alone
Kamalifard et al. <sup>15</sup>	Iran	8 weeks	Parallel	45-60	Pre-post meno-pause	PSIQ > 5	PSIQ	Capsules contain 500 mg of bitter orange powder/500 mg of lavender flower /placebo	52/52/52	0.0%	Both intervention group improved significantly compared to placebo
Taavoni et al. <sup>16</sup>	Iran	4 weeks	Experimental group = 52, placebo = 53	Postmeno-pause	PSIQ > 5	PSIQ	Two capsules containing 160 mg of essence of Valerian officinalis and 80 mg of lemon balm	50/50	50/50	0.0%	There was a significant decrease in the combined group compared to the placebo
Park and Kim <sup>17</sup>	Korea	12 weeks	Parallel	40-70	Meno-pausal transition or post-meno-pause	KI > 15	KI	Two tablets containing 784 mg of Schisandra chinensis (BMO-30) extract/placebo	20/21	12.0%	A decrease non-significant in intervention group compared to placebo group (P = 0.188)
Yang et al. <sup>18</sup>	Taiwan	6 months	Parallel	45-55	Perimeno-pausal	-	WHQ	French maritime pine bark extract (Pycnogenol)/placebo	100/100	22.5%	Sleep problem improved significantly in intervention group compared to placebo group at 1, month, 3 months, and 6 months

KI: Kupperman Index, GCS: Greene Climacteric Scale, PSQI: Pittsburgh Sleep Quality Index, VAS: visual analog scale, MRS: Menopause Rating Scale, WHQ: Women's Health Questionnaire

**Table 2.** Quality assessment using Cochrane Collaboration’s tool

References	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition)	Selective reporting	Other biases
Lipovac et al. <sup>7</sup>	?	+	?	?	+	+	+
Shamshad Begum et al. <sup>8</sup>	+	?	+	+	+	+	+
Balk et al. <sup>9</sup>	+	+	+	+	-	+	+
Kotsopoulos et al. <sup>10</sup>	?	?	?	?	-	+	+
Liu et al. <sup>11</sup>	+	+	+	+	+	+	+
Davinelli et al. <sup>12</sup>	+	+	+	+	+	+	+
Carmignani et al. <sup>13</sup>	+	+	+	+	+	+	+
Hanachi and Golkho <sup>14</sup>	?	?	?	?	?	+	+
Kamalifard et al. <sup>15</sup>	+	+	+	+	+	+	+
Taavoni et al. <sup>16</sup>	?	?	+	+	?	+	+
Park and Kim <sup>17</sup>	?	?	+	+	+	+	+
Yang et al. <sup>18</sup>	+	+	+	+	+	+	+

**6. Statistical analyses**

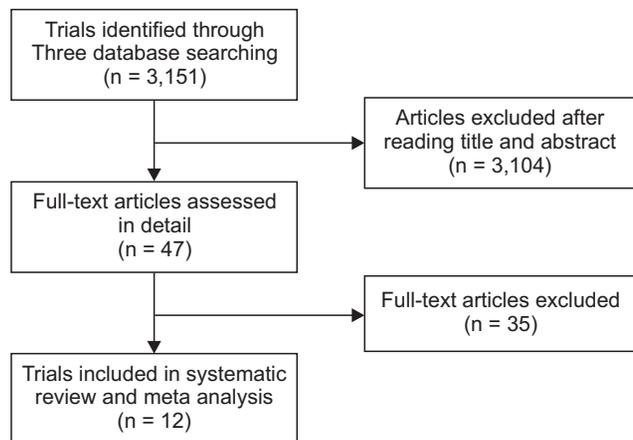
Standardized mean difference (SMD) was chosen to pool the result from different trials. The Fixed effect model was applied because the result was homogeneous. The Cochrane Q and I<sup>2</sup> index were performed to evaluate the heterogeneity. All of mentioned analyses were done using comprehensive Meta-analysis Version 2 (Biostat Inc., Englewood, NJ, USA).

**Results**

The processes of selecting articles for the systematic review are displayed in Figure 1. Overall, 12 randomized, placebo –controlled trials included to systematic review Characteristics of these trials showed in (Table 1).

**1. Red clover**

One trial compared the effect of red clover and placebo. Lipovac et al.<sup>7</sup> in a crossover study (with a wash out period of 7 days) evaluated the effect of red clover–driven isoflavone on the sleep problems. Thus, 109 patients were ran-



**Fig. 1.** Process of selecting articles for systematic review.

domized into 2 groups to receive red clover or placebo. The sleep dysfunctions were decreased significantly in the red clover group compared to the placebo group.

**2. Fenugreek husk**

A trial<sup>8</sup> assessed the effect of fenugreek husk to manage the insomnia. In this study, 88 menopausal women were divided equally into 2 groups of fenugreek husk (n = 44) and

placebo (44). Treatment with the fenugreek husk caused a statistically significant improvement (75%) in the insomnia in the intervention group as compared to the placebo group.

### 3. Soy

Six trials assessed the effect of soy on sleep problem. Two trials<sup>9,10</sup> had suitable data for including to the meta-analysis. The SMD of sleep problem was lower in the soy group than in the placebo group (SMD = -0.996;  $P < 0.001$ ; 95% confidence interval [CI], -1.42 to -0.563; 2 trials; fixed effect model; heterogeneity  $I^2 = 0\%$ ,  $P = 0.575$ ; Fig. 2).

Four trials had inconsistent data to include in the meta-analysis. Therefore, we assessed them qualitatively. The first were performed by Liu et al.<sup>11</sup> and compared 3 groups of soy, isoflavone and placebo. Comparison of 3 groups using analysis of covariance (ANCOVA) with baseline as covariate showed no significant difference in frequencies of insomnia among 3 groups ( $P = 0.199$ ).

In second studies, Davinelli et al.<sup>12</sup> compared soy containing equol and resveratrol with placebo. Percentage of women affected by sleep problems declined 37% ( $P < 0.001$ ) at 1 month and 46% ( $P < 0.001$ ) at months 6 in soy group. The greater improvement was observed in soy group regarding insomnia compared to placebo at 6 months but not at 1 month.

In third trials, Carmignani et al.<sup>13</sup> studied 3 groups HT, placebo and soy. Comparison of 3 groups using one-way analysis of variance (ANOVA) indicated no statistical significant difference in the sleep problem among 3 groups ( $P = 0.42$ ).

In last trials, Hanachi and Golkho<sup>14</sup> randomized patients into one of 3 groups of soy milk pulse exercise, soy milk

and placebo. Both soymilk plus exercise and soymilk groups were not different from placebo. However, pre- and post-comparisons were significant in both soymilk plus exercise and soy milk alone ( $P < 0.005$ ). The improvement rate was 25% for soymilk plus exercise and 30% for soymilk alone. Authors reported no comparison between 2 intervention groups.

### 4. Bitter orange and lavender

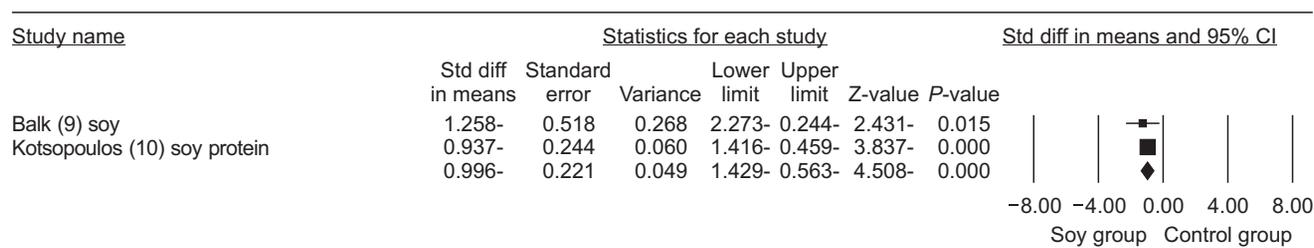
One trial<sup>15</sup> compared 3 groups of bitter orange, lavender and placebo. The mean difference of Pittsburgh Sleep Quality Index (PSQI) total score showed more prominent decrease in the lavender group (MD = -0.596;  $P = 0.003$ ; 95% CI, -0.989 to -0.203;  $P = 0.003$ ; 1 trial) and bitter orange (MD = -0.665;  $P = 0.001$ ; 95% CI, -1.059 to -0.270; 1 trial) compared to placebo. The Same effect was observed between lavender and bitter orange group (MD = -0.220;  $P = 0.0263$ ; 95% CI, -0.606 to 0.165; 1 trial).

### 5. Valerian

Taavoni et al.<sup>16</sup> compared the valerian and placebo sleep disorder; 36% of women reported a significant improvement as comparison to only 8% in the placebo group, difference between group were significant.

### 6. Schisandra chinensis

One trial conducted by Park and Kim<sup>17</sup>. They compared the effect of *Schisandra chinensis* with placebo on insomnia symptoms. Repeated measurement ANOVA analysis showed that score of insomnia in patients receiving *Schisandra chinensis* was not different from patient receiving placebo ( $P = 0.188$ ).



Meta Analysis

**Fig. 2.** Effect of soy on sleep disorders among peri- and postmenopausal women. CI: confidence interval, ■: point estimate, ◆: combined overall effect of intervention.

## 7. Pin bark extract

A trial was performed by Yang et al.<sup>18</sup>. They examined pin bark extract (Pycnogenol®) effect on sleep. Prominent improvement occurred in the Pycnogenol® group compared to the placebo at month 1, 3, and 6. All *P* values of less than 0.05 were considered to indicate statistical significance.

## Discussion

This meta-analysis systematic review investigated the effect of medicinal plants on the management of insomnia. This review found 12 trials assessing the effect of herbal medicine on promoting the sleep disorders; including pin bark extract, *Schisandra chinensis*, valerian, the blend of lavender and bitter orange, fenugreek husk, soy and red clover.

Three trials<sup>9,10,12</sup> demonstrated a significant improvement after the administration of soy. Three trials<sup>11,13</sup> showed no significant improvement. Accordingly, it is difficult to reach definite conclusion based on these findings. According to a trial, there is of any significant beneficial effect of *Schisandra chinensis*. Evidence supported the impacts of red clover, the blend of lavender and bitter orange, pin bark extract in reducing the sleep disorders.

After the administration of 530 mg of valerian twice a day for one month, a statistically significant effect was observed on the quality of sleep in the menopausal women;<sup>16</sup> whereas nightly dosing of valerian (valerian root extract of 100 mg) over 2 weeks failed to show significant result in elderly women.<sup>19</sup> Since several weeks are required for many herbal agents to have positive impacts and that higher doses of valerian might be more effective,<sup>20</sup> it is possible that discrepancy between 2 trials<sup>16,19</sup> may be related to higher dose and longer duration in the trial of Taavoni et al.<sup>16</sup>. A previous meta-analysis on the effect of valerian on the sleep problem in adult aged over 18 years found no more effective than the placebo,<sup>20</sup> inconsistent with the study of Leach and Page<sup>20</sup>. The therapeutic response might be different between various age group due to varied etiologies of insomnia throughout the lifespan<sup>20</sup>. The valerian seems to be more beneficial in menopausal women with lower levels of estrogens. Therefore, larger trials are required to assess the effect of va-

lerian on various subgroups (reproductive and menopausal women).

It should be noted that, there were some limitations in the current systematic review. Despite believing to comprehensive search, it is possible that we could not find some published respective trials. Many of trials included to this review had poor methodologic quality due to lack of intention to treat, insufficient randomization, and concealment and blinding. Therefore, there is a necessity for well-designed trials. As well, there is need for further studies with larger sample size to confirm the present findings. Any of these trials calculated post hoc analysis power. Hence, future trials are suggested to determine test power of findings. Few trials used the standardized tool, so future trials should assess the quality of sleep using reliable tool such as PSQI, Morning Sleep Questionnaire (MSQ) or sleep tested in laboratory using Polysomnography.

## Conclusion

The present systematic review and meta-analysis found inadequate evidence to draw conclusion on recommendation or refuse the herbal medications especially soy. Findings about the positive effect of valerian, pin bark extract, fenugreek husk, lavender in combination with bitter orange and red clover should be introduced cautiously due to low number trials.

## Conflict of Interest

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

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