

Impacts of Herbal Medicines on Hot Flash: A Systematic Review

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Abstract

Background: the most common symptoms experienced by women are Hot flashes are around the time of menopause. Many women are interested in herbal medicines because of fear of side effect of Hormone therapy.

Objective: In this study, we seek to assess the effectiveness of herbal medicine on the recurrence of hot flash in menopausal women.

Methods: The database of MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials (RCT) were searched to investigate trials on the efficacy of herbal medicines on hot flash.

Results: RCTs were incorporated into this accurate review, with the results demonstrating that herbal medicines such as evening primrose, oil hop and Valerian, red clover, of black Cohosh flaxseed and *hypericum perforatum* can ease the side effects of hot flash.

Conclusion: Our study indicated that herbal medicines can reduce the negative effects of hot flash. However, desirable impacts still remain indeterminate due to the number of RCTs, limited sample size and unsystematic methodology. As such, larger RCTs with more reliable design and improved measurable reporting of the outcomes are required to support this conclusion.

Keywords: Iran, Herbal medicine, Hot flash, Systematic review

Introduction

Menopause is a phase experienced by all women in their life time [1]. It takes place roughly at the age of 50, which is often diagnosed by no less than 12 months of amenorrhea. Menopause is usually associated with a group of symptoms such as hot flashes, night sweat, vaginal atrophy, tension, apprehension and diminished libido. Meanwhile, hot flashes are the most common repulsive side effects experienced in roughly 70% of women [2], which are often reported as severe feeling of warmth as well as sweating, flushing, and chills. Sweating is mainly reported in the specific areas of the body like face, neck and chest. HFs generally persists for 1–5 min, but in some cases the lapses may last for an hour. The mean length of symptoms is around four years, but some may endure for as long as 20 year. Hot flashes are generally ascribed to the reduced estrogen levels [3]. Estrogen therapy is a powerful treatment of hot flashes. The discoveries of the Women's Health Initiative (WHI) in an extensive randomized trial assessing the adequacy of hormone treatment (HT) in the prevention of this disease have revealed that the utilization of estrogen coupled with progestin therapy for at least 5 years can heighten the chance of breast cancer, stroke, and the risk of coronary illness in healthy postmenopausal women. In more recent studies, the results of WHI have demonstrated an increased risk of stroke in the absence of breast cancer or coronary illness in which the estrogen treatment lasts around 7 years in postmenopausal women. The results of this trial have been connected to a decrease in

users HT [4]. Increasingly, a large portion of the past users of HT are getting attracted to the flaxseed, *Vitexagnus-castus* and, evening primrose and oil hop as substitutes for HT to tackle menopausal side effects. The goal of this methodical review is to investigate the impact of herbal medicines on mitigating the effect of hot flash.

Materials and method

Search strategy

In this review, the popular databases like MEDLINE (1966 to February 2016), Scopus (1990 to February 2016), and the Cochrane Central Register of Controlled Trials (The Cochrane Library issue 1, 2016) were searched to explore of the impact of herbal medicines on hot flash. For this purpose, terms such as hot AND flash OR flush AND complementary treatments or alternative treatments phytomedicine herbal treatments herbs evening primrose oil or *hypericum perforatum* or St. John's wort, or black cohosh or phytomedicine, *vitexagnuscastus*, dong quai or ginseng kava or licoriced, or clover *Trifolium*, orpratenseor evening, primrose oil, yam, hop or evening primrose oil or *Vitexagnus-castus*) were searched. No language limit was imposed on the search. Further, references cited for the retrieved trials and methodical reviews were screened to find any further pertinent study. In the process of our search, no language limit was considered.

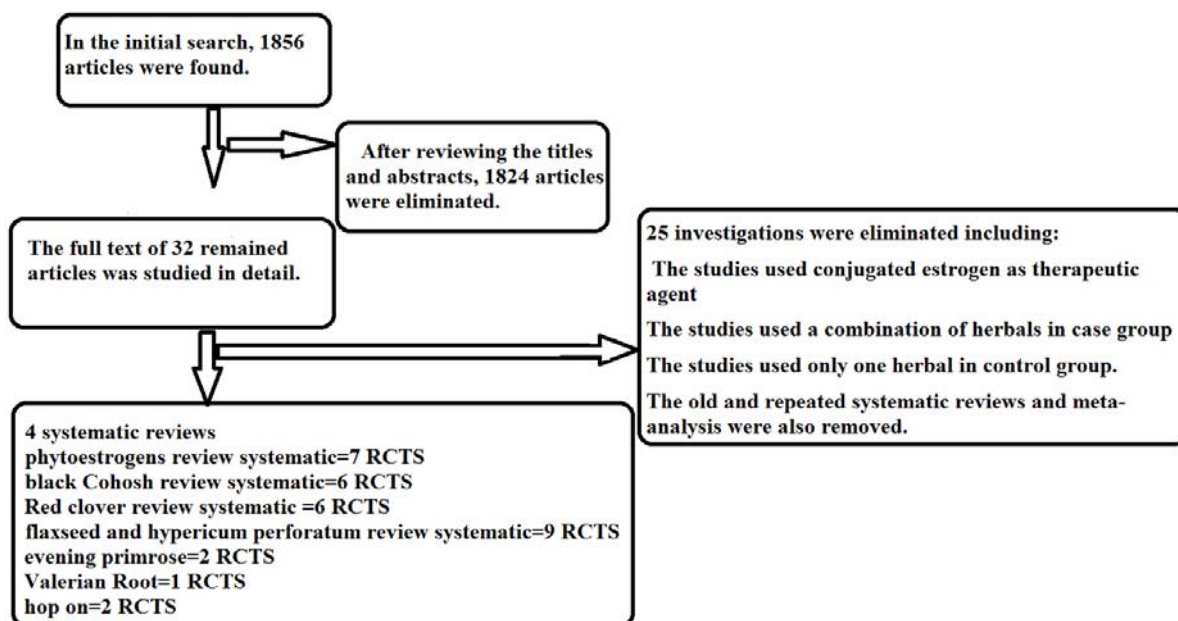
Inclusion criteria

Trials were included systematic review if they reported the following criteria: (1) Include peri-and post- menopause women with

complaints of hot flashes. (2) Was parallel-group or crossover RCT. (3) Compared oral herbal as the mono-preparations in the intervention arm were included regardless of

the control group type. (4) Having randomized controlled trials design. (the flowchart as seen in below).

Chart 1- The flowchart of data collection



Results

The effect of phytoestrogens on alleviating hot flashes

The results of a newly published meta-analysis on the basis of seven randomized clinical studies have demonstrated that phytoestrogens can significantly mitigate the recurrence of hot flash in comparison to the placebo (pooled mean difference = 0.89, $P < 0.005$) [5].

The effect of black Cohosh on alleviating hot flashes

The results of a newly published meta-analysis assessed black cohosh (*Cimicifuga*

spp.) for menopausal symptoms. Black cohosh compared with and placebo did not show any significant difference regarding frequency of hot flushes (mean difference (MD) 0.07) [6].

Impacts of flaxseed and *hypericum perforatum* on hot flash

In a new meta-analysis, a review of the studies on the impacts of *flaxseed* and *hypercom perforatum* on hot flash has been presented. Nine RCTs were incorporated into this review. Flaxseed can have positive impacts on hot flash recurrence and intensity, though its effect was not statistically significant. The result suggested that flaxseed

could exert estrogenic effect, though no definitive conclusions concerning the promotion of cancer or protection effects can be made. According to a trial, *Vitex agnus-castus* and *H. perforatum* demonstrated practically identical decline in the frequency of hot flashes [7].

Red clover as a treatment of hot flashes

The authors have recently published a meta-analysis that offers a review of six randomized clinical trials. The results suggest that the consumption of red clover can reduce the average frequency of hot flashes in the experiment group compared to the control group (which is rather statistically significance). The mean difference (MD) of hot flash recurrence was 1.99 [7].

The impact of evening primrose and oil hop on the recurrence of hot flashes

Two studies evaluated the impact of evening primrose oil on hot flashes. In the first trial, Chenoyet [8] examined 56 diaries, 28 retrieved from women consuming gamolenic acid and 28 from those taking placebo. In their study, only 18 women from the experiment and 17 from the control group were able to complete the trial. The primary results were modified frequency of hot flushes or sweating fits in a month. The average (SE) enhancement in the frequency of flashes compared to the baseline was 1.9 ± 0.4 ($P < 0.001$) for flashes during the daytime and 0.7 ± 0.3 ($P < 0.05$) for flashes during the evening for women in the control group. The corresponding values for women in the experiment group were 0.5 ± 0.4 and 0.5 ± 0.3 . Nonetheless, the two groups

were not significantly different in terms of daytime flashes (-1.5 ± 0.6) and evening flashes -0.2 ± 0.4 .

In the study of Farzaneh et al [9] on the impact of evening primrose oil on hot flashes, the recurrence of hot flash diminished from 5.2 ± 1.9 to 3.2 ± 1.8 (-2 ± 1.2) in the evening primrose and from 5.4 ± 1.9 to 3.7 ± 2.0 (-1.6 ± 1.2) in the placebo group. The intensity of hot flash decline was more conspicuous than the control group, though the two groups were not significantly different in this regard ($P=0.23$). The intensity of hot flashes varied from 5.9 ± 1.5 to 3.4 ± 1.4 (-2.6 ± 1.60) in the experiment and from 5.9 ± 1.7 to 4.1 ± 2.0 (-1.8 ± 1.2) in the control group, which was statistically significant. To sum up, it appears that evening primrose oil was more powerful in mitigating hot flashes in comparison with the placebo. Once more, more studies are required to affirm the present results.

The impact of Valerian Root on the recurrence of hot flashes

A review of the previous studies shows that only in a trial by Mirabi et al [10] a significant reduction in the intensity and recurrence of hot flashes in the valerian group ($P < 0.001$) has been reported, though the subjects in the placebo group remained unaffected. Further, a comparison of two groups demonstrated a significant distinction at week 4 and week 8 ($P < 0.001$). It appears that valerian can significantly mitigate the intensity of hot flashes, albeit further studies are required to confirm the present evidences.

The impact of hop on the recurrence of hot flashes

Heyerick et al [11] investigated the impact of hop on hot flash. Accordingly a gradual decline in the mean hot flush scores was observed in the placebo group (2.7, 2.5 and 2.2) in 100 microgram of dosage group (2.7, 1.8 and 1.6) and in 250 microgram of dosage group (2.5, 1.8 and 1.7) in three measurement points (baseline, 6 and 12 weeks respectively). The reduction in KI hot flash subscale was found to be significant in both treatment groups after 6 weeks ($P < 0.01$).

Finally, Aghamiri et al. [12] carried out a study on a sample group of 120 postmenopausal women receiving 500 mg of hop or placebo for 12 weeks. The frequency of flashes were registered at the baseline, 4, 8 and 12 weeks after intervention with the results showing a significant reduction in the occurrence of hot flash in the intervention group compared to the control group in week 4 (-8.4), 8 (-17.1) and 12 (-23.8).

Discussion

This paper was an attempt to evaluate the impacts of herbal medicines on the mitigation of hot flashes. The use of *Red Clover* can be reduced frequency of hot flushes especially in women with severe hot flushes (≥ 5 per day) and post-menopausal women [7]. Phytoestrogens can significantly mitigate the recurrence of hot flash in comparison to the placebo [5].

Advantageous effect of *Hypericum perforatum* and flaxseed on hot flash

In general, in Ghazanfarpour et al in 2015 reported that herbal medicines can reduce the negative effects of hot flash [7]. Black cohosh

compared with and placebo did not show any significant difference regarding frequency of hot flushes (mean difference (MD) 0.07) [6]. Evening primrose oil was more powerful in mitigating hot flashes in comparison with the placebo [8, 9] valerian can significantly mitigate the intensity of hot flashes, albeit further studies are required to confirm the present evidences [10]. The hop on can significantly reduce hot flashes [11, 12]. In general, studies demonstrate that our study indicated that herbal medicines can reduce the negative effects of hot flash.

Action mechanism of hop

As a rich source of prenylated flavonoids, hops include 8-prenylnaringenin (8- PN) and a prenylated flavanone (Heyerick, Vervarcke et al. 2006). A comparison with well-known phytoestrogens, e.g., coumestrol (from clover and/or alfalfa), and genistein and daidzein (from soy) indicates that 8-PN is the most powerful phytoestrogens (Milligan, Kalita et al. 1999, Milligan, Kalita et al. 2000, Milligan, Kalita et al. 2002).

Unlike other phytoestrogens, 8-PN was discovered to be a weaker agonist of the estrogen receptor *B* (ERB) compared to the estrogen receptor *a* (ERa) [20]. As such, it corresponds closely to the activity profile of the endogenous 17-estradiol (E2) (Heyerick, Vervarcke et al. 2006).

Action mechanism of hop evening primrose and Valerian

There is a paucity of studies on discovering the exact mechanism through which herbal medicine (evening primrose and Valerian) can mitigate hot flashes and night sweating

(Chenoy R 1994, Mirabi and Mojab 2013). In fact, the current understanding of the reason and causes of hot flashes is flawed, although a few studies have exhibited an unnoticeable rise in the body temperature (Tc) acting in an incredibly diminished thermoneutral zone, namely the Tc area between the upper (sweating) and lower (trembling) limits. This is partly due to estrogen exhaustion at menopause (Freedman 2014).

The authors were cautious to avoid any bias in the study. As such, no language or time threshold was imposed on our search procedure. We asked two reviewers to evaluate the inclusion criteria of the studies independently, perform data extraction and evaluate the bias risk. We are cognizant of the fact that some studies may not be published in seminal journals, and thereby unavailable in major databases.

Limitations of this meta-analysis

There were several limitations in our methodical review including the low number of RCTs, restricted example size and weak methodology of the some relevant studies. A larger portion of studies included in the review had failed to examine their negative consequences and side effects. Future studies need to assess the side effects of this herbal medicine. In terms of quality, almost all

studies included in our review were below optimal level. Therefore, it can diminish the reliability of our findings. Future trials need to work on the basis of CONSORT guidelines to promote the quality of their results.

Recommendation for future studies

In HF studies, it is common to use diaries as a way of evaluating the treatment results. Nonetheless, this type of measurement has several shortcomings. Error in consistence constitutes a major source of bias.

Further, HFs at the time of sleep is often inaccurately reported due to the poor remembrance of such events and the fact that many HFs do not disturb the sleep.

Also, a placebo effect as large as 40–50% has been mentioned in some self-reports. As such, accurate and objective measures of HFs should be developed in any studies.

Conclusion

Our study indicated that herbal medicines can reduce the negative effects of hot flash. However, desirable impacts still remain indeterminate due to the number of RCTs, limited sample size and unsystematic methodology. As such, larger RCTs with more reliable design and improved measurable reporting of the outcomes are required to support this conclusion.

References

1. Ghaderi E, Ghazanfarpour M and Kaviani M. Evaluation of menopausal women's attitudes towards menopause in Shiraz. *Pak. J. Med. Sci.* 2010; 26: 698 - 703.
2. Stearns V, Beebe KL, Iyengar M and Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *Jama.* 2003; 289

(21): 2827 - 34.

3. Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treatment. *The Journal of Steroid Biochemistry and Molecular Biol.* 2014; 142: 115 - 20.

4. Krebs EE, Ensrud KE, MacDonald R and Wilt TJ. Phytoestrogens for treatment of menopausal symptoms: a systematic review. *Obstetrics & Gynecol.* 2004; 104 (4): 824 - 36.

5. Chen M, Lin C and Liu C. Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric* 2015; 18 (2): 260 - 9.

6. Leach MJ and Moore V. Black cohosh (*Cimicifuga* spp.) for menopausal symptoms: Wiley Online Library 2012.

7. Ghazanfarpour M, Sadeghi R, Latifnejad Roudsari R, Khadivzadeh T, Afiat M and Esmaeilizadeh M. Effects of flaxseed and *Hypericum perforatum* on hot flash, vaginal atrophy and estrogen-dependent cancers in menopausal women: a systematic review and meta-analysis. *Avicenna Journal of Phytomedicine* 2015; 1: 6 (3): 273 - 83.

8. Chenoy R, Hussain S, Tayob Y, O'Brien P, Moss M and Morse P. Effect of oral gamolenic

acid from evening primrose oil on menopausal flushing. *Bmj.* 1994; 308 (6927): 501 - 3.

9. Farzaneh F, Fatehi S, Sohrabi M-R and Alizadeh K. The effect of oral evening primrose oil on menopausal hot flashes: a randomized clinical trial. *Archives of Gynecology and Obstetrics* 2013; 288 (5): 1075 - 9.

10. Mirabi P and Mojab F. The effects of valerian root on hot flashes in menopausal women. *IJPR.* 2013; 12 (1): 217.

11. Heyerick A, Vervarcke S, Depypere H, Bracke M and De Keukeleire D. A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. *Maturitas* 2006; 54 (2): 164 - 75.

12. Aghamiri V, Mirghafourvand M, Mohammad-Alizadeh-Charandabi S and Nazemiyeh H. The effect of Hop (*Humulus lupulus* L.) on early menopausal symptoms and hot flashes: A randomized placebo-controlled trial. *Complementary Therapies in Clinical Practice* 2016 May 31; 23: 130 - 5.