The efficacy of Iranian herbal medicines in alleviating hot flashes: A systematic review

Masumeh Ghazanfarpour¹ Ph.D. Candidate, Ramin Sadeghi² M.D., Somayeh Abdolahian³ M.Sc., Robab Latifnejad Roudsari⁴ Ph.D.

Abstract

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

Objective: The aim of this systematic review was to assess the effectiveness of Iranian herbal medicines in alleviating hot flashes.

Materials and Methods: MEDLINE (1966 to January 2015), Scopus (1996 to January 2015), and Cochrane Central Register of Controlled Trials (The Cochrane Library, issue 1, 2015) were searched along with, SID, Iran Medex, Magiran, Medlib and Irandoc. Nineteen randomized controlled trials met the inclusion criteria.

Results: Overall, studies showed that Anise (Pimpinella anisum), licorice (Glycyrrhiza glabra), Soy, Black cohosh, Red clover, Evening primrose, Flaxseed, Salvia officinalis, Passiflora incarnata, Agnus Castus, Piascledine (Avocado plus soybean oil), St. John's wort (Hypericum perforatum), and valerian can alleviate the side effects of hot flashes.

Conclusion: This research demonstrated the efficacy of herbal medicines in alleviating hot flashes, which are embraced both with people and health providers of Iran. Therefore, herbal medicine can be seen as an alternative treatment for women experiencing hot flashes.

Key words: Herbal medicines, Hot flash, Iranian, Systematic review.

Introduction

Hot flashes are the most common symptoms experienced by women around menopause time (1). Racial and cultural differences may play a role in variation of hot flashes in Western and Eastern societies (2). Hormone therapy is an effective treatment recommended for alleviating hot flashes (1, 3). In Iran, only 15% of menopausal women use hormone replacement therapy (HRT) (4, 5).

The most frequent reason for discontinuing HRT is side effects like vaginal bleeding. There has been growing interest in natural alternatives among women in Iran, with many women efficiency accepting, safety, and lower side effects of natural therapies compared to chemical medicines (5). To our knowledge, effect of Iranian herbal medicines in alleviating hot flashes in menopausal women has not been systematically assessed. This systematic review seeks to examine the efficacy of Iranian herbal medicines in alleviating hot flashes based on the literature in this field.

Search Strategy

To find relevant studies, a number of English and Persian databases such as MEDLINE (1966 to January 2015), Scopus (1990 to January 2015), and the Cochrane Central Register of Controlled Trials (The Cochrane Library, issue 1, 2015) were searched using keywords such as: hot AND (flash OR flush) AND (complementary treatments or alternative treatments or phytotherapy herbal treatments herbs evening primrose oil or St. John's wort or Hypericum perforatum or Black cohosh or...
Cimicifuga racemosa rhizome or phytomedicine, or dong quai or Piascledine or Avacado plus or Soy or Ginseng or kava, Trigonella foenum- graecum or fenugreek or licoricered or Red clover or Evening primrose oil or yam or Flaxseed or Salvia officinalis or Vitex Agnus Castus". In addition, SID, Iran Medex, Magiran, Medlib, Iran doc, and Google Scholar were searched in June 2014 to find equivalent keywords in Persian.

**Criteria for inclusion of studies**

1) Randomized controlled trials (RCTs) that compared oral herbs as mono/ combined preparations with control group. 2) participants included post-perimenopause with hot flashes.

**Data extraction**

Data were extracted independently by two authors and predefined checklist included age, menopausal status, sample size, duration of treatment, randomization technique, blinding method, intention- to-treatment reporting, baseline comparability, outcome measures and results.

**Results**

The process of searching and selecting RCTs has been described in figure 1. In total, 19 studies were included in this systematic review. Summarized characteristics of included studies are shown in table I.

### Table I. Characteristics of 22 randomised trials included in our systematic review

| Author, Year | Duration (Wk) | Age (Y) | Status menopause | Frequency hot flashes | Outcome | Drop out (%) | Intervention mg | Type of control | Participants intervention | Participants control | Randomization technique | Blinding method | ITI | Baseline comparability | Major relevant findings |
|--------------|---------------|---------|------------------|----------------------|---------|--------------|-----------------|-----------------|------------------------|-----------------------|----------------------|-----------------|-----|----------------------|----------------------|
| Saghafi, 2013 | 12            | 51      | Post             | ≥2 hot flashes frequency a day | Severity of hot flash   | 31%      | Black Cohosh Capsule (containing dried roots 6.5 of black cohosh) | Fluoxetine 20 mg | Black Cohosh Capsule | 29 | No | Unclear | No | Yes | Black cohosh group had significantly more improvement compared with Fluoxetine group (p=0.001) |
| Shahnazi , 2013 | 8             | 51      | Post             | Symptom Vasomotor Severity≥2 | Hot Flashes Frequency and Severity | 0%      | Black Cohosh Capsule (containing dried roots 6.5 of black cohosh) | Placebo | Placebo | 28 | No | Yes | Yes | Yes | Results of the Repeated-Measures Analysis of Variance for Within- and Between-Groups showed significant difference (p<0.001) |
| Nahidi, 2012 | 4             | 53      | Post             | Women having experience of hot flashes | Hot Flashes Frequency and Severity | 0%      | Capsules, Containing 330 mg of Pimpinella anisum /3 times a day | Placebo | Placebo | 36 | No | Yes | Yes | Yes | Glycerizia glabra and HRT was similarly effective in alleviating frequency of hot flash but not for flashes intensity |
| Meinati, 2013 | 12            | 50      | Peri & post      | Experience of hot flashes | Frequency of hot flashes | 0%      | Glycyrriza glabra Supplementation 1140 mg | HRT | Placebo | 26 | No | Unclear | No | Yes | Glycyrriza glabra and HRT was similarly effective in alleviating frequency of hot flash but not for flashes intensity |

---

*International Journal of Reproductive BioMedicine Vol. 14. No. 3. pp: 155-166, March 2016*
| Author, Y | Duration (Wk) | Age (Y) | Status menopause | Frequency hot flashes | Outcome | Drop out (%) | Intervention mg | Type of control | Participants intervention | Participants control | Randomization technique | Blinding method | Baseline comparability | Major relevant findings |
|-----------|-----------------|---------|------------------|---------------------|---------|--------------|-----------------|-----------------|------------------------|----------------------|----------------------|----------------|--------------------------|----------------------|
| Nahidi, 2012 (9) |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 8 | T/50 | 4 and 8 W | Post | Women having experience of hot flashes | Hot flash frequency | 0% | Glycyrriza glabra supplementation 1140 mg |  |  |  |  |  |  |  |
| 49 | T/52 | 52/76 | Post | Women having experience of hot flashes | Hot flash frequency | 125 |  |  |  |  |  |  |  |
| Peirizad &post | Post12 | pre Peri &post | Pre & post | Women having experience of hot flashes | Hot flash frequency | 11 |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Abdo, 2006 (10) |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 12 | T/50 | 4 | Post | Women having experience of hot flashes | Hot flash frequency | 0% | Glycyrriza glabra supplementation 250 mg containing 30-60 mg of glycosides |  |  |  |  |  |  |  |
| 4 | T/51.2 | 51.1 | Post | Women having experience of hot flashes | Hot flash frequency | 125 |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Abbaspoor, 2011 (15) |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 8 | T/50 | 4 | Post | Women having experience of hot flashes | Hot flash frequency | 0% | Vitex agnus-castus drop/day |  |  |  |  |  |  |  |
| 40 | Vitex agnus-castus drop/day | Red clover Capsule containing 45 mg isoflavones | Capsule valerian containing 350 mg of valerian root 2 times a day | Capsules containing 225 mg of valerian root 3 times a day | Hot flash frequency | 0% |  |  |  |  |  |  |  |
| 27 | 25 | 28 | 29 | 35 | 24 | 34 |  |  |  |  |  |  |  |
| 27 | 16 | 27 | 19 | 33 | 29 | 34 |  |  |  |  |  |  |  |
| Placebo | Vitex agnus-castus | Placebo | Placebo | Placebo | Placebo | Placebo |  |  |  |  |  |  |  |  |
| Yes | Yes | Yes | unclear | Unclear | Unclear | No |  |  |  |  |  |  |  |
| Yes | Yes | Yes | unclear | Yes | Unclear | Yes |  |  |  |  |  |  |  |
| No | No | No | No | No | No | No |  |  |  |  |  |  |  |
| Yes | Yes | Yes | Yes | Yes | Yes | Yes |  |  |  |  |  |  |  |
| Vitex agnus-castus group showed a statistically significant decrease in hot flashes intensity compared with placebo. Passion Flower and vitex agnus-castus was similarly effective in alleviating hot flashes intensity. | The difference between groups was statistically significant in the 10 week of the study (P=0.004). | Valerian group showed a statistical significant decrease in regarding severity of hot flashes compared with placebo while this difference was not significant in regarding hot flash frequency | Hot flash frequency and intensity showed a statistical significant difference in valerian compared with placebo group | The difference between groups was not statistically significant (p=0.05). | Glycyrriza glabra group showed statistically significant decrease in regarding hot flashes frequency and intensity compared with placebo. |  |  |  |  |  |  |  |  |
| Author, Year | Duration (Wk) | Age /Y | Status | Frequency hot flashes | Outcome | Drop out (%) | Intervention mg | Type of control | Participants intervention | Participants control | Randomization technique | Blinding | Method | Baseline comparability | Major Relevant Findings |
|--------------|---------------|--------|--------|----------------------|---------|-------------|----------------|-----------------|------------------------|---------------------|------------------------|----------|--------|---------------------|----------------------|
| Akbari Torkestani, 2013 (21) | 8 | 30 | Post | ≥3/day | Flaxseed 50 mg, Soy 50 mg, wheat flour 25 mg | Flaxseed Capsule 25 mg, placebo 50 mg | 0 | Wheat flour | 23 | 23 | Yes | Yes | No | No | | Flaxseed group showed a statistically significant reduction compared with placebo in regarding hot flash intensity in (p= 0.045)
| Baghdari, 2011 (22) | 12×2 Wk, 4 WK wash out | 52 | Post | ≥3/day | Flaxseed 40 mg, placebo 40 mg | Capsules containing 40 mg of Flaxseed oil one part, Soybean oil two parts | 0 | | 23 | 23 | No | Yes | No | No | | Flaxseed group was equally effective in alleviating hot flashes severity (HFQ and VAS).
| Panahi, 2011 (20) | 8 | 51 | Post | ≥6/day | Piascledine 480 mg (Avocado oil one part, Soybean oil two parts), HRT 0.625 mg Conjugated Estrogen | Piascledine Capsule 480 mg, placebo 440 mg | | | 32 | 32 | Yes | Yes | No | No | | Piascledine (Avocado plus bean oil) and HRT was similarly effective in alleviating hot flashes severity (HFQ and VAS).
| Hanachi, 2008 (18) | 12 | 52 | Post | Women having experience of hot flashes | Hot flash Intensity and Frequency | The content not known | Not known | | 42 | 42 | Yes | Yes | No | No | | Hot flashes frequency and intensity showed statistically significant decrease in protein soy compared placebo group in 3 and 4 but 2 week.
| Abbaspoor, 2003 (19) | 4 | 49 | Peri | ≥3/day | Soy powder 50 mg containing 75 isoflavones, casein powder | Soy powder 50 mg, casein powder 31 mg | | | 30 | 30 | Yes | Yes | No | No | | Hot flashes frequency and intensity showed statistical significant decrease in protein soy compared placebo group.
| Sadeghi, 2011 (23) | 8 | 51 | Post | ≥3/day | Frequency of Hot flashes | Daily intake of 100 mg capsules of Salvia officinalis extract | | | 42 | 42 | Yes | Yes | No | No | | The comparison between the Salvia officinalis and placebo arms was statistically significant.
| Asali l, 2013 (24) | 8 | 50 | Post | Women having experience of hot flashes | Frequency of hot flash | Hypericum perforatum Capsule 120 mg (containing 990 hypercin) | | | 30 | 30 | Yes | Yes | No | No | | A statistically significant decrease in both groups (St john’s wort and passion flower) at 3 and 6 week compared with baseline.
| Ghazanfarpour, 2013 (25) | 8 | 53 | Post | Women having experience of hot flashes | Hot flash Intensity | Hypericum perforatum Capsule 480 mg (containing 990 hypercin), Vitex agnus-castus | | | 13 | 13 | Yes | Yes | No | No | | Any significant difference was observed between two groups Hypericum perforatum and Vitex agnus-castus.
| Ghazanfarpour, 2013 (26) | 8 | 52 | Post | | Baseline comparability | No | | | | | | | | | The comparison of both groups Hypericum perforatum and Vitex agnus-castus was not statistically significant.
Table 1 cont. Characteristics of 22 randomised trials included in our systematic review

| Author                        | Year       | Duration (Wk) | Age (Y) | Status menopause | Frequency hot flashes | Intervention mg | Type of control | Participants intervention | Randomization technique | Blinding method | Baseline comparability | Major Relevant Findings                                                                 |
|-------------------------------|------------|---------------|---------|------------------|-----------------------|------------------|------------------|------------------------|------------------------|----------------|------------------------|-----------------------------------------------------------------------------------------|
| Farzaneh                     | 2013       | 6             | 51.9    | Post             | Women having experience of hot flashes | Evening primrose oil 1000 mg | P               | 33                      | Yes                    | Yes            | No                     | Significant decrease on severity of hot flashes and a non-significant decrease on frequency of hot flashes |
| Hakimi                        | 2004       | 8             | T/53    | Post             | Women having experience of hot flashes | Trigonella 6 g | HRT             | 25                      | Yes                    | No             | Yes                    | HRT showed the better effect than Trigonella (Fenugreek).                                   |
| Akbari Torkestani,            | 2013       | 8             | Flaxseed/50 | Post            | ≥5/day                | Trigonella 6 g | Flaxseed Capsule 25 mg, HRT | 25                      | Yes                    | Yes            | No                     | a decrease from 2.20 ±0.74 to 1.31± 0.604 (40%) in Trigonella and from 2± 0.74 to 0.8±0.644 (60%) in flaxseed group |
|                             |            |               | Trigonella foenum-graecum /51 |                  |                       |                  |                  |                        |                        |                |                        | Effect of Pimpinella anisum on hot flashes                                                                 |

The effect of Black cohosh on hot flashes

Fluoxetine vs. Black cohosh

Saghafi et al compared two groups of Fluoxetine and Black Cohosh findings that both groups significantly reduced hot flash frequency(6). Frequency of hot flash/day in Black Cohosh (1.82±1.12) decreased compared to Fluoxetine group (1.11±1.48), which was marginally statistically significant (p=0.08). 60% and 65% of patients in Fluoxetine and black Cohosh groups were satisfied with their treatment, respectively. Also, the comparison of two groups showed significant difference (p=0.04).

Black cohosh vs. placebo

In another trial, Shahnazi et al used repeated measures analysis of variance to assess the differences within and between groups (7). The frequency of hot flashes in inter-group comparison revealed a statistically significant difference in both Black Cohosh (p<0.001) and placebo (p=0.006) group across three time intervals. Comparison between groups was statistically significant at 4 (p<0.001) and 8 (p<0.001). To sum up, more clinical trial data are needed to confirm these findings.

Effect of Pimpinella anisum on hot flashes

Nahidi et al assessed the effect of pimpinella anisum on hot flashes, using repeated measures ANOVA to assess the difference between and inter group differences (8).

Gradual decrease in frequency of hot flashes was observed in Pimpinella anisum group (4.21±1.84, 3.60±1.70, 2.50±1.04, 1.63±0.80 and 1.10±0.61) and placebo group (4.24±1.87, 4.27±1.71, 4.20±1.52, 4.27±1.55 and 4.38±1.73, for five-time point’s baseline, 1, 2, 3, 4 wk respectively. Repeated measures ANOVA demonstrated statistically significant difference between 4 intervals only for Pimpinella anisum in intra group comparison (p<0.001).

Results of t-test showed statistically significant decrease in severity of hot flash in Pimpinella anisum group compared with placebo group, (p<0.001). 11.1%, 63.9% and 25% of women suffered from severe, moderate and mild hot flashes at baseline, while it was reduced respectively to 5.6%, 69.4% and 25% at the end of study. The corresponding results in placebo group were (13.9%, 55.6 and 30.5) and (5.6%, 69.4 and 25), respectively.

Effect of Glycyrrhiza glabra (Licorice) on hot flashes
Glycyrrhiza glabra vs. placebo

Nahidi et al assessed the effect of Glycyrrhiza glabra (Licorice) on relief and recurrence of hot flashes (9). To detect recurrences, they interviewed patients 1, 2, 3, and 4 wk after cessation of treatment, finding that frequency and severity were similar in both groups at baseline. Repeated measures ANOVA regarding the frequency of hot flashes in inter-group comparison revealed a statistically significant difference in Licorice group across eight time intervals, though this difference was not significant in placebo group.

Glycyrriz aglabra group showed statistically significant decrease in hot flashes frequency compared to placebo group in 8 intervals, 1 (p<0.002), 2 (p<0.001), 3 (p<0.001), 4 (p<0.001), 5 (p<0.001), 6 (p<0.001), 7 (p<0.002), and 8 (p<0.001) wk. At the baseline, 22.2%, 46.6% and 31.1% of women suffered severe, moderate, and mild hot flashes, while it was reduced to 2.3%, 33.3%, and 64.4% at the end of study, respectively.

Corresponding results for placebo group were (24.4%, 40% and 35.5) and (22.3, 33.3 and 44.4). As indicated by repeated measures ANOVA, hot flash severity reduced significantly from 1-8 wk in Glycyrriza glabra group while for Placebo group, this reduction was significant only for 1 wk. Also, 2 wk after cessation of treatment, women reported significant relief of hot flashes frequency and intensity.

Another trial by Abdolahi et al showed gradual decrease in frequency of hot flashes in both Glycyrriza glabra group (6±2.8, 3.95±2.86, 2.66±1.68 and 1.06±1.19) and placebo group (4±2.4, 2.92±2.52, 3.5±2.62 and 2.38±2.59) (10). After 12 wk, only Glycyrriza glabra- treated patients experienced statistically significant reduction (p<0.05) compared to the baseline. After 12 wk, the reduction in frequency of hot flashes in Glycyrriza glabra-treated patients was more significant than placebo group.

Glycyrriza glabra (Licorice) vs. HRT

Menati et al reported statistically significant decrease in frequency of hot flashes in HRT (p=0.008) and a non-significant decrease in Glycyrriza glabra group (p=0.157), however, the comparison between groups showed no significant difference (p=0.134) (5). Hot flashes severity reduced significantly in HRT group (p=0.031), but this reduction was not significant in Glycyrriza glabra group (p=0.698) and the comparison between two (p=0.019). In fact, Glycyrriza glabra group was not significantly different from HRT with respect to frequency of hot flashes, but latter experienced more effective reduction in hot flash intensity. To sum up, based on three trials discussed above, it seems that Glycyrriza glabra (Licorice) has alleviating effect on hot flashes, though further studies are needed to support the current evidences.

Effect of valerian on hot flashes

Kazemian et al found significant decrease in the frequency of hot flashes in period between baseline and 4 (p<0.05) or 8 (p<0.01) wk after trial in Valerian group (11). However, Valerian and placebo groups were not compared. The comparison of two groups in terms of severity of hot flash by Mann-Whitney test showed statistically significant difference after 8 wk (p<0.01), but this was not case after 4 wk. Another trial by Mirabi et al showed statistically significant decrease in intensity and frequency of hot flashes in Valerian group (p<0.001) while placebo group remained unaffected (12). Also, comparison of two groups showed a statistical significant difference at 4th and 8th wk of study (p<0.001).

It seems that Valerian group can remarkably alleviate severity of hot flashes, though more studies are needed to support current evidences.

Effect of red clover on hot flashes intensity

Salehi et al and Ehsanpour et al assessed the effect of red clover on hot flashes intensity (13, 14). According to Friedman test, frequency of mild, moderate and severe hot flash decreased significantly compared to baseline in both red clover (p<0.001) and placebo groups (p<0.001). Mann-Whitney test showed statistically significant decrease between groups at wk 10 the 10th wk of study (p=0.04), but it was not significant at 2nd and 4th wk. In a meta-analysis of six trials about effect of red clover, a subgroup analysis was conducted to determine most effective dose of red clover in frequency decreasing of
Herbal and hot flashes

hot flashes (15). Pooled effect size was larger in trials in which red clover was administrated at a dose of 80 mg -0.79 (-2.35 to 0.78) followed by a dose of 40 mg -0.40 (-2.33 to 1.53) and 160 mg -0.30 (-5.54 to 4.94). It seems that higher dose of red clover might be more effective.

Effect of Vitexagnus-castus on hot flashes

Vitexagnus-castus vs. placebo

Study by Abbaspoor et al showed progressive decline in frequency of hot flashes in Vitexagnus-castus (6±2.58, 4±2.52, 2±2.38, 1.28±2.26 and 0.76±2.16) and placebo group (5.94±2.2, 6±2.34, 5.81±2.40, 5.44±2.42 and 4.75±2.84) at baseline, 2, 4 and 6 wk after trial (16). More statistically significant decrease in hot flashes frequency was also observed in Vitexagnus-castus group after 2 (p=0.015), 4 (p=0.012), 6 (p=0.001) and 8 (p=0.001) wk compared to placebo groups. Also, reduced severity of hot flashes in women receiving Vitexagnus-castus was more significant than placebo group after 2 (p=0.015), 4 (p>0.001), 6 (p>0.001) and 8 (p>0.001) wk.

Vitexagnus-castus vs. Passionflower

Another study by Kazemian et al which compared three groups (Passion Flower, Vitexagnus-castus and placebo), found statistically significant decrease in hot flashes intensity 2 and 4 wk after trial in Passion Flower group (17). However, no statistically significant decrease was observed between baseline and 2nd wk. Significant decline was observed between baseline and 2nd or 4th wk in Vitexagnus-castus group. No statistically significant difference, nevertheless, was observed between 2nd and 4th wk. The comparison of three groups by Kruskal-Wallis test showed statistically significant difference between them after a 30-day period, but it was not significant after 15 days. Mann-Whitney test was used to determine the difference between groups, and it indicated that mean change of Vitexagnus-castus was significantly higher than placebo group.

Passion Flower group and vitexagnus-castus group were similarly effective in alleviating hot flashes intensity. Therefore, it appeared that Vitexagnus-castus and Passion Flower is was significantly different from placebo. In a duplicate trial in 2010, Kazemian et al assessed the effect of Passion Flower on hot flash frequency (18). A gradual decrease in the frequency of hot flashes in Passion Flower group (7.26, 5.48 and 4.52) and placebo group (38.81, 23.07 and 21.7) was reported 2 and 4 wk after trial beginning. Significant decrease was observed in hot flashes frequency after 2 or 4 wk in both groups, the decrease was significance between 2nd and 4th wk only in Passion group. No statistical comparison between Passion Flower and placebo was provided. In sum, vitexagnus-castus has had significantly alleviating effect on hot flashes, though further studies are needed to support these evidences.

Effect of soy on hot flashes

Soy vs. placebo

Hanachi et al divided patients randomly in three groups of soy milk, soy milk plus exercise and placebo (19). Reduction of hot flashes in both soy milk (72%) and soy milk +exercise groups (83%) was significantly higher than placebo group. Another study by Abbaspour showed a gradual reduction in frequency of hot flashes in protein soy (10.38±3.38, 9.43±3.13, 7.17±2.38, 5.45±1.74) and placebo groups (10.41±2.76, 10.91±3.22, 9.94±2.84, 9±2.54) at the baseline, after 2, 3 and 4 wk of study (20). The difference between groups was observed after 2 wk (p=0.06), 3 wk (p<0.001), and 4 wk (p<0.001). This was not the case of baseline (p=0.973). The corresponding findings about hot flashes intensity were (28.9±11.06, 25.41±10.31, 16.76±6.48, 9±2.75 and 9±2.75) for the protein soy group, and (29.16±9.07, 30.22±10.17, 26.97±8.75, and 24.69±7.66) for the placebo group at the baseline (p=0.92), after 2 (p=0.07), 3 (p<0.001), and 4 wk (p<0.001) of the study.

Piascledine (Avacado plus soybean oil) vs. HRT

Panahi et al divided the participants into two groups: Piascledine (Avacado plus soybean oil) and HRT menopausal (21). The severity of hot flashes was measured using two different methods, hot flash questionnaires (HFQ) and visual analog scale (VAS) of hot flash severity. Former contained four questions: (the length of hot flash, the
impact of hot flashes on waking up, the interference of hot flash with daily activities and possibility of having night sweat. The latter is a horizontal line graded from 0-100 (0=no hot flash and 100=unbearable hot flash). Piascledine (Avocado plus soybean oil) and HRT were similarly effective in alleviating hot flashes severity, (length of hot flash (p=0.796), the impact of hot flashes on waking up (p=0.111), the interference of hot flash with daily activities (p=0.949) and possibility of having night sweat (p=0.671). Also, VAS showed 23.57 points reduction in Piascledine group compared to a 16.21-points decrease in HRT group (p=0.800).

**Comparison of soybeans and flaxseed with wheat flour control group**

The comparison of three groups based on Kruskal-Wallis test showed statistically significant difference between groups in a 30-day period. Akbari Torkestani et al divided the participants randomly into three interventions, soybeans, flaxseed, and wheat flour groups (22). According to Kruskal-Wallis test, the intensity and frequency of hot flashes were similar in all three groups at baseline. There was not any statistically significant difference with respect to hot flash intensity between three groups at 4th wk (p=0.485) and 8th wk (p=409). The comparison of three groups based on Kruskal-Wallis test showed significant difference between groups at 8th wk of the trial, but this was not the case at 4th wk. There was statistically significant decrease in hot flash frequency only in soy group. To sum up, it seems that soy was more effective in alleviating hot flashes, though further studies are needed to support these evidences.

**Effect of flaxseed on hot flashes**

The effect of flaxseed on hot flashes was also evaluated by Baghdarin et al (23). They conducted a double-blind, randomized, cross-over study (with a wash out period of two wk) on two groups of flaxseed and placebo for six wk. Flaxseed group showed a significant reduction compared to placebo group with respect to hot flash intensity (p=0.045), but this difference was not significant with regard to hot flashes frequency. Therapeutic effect was only significant in women experiencing 5-7 cases of daily hot flashes (p<0.001). In contrast, Akbari Torkestan et al did not find any significant decrease in frequency and intensity of hot flashes, which was probably due to low dose administration (25 mg vs. 40 mg) (22). Again, more studies are needed to clarify whether high dose (40 mg) is more effective than low dose (25 mg).

**Effect of Salvia officinalis on hot flashes**

Sadeghi et al found the significant effects of Salvia of ficinaxis extract and placebo on the frequency of hot flashes (24). Although the comparison of Salvia officinalis and placebo groups was significant, still further studies are needed to confirm these evidences.

**Effect of St. John’s wort (hypericum perforatum) on hot flashes**

**St. John’s wort vs. passion flower**

Asali et al showed a progressive decrease in intensity of hot flashes in passion flower (8.1, 5.6 and 4) and St. John's wort group (9.3, 5.8 and 4.4) at the baseline, after 3 and 6 wk of study (25). Significant decrease was observed in both groups (St. John’s wort and passion flower) at 3rd and 6th wk (p<0.05) compared to baseline. Although 60% and 27.5% of women suffered severe hot flashes in St. John's wort and passion flower groups respectively, it was reduced to 10% and 3.4% at 6th wk (the end of study).

**St. John’s wort vs. vitexagnus-castus**

Ghazanfarpour et al found significant decrease in both groups (St. John's wort and vitexagnus-castus), but this difference was not significant between flower and vitexagnus-castus groups after 1 (p=0.98) and 2 months (p=0.68) (26).

**Effect of evening primrose oil on hot flashes**

In a trial on effect of evening primrose oil on hot flashes, frequency of hot flash decreased from 5.2±1.9 to 3.2±1.8 in the evening primrose and from 5.4±1.9 to 3.7±20 in placebo group (27). The severity of hot flash reduction was greater than placebo group, but, the difference between groups was not significant (p=0.23). The severity of hot flashes changed from 5.9±1.5 to 3.4±1.4 (-2.6±1.60) in evening primrose and from 5.9±1.7 to 4.1±2.0 (-1.8±1.2) in placebo group,
which was statistically significant. In conclusion, it seems that evening primrose oil is more effective in alleviating hot flashes. Again, more studies are needed to confirm the current results.

**Trigonella foenum-graecum (fenugreek) on hot flashes**

Hakimi et al divided the patients randomly into two groups of trigonella foenum and HRT (28). A gradual decrease was observed in Trigonella foenum (7.08±0.596, 4.36±0.53 and 2.60±0.46) and HRT group (7.47±0.71, 1.72±0.34, 0.84±0.23) at the baseline, after 4 and 8 wk of study. The frequency of hot flashes decreased significantly Trigonella foenum group, at wk 4 and wk 8 of the study compared baseline. That is, the effectiveness of HRT group was greater than Trigonella foenum group.

**Trigonella foenum**

Another trial by Akbari Torkestani et al showed a decrease from 2.20±0.74 to 1.31±0.604 (40%) in Trigonella foenum and from 2±0.74 to 0.8±0.644 (60%) in the flaxseed group (29). The comparison of two groups was significant at 8th wk. To sum up, it seems that Trigonella foenum may be effective in alleviating hot flashes.

To our knowledge, this is the first systematic review about therapeutic effect of Iranian herbal medicine on hot flashes. Herbal medicine plays a key role in treatment of many diseases. Both Iranian people and health providers are interested in herbal medicine. Overall, studies have shown that Pimpinella anisum, licorice (Glycyrrhiza glabra), soy, black cohosh, red clover, evening primrose, Pimpinella anisum, Flaxseed, Salvia officinalis, Passi-Vitagnus, Piacsledine (Avacado plus soybean oil), St. John's wort (Hypericum perforatum), passion flower and Valerian may have alleviate side effects of hot flashes.

**Determining the suitable wash-out period for cross-over design**

Nahidi et al conducted several interviews with women at 1, 2, 3 and 4 wk after cessation of treatment to detect recurrence of hot flashes (30). Women, who reported significant relief 2 wk after therapy cessation, suggested that effects of phytoestrogen in licorice can persist even 2 wk after cassation of treatment. This finding may help determine the sufficient wash-out periods essential between periods of a crossover design. However, it should not be generalized to other phytoestrogens, as Baber et al showed that effects of phytoestrogen in red clover persisted one wk after cassation (2).

**Clinically treatment effect**

To assess the treatment satisfaction threshold, Wyrwich et al used Menopause symptoms treatment satisfaction questionnaire (MS-TSQ) (31). This questionnaire was designed by Hill et al to assess satisfaction of women with level of menopausal symptoms treatment over 4 levels of treatment with desvenlafaxine. It is composed of 7 items on menopausal symptoms, including hot flashes, sweats night,
sleep, mood, libido, concentration ability, medication tolerability along with one overall question about treatment satisfaction. Each item is rated on scale of 0-4, which includes “extremely dissatisfied,” “dissatisfied,” “neutral,” “dissatisfied,” and “extremely satisfied.” The treatment satisfaction threshold is difference between average reductions in two mentioned symptoms for women who reported were “neutral” and “satisfied” about treatment.

Hill et al used only two of 7 items (hot flash and sweat) to measure women’s satisfaction reduction of 1.64 in hot flashes is considered as clinically meaningful threshold with respect to 50% placebo effect (32). It is important to note that they determined the treatment satisfaction threshold based on 50% of placebo effect. Future studies are needed to focus on determining the threshold of treatment satisfaction base on low effect of placebo. Also, future studies should be taken into account both statistical and clinical significance.

Low placebo effect

Several factors may involve in placebo response, including doctor-patient relationship, patients' positive or negative expectations of treatment, cultural factors like patients' perception of colors, forms, and drug names, along with their experience and perception of fate and faith are involved in this process (33, 34). This systematic review showed that placebo had a slight effect on alleviating hot flash. One possible explanation for this can be cultural difference. Future research can use mixed method designs with semi-structured interviews and open-ended questions such as RCTs to explore why some participants show low responses to placebo.

Suggestion for future trials

Many studies have shown beneficial effects of herbal medicine in decreasing hot flashes. Future studies can compare the effectiveness of herbal medicines with HRT groups. Further studies are required to measure biological parameters of estrogen, including estradiol, estron, Follicle-stimulating hormone (FSH) and Sex hormone-binding globulin (SHBG) to investigate the relationship between biological parameters and intensity and frequency of hot flashes.

Limitations

The weak methodology of many studies used in our systematic review can be one of the potential limitations of this study. Small sample sizes, inadequate treatment allocation, lack of intention to treatment report, unclear blinding method and unmentioned randomization technique can degrade the validity of the results.

Conclusion

This research demonstrated the efficacy of herbal medicines in alleviating hot flashes, which are embraced both with people and health providers of Iran (5, 35). Therefore, herbal medicines can be considered as an appropriate alternative for women experiencing hot flashes.

Conflict of interest

Authors have no conflict of interests.

References

1. MacLennan A, Broadbent J, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev 2004; 4: CD002978.
2. Baber R, Templeman C, Morton T, Kelly G, West L. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. Climacteric 1999; 2: 85-92.
3. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomized controlled trial. Lancet 2000; 356: 2059-2063.
4. Haghhighi L, Zadmohammadi M. [Hormon replacement therapy in menopausal menopausal women reffered referred t o Iran University clinics during 2000-2001]. Iran J Med Sci 2003; 10: 25-30. (In Persian)
5. Menati L, Khaleghinezhad K, Tadayon M, Siahpoosh A. Evaluation of contextual and demographic factors on licorice effects on reducing hot flashes in postmenopause women. Health Care women Int 2014; 35: 87-99.
6. Saghafigh N, Mahmooninya M, Ayati S, Behdani F, Shaken MT, Rakhshandeh A. [Comparison of Effects
of Black Cohosh and Fluoxetine in Treatment of Menopausal Symptoms]. Iran J Obstet Gynecol Infertil 2013; 15: 29. (In Persian)
7. Shahnazi M, Nahaei J, Mohammad-Alizadeh-Charandabi S, Bayatpayan S. Effect of black cohosh (cimicifuga racemosa) on vasomotor symptoms in postmenopausal women: a randomized clinical trial. J Caring Sci 2013; 2: 105.
8. Nahidi F, Kariman N, Simbar M, Mobaj F. The study on the effects of Pimpinella anisum on relief and recurrence of menopausal hot flashes. Iran J Pharm Res 2012; 11: 1079.
9. Nahidi F, Kariman N, Simbar M, Mobaj F. The Study on the Effects of Pimpinella anisum on Relief and Recurrence of Menopausal Hot Flashes. Iran J Pharm Res 2012; 11: 1079-1085.
10. Abdolahi F, Azad Bakht M, Shabankhani M, Rezaei Abhari F, Moslemizade N. [The effect of aqueous extract of Glycyrriza glabra on menopausal symptom]. Mazandran J Med Sci 2007; 16: 75-82. (In Persian)
11. Kazemian A, Sh B, Parvin N, Delaram M. [The effect of valerian on hot flash in menopausal women]. J Shahrekord Univ Med Sci 2006; 8: 35-40. (In Persian)
12. Mirabi P, Mobaj F. The effects of valerian root on hot flashes in menopausal women. Iran J Pharm Res 2013; 12: 217-222.
13. Salehi K, Ehsanpour S, Zolfaghari B, Salehi Z, Honargoo M. [Effect of red clover Isoflavonates extract on menopausal symptoms]. J Gorgan Univ Med Sci 2013; 15: 21-28. (In Persian)
14. Ehsanpour S, Salehi K, Zolfaghari B, Bakhtiar S. The effects of red clover on quality of life in postmenopausal women. Iran J Nurs Midwif Res 2012; 17: 34-40.
15. Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006; 295: 2057-2071.
16. Abbaspoor Z, Hajjikhani NA, Afshari P. Effect of vitex agnus-castus in hot flushes: A double-blind randomized controlled trial. Chronic Diseases J 2013; 1: 67-73.
17. Farzaneh F, Fatehi S, Sohrabi M-R, Alizadeh K. The effect of oral evening primrose oil on menopausal hot flashes: a randomized clinical trial. Arch Gynecol Obstet 2013; 288: 1075-1079.
18. Hakimi S, Mohammad Alizadeh Charadabi S, Siahi Shadbad M, Bamdad Mohgadam R, Abbasalizadeh F, Mustafa Ghebaghi P, et al. [Effect of Fenugreek seed on early menopausal symptoms]. Pharm Sci 2005; 2: 9. (In Persian)
19. Akbari Torkestani N, Davoodabadi F. [Comparative effects of flaxseed, soy on menopausal hotflashes]. Iran J Nurs Midwif Res 2012; 3: 46-57. (In Persian)
20. Nahidi F, Zare E, Mobaj F, Alavi-majd H. Effects of licorice on relief and recurrence of menopausal hot flashes. Iran J Pharm Res 2012; 11: 541.
21. Wynich KW, Spratt DI, Gass M, Yu H, Bobula JD. Identifying meaningful differences in vasomotor symptoms among menopausal women. Menopause 2008; 15: 698-705.
22. Hill CD, Fehnel SE, Bobula JD, Yu H, McLeod LD. Development and preliminary validation of the Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ). Menopause 2007; 14: 1047-1055.
23. Moerman DE. Cultural variations in the placebo effect: ulcers, anxiety, and blood pressure. Med Anthropol Quarterly 2000; 14: 51-72.
24. Giorno CD, Fonseca AMd, Bagnoli VR, Assis JSD, Soares Jr JM, Baracat EC. Effects of Trifolium pratense on the climacteric and sexual symptoms in postmenopause. Revista da Associação Médica Brasileira 2010; 56: 558-562.
35. Adib-Hajbaghery M, Hoseinian M. Knowledge, attitude and practice toward complementary and traditional medicine among Kashan health care staff, 2012. Comp Ther Med 2014; 22: 126-132.