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Protocol for systematic review and meta-analysis: hop (*Humulus lupulus* L.) for menopausal vasomotor symptoms

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ABSTRACT

Introduction: Menopause is a critical stage in every woman's life. It can cause a distressing time for women by creating various vasomotor symptoms (VMS). Phytoestrogens can potentially exert various favourable effects and alleviate VMS in postmenopausal women. The hop (*Humulus lupulus* L.) contains 8-prenylnaringenin (8-PN), the most potent phytoestrogen known to date. The hop is eight times stronger than any other herbal oestrogens. This study aims to conduct a comprehensive systematic review and a meta-analysis survey of the effects of hop in the management of VMS in postmenopausal women.

Methods: Only randomised controlled clinical trials, with cluster randomisation and crossover, blinded and non-blinded designs, conducted between 2000 and 2015, will be included in this review. Quasi-experimental and observational studies as well as case reports will be excluded. The studies will be selected if their participants were aged 40–60 years, had elevated follicle-stimulating hormone (FSH) levels and/or menstrual irregularities, and experienced discomforting VMS (at least hot flashes or night sweats). The primary outcome will be the rate of response to treatment, such as changes in frequency and intensity of symptoms in the intervention and placebo groups. 'Hop', 'Humulus', 'menopause', 'vasomotor', 'hot flashes', 'phytoestrogen' and 'night sweats' will be used as search key words. Prior to their inclusion in the review, the selected papers will be assessed by two independent reviewers for methodological validity. Any disagreements will be resolved through a third reviewer. The risk of bias will be independently determined using the Cochrane Risk of Bias Tool. The quality of the papers will be assessed based on the CONSORT checklist.

Ethics and dissemination Results will be disseminated through traditional academic literature. Dissemination of results will occur by peer-reviewed publications. The results of our project can help reproductive health researchers when evaluating the discomforts of research procedures described in study protocols or when designing a study. Information on experiences of menopausal women involved in previous studies may also help in future research. The expected dissemination actions are effective treatment in designing strategies that aim to develop women's health and healthcare providers when offering treatment for women with vasomotor symptoms.

Strengths and limitations of this study

- Systematic reviews and meta-analyses will provide the highest level of evidence for informed decisions. To the best of our knowledge, no meta-analysis has been conducted on this topic.
- One limitation of this study is that the authors are only fluent in Persian and English. Therefore, a translator will be required when the papers are published in other languages.

INTRODUCTION

Menopause, sometimes called a second puberty, is a critical stage in every woman's life.[1] Certain characteristics of this multidimensional evolutionary process affect women's quality of life and put them at high risk of developing various health conditions.[2 3] Following recent medical advances and the consequent increase in life expectancy (LE), the number of menopausal women is on a rapid rise. According to the WHO, the population of women aged over 50 years will exceed one billion in 2030.[4] Despite the mentioned improvement in LE, menopause age has remained relatively constant, that is, postmenopausal years constitute about one-third of women's lives.[5] Therefore, menopause can potentially be a major health issue.[6] Postmenopausal women experience a variety of symptoms including hot flashes, night sweats, sleep disorders, anxiety, irritability and mood swings.[7] Owing to considerable negative effects of menopausal symptoms,[5 8] most women tend to seek appropriate treatments. Hormone therapy (HT), using oestrogen either alone or in combination with progestogens, is often recommended for the management of menopausal symptoms.[9] However, the Women's Health Initiative (WHI) has reported increased risk of breast cancer, thromboembolic events, stroke and coronary heart diseases following HT.[10 11] Hormone replacement therapy is also believed to cause

a gradual reduction in the cytotoxicity of natural killer (NK) cells and thus weaken the immune system. In fact, a two times higher incidence of breast cancer was seen in women receiving HT for 9 years.[12]

Herbal medicines, especially those containing oestrogen, can have various favourable effects and alleviate vasomotor symptoms in postmenopausal women.[13] Phytoestrogens are plant derivatives of which the structural similarity to oestrogens makes them capable of exerting both oestrogenic and anti-oestrogenic effects.[14] Since phytoestrogens can produce stronger oestrogenic effects in the absence of adequate oestrogen, they can compensate for the reduced levels of endogenous 17β-oestradiol during menopause. Substantial amounts of 8-prenylnaringenin (8-PN), the strongest known phytoestrogen capable of binding to both oestrogen receptors in the human body, are found in *Humulus lupulus* (commonly known as hop). As a member of the Cannabaceae family, *H. lupulus* contains volatile oils and oestrogenic, resin-based and polyphylic compounds. Owing to its potent phytoestrogenic compounds and humulene, tannin, β-myrcene, pectin, potassium and flavonoid contents along with its ability to create oestrogenic, sedative, hypnotic, antipyretic, anti-inflammatory and antiseptic effects,[15 16] *H. lupulus* has found wide medicinal and industrial applications. The presence of oestrogenic compounds, such as isoxanthohumol, progesteronic xanthohumol and 8-PN, in hop, has also made it an appropriate herbal medicine for treatment of menopausal symptoms.[17] Heyerick *et al*[18] examined the efficacy of a hop extract enriched in 8-prenylnaringenin on relief of menopausal symptoms. They showed that daily intake of a hop extract has favourable effects on vasomotor symptoms. Rosic *et al*[19] noticed significant improvements in the physical, psychological and genitourinary symptoms of menopause following the administration of phytoestrogens. In this regard, another study observed that hop effectively reduced vasomotor symptoms.[20] Likewise, a clinical trial by Mohammad-Alizadeh-Charandabi *et al*[21] showed significantly that hop can reduce early menopausal symptoms.

Numerous scales, including the Greene Climacteric Scale and Cooperman's index, have been developed to determine the incidence and severity of menopausal symptoms.[21 22] However, based on our knowledge and understanding, no systematic review has evaluated the effects of hop in the management of menopausal vasomotor symptoms. Therefore, the results of this study can potentially help to select appropriate treatment options for menopause. The aim of this study is to conduct a comprehensive systematic and meta-analysis survey of the effects of hop in the management of menopausal vasomotor symptoms.

OBJECTIVES

This Systematic review will aim to clarify whether *H. lupulus* is more effective than placebo in reducing menopausal vasomotor symptoms. Our secondary objective will be to answer the following two questions:

1. Does response to treatment with *H. lupulus* depend on the dosage or duration of treatment?
2. What are the side effects of *H. lupulus* compared to placebo?

METHODS

Criteria for considering studies for this review.

Types of studies

Only randomised controlled clinical trials conducted between 2000 and 2015 will be included in this review. This includes cluster and crossover, and blinded and non-blinded designs. Quasi experimental (studies without controls) and observational studies, as well as case reports, will be excluded. There are no language restrictions to using and entering articles in this study. If the language used in an article is other than Persian or English, we will ask for a translator to translate the article.

Types of participants

The studies will be selected if their participants:

- Were aged 40–60 years with elevated FSH or menstrual irregularities or both, and those who reported a minimum of some hot flashes or night sweats that caused discomfort;
- Were recruited based on the Greene Climacteric Scale, Cooperman's index, Menopause Rating Scale (MRS), or visual analogue scale (VAS);
- Were assessed using the Greene Climacteric Scale, Cooperman's index, MRS or VAS, to determine the effects of the intervention;
- Used hop and placebo for at least 4 weeks;
- Comprised at least 80% of those completing the whole course of the intervention.

Types of interventions

The studies will be reviewed if:

- Hop are used in the intervention (no time limits are imposed);
- The effects of hop are compared to those of placebo;
- Placebo is used for symptom relief.

Studies with scores over 15 on the CONSORT checklist will be included. No time limits will be imposed on the treatment period (see online supplementary appendix: 1).[23]

Primary outcome

The primary outcome will be the rate of response to treatment, such as changes in frequency and intensity of symptoms in the intervention and placebo groups. Treatment outcome measurements will be based on the Greene Climacteric scale, Cooperman's index, MRS or VAS.

Secondary outcomes

The side effects of hop and the mean scores of the Greene Climacteric scale, Cooperman's index, MRS and VAS in the studied clinical trials will be evaluated as secondary outcomes. All outcomes will be examined during a period of 6 months (short-term outcomes). The number of hot flashes is one of the items in the Green Climacteric scale that will be assessed as secondary outcome.

Search strategies for identification of studies

The following resources will be searched:

- The Cochrane Central Register of Controlled Trials
- MEDLINE (via PubMed, from 2000 to the president)
- EMBASE (via Scopus, from 2000 to the present)
- PsycINFO
- Scopus
- ProQuest
- Google Scholar
- CINAHL (via EBSCO)

Our key terms for preliminary analysis of previous research will be Hop, Humulus, menopause, vasomotor, Hot Flashes, phytoestrogen, Night sweats, which will be combined using Boolean operators AND and OR. Further relevant keywords and Boolean operators will also be selected for a change of strategy in each particular database. Neither directly during the database search nor indirectly during the evaluation of study reference lists will any particular language criterion be defined.

Database of ongoing clinical trials

The search for ongoing clinical trials will be performed in the following databases:

- www.controlled-trials.com;
- www.clinicaltrials.gov;
- www.who.int/trialsearch.

Searching other resources

Manual searches will be conducted in key journals. Government reports, theses and dissertations, papers published by research committees, and abstracts of papers presented at different conferences and seminars, will be evaluated.

Data collection and analysis

Selection of relevant studies

The first stage of this systematic review will involve the evaluation of titles, abstracts and eligibility of studies (by FK). In the second stage, the full text of the papers will be independently assessed by three co-authors (FA, NR and FRT) to confirm their eligibility. Areas of disagreement will be discussed until a consensus is reached. In cases where the disagreement cannot be resolved, the viewpoints of an external observer will be used. Authors of papers with available abstracts, whose results are published on posters, will be emailed and requested to send the full text.

Data extraction and management

Three co-authors (FA, NR and FRT) will independently extract data from the full texts of papers that were published previously and will design a form accordingly. Data will be collected as follows (see online supplementary appendix: 2)[24]

1. Research information (the first author, geographic location, year of publication, beginning and end dates, research design, sample size, duration of follow-up);
2. Characteristics of the participants (age, gender and number of participants, inclusion and exclusion criteria, menopausal symptoms, keywords definitions and measurement tools);
3. Intervention and comparison of the details (number of groups, blinding procedure, dose and type of intervention, dose based on body weight, factors determining the duration of treatment, treatment withdrawal and sample loss);
4. Outcome measures (explanations on the administered measurement tools, and methods evaluating outcomes, side effects and serious side effects).

The fourth author (FK) will review the collected data. Cases of disagreement between the authors will be resolved based on the opinions of an external observer.

Quality assessment of studies

The risk of bias will be independently determined by two external observers using the Cochrane Risk of Bias Tool (see online supplementary appendix: 3).[25] The quality of the papers will be assessed based on the CONSORT checklist, which contains 25 items scored as zero or one.

Only studies that scored over 15 on the CONSORT checklist will be included. As in previous stages, points of disagreement will be resolved based on the viewpoints of an external observer.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using Rev Man software. Two models of meta-analysis will conduct for outcomes: the fixed-effect model and the random-effect model. A fixed-effect model using the Mantel-Haenszel method assumes that studies are sampled from populations with the same effect size, making an adjustment to the study weights according to the in-study variance. A random-effect model assumes that studies are taken from populations with various effect sizes and calculates study weights both from in-study and between-study variances, considering the extent of variation or heterogeneity. The random-effect model is more appropriate when heterogeneity is present. For each model, we will estimate the between-study heterogeneity in all of the eligible comparisons, using the χ^2-based Q statistic. All results will be subject to double data entry. Effect sizes expressed as OR (for categorical data) and weighted mean differences (for continuous data) and their 95%

CIs will be calculated for analysis. Heterogeneity will be assessed statistically using the standard χ^2. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. We will also consider subgroup meta-analysis such as menopausal status including premenopause and postmenopause.

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Contributors FA and NR were responsible for design of the protocol and conception of the manuscript. FK was responsible for evaluation of eligibility of studies, and review of the collected data. FA, FRT and NR were responsible for assessment of the full text of papers and data collection. also authors read, provided important revisions and approved the final version of the manuscript.

Competing interests None declared.

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