

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for Systematic Review and meta-analysis: Hop (<i>Humulus Lupulus L.</i>) for Menopausal Vasomotor Symptoms
AUTHORS	Abdi, Fatemeh; Kazemi, Farideh; Roozbeh, Nasibeh; Ramezani Tehrani, Fahimeh

VERSION 1 - REVIEW

REVIEWER	Mojgan Mirghafourvand Tabriz University of Medical Sciences-Iran
REVIEW RETURNED	22-Dec-2015

GENERAL COMMENTS	<p>Thank you for the opportunity to review this protocol. I appreciate the authors' time and attention. However, there are several areas of the protocol that need further attention.</p> <ul style="list-style-type: none">- The aim of the study was generally written at the end of introduction subsection of abstract not in material and methods subsection.- PICOS, search strategy, keywords for search, time limits, the method for assessing the included studies and meta-analysis if possible should be reported in Methods and analysis subsection of abstract shortly.- The number of hot flashes should be assessed as secondary outcome.- Why RevMan software won't use for data analysis as specific software for systematic reviews.- It is better that subgroup meta-analysis is conducted based on menopausal status including premenopause and postmenopause.- There are a number of language and grammar problems with this protocol that require editing. <p>Thank you again for the opportunity to review this paper. I look forward to receiving a revision.</p>
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REVIEWER	Maida Taylor University of California San Francisco San Francisco, California, USA
REVIEW RETURNED	05-Jan-2016

GENERAL COMMENTS	<p>Several references are incomplete or improperly formatted -1, 2,3, 4, 7, 12, 13, 20, 22. Some of the references may not be accessible to international readers. There may be more recent, up to date references on patient attitudes toward menopause, hormone therapy and alternative treatments that you might cite. We recently did a review of botanical therapies (for theNorth American Menopause Society), and could only identify 2 adequate trials of hops. I hope your 'hunting' is more successful.</p>
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REVIEWER	Marcianna Nosek University of San Francisco United States
REVIEW RETURNED	12-Jan-2016

GENERAL COMMENTS	<p>This is an exciting proposal that could add to the knowledge on alternative treatment modalities for women experiencing vasomotor symptoms of menopause. Therefore this study should be conducted. I have a few suggestions and questions for the researchers.</p> <ol style="list-style-type: none"> 1. I would like to address a few grammatical concerns throughout the protocol. The most efficient manner to do this would be for the authors to review the pdf that I have uploaded. I had added suggestions using the annotation feature. 2. There was a mentioning of conducting a quantitative analysis of pooled data from chosen studies which qualifies this study to be a meta-analysis. It also appears that the researchers will be doing a qualitative analysis of the synthesized results. If this is the case, I would suggest to at least mention meta-analysis earlier perhaps even in the title of the article or at least in the purpose statement. 3. In page 1, line 43 in the abstract, it is stated that "hop is 8 times stronger than other herbal estrogens." This needs to be clarified. Eight times stronger than any other herbal estrogen? than the highest herbal estrogen after hop? It is just not clear. 4. In page 2, line 18, I would stay away from the word, 'disease'. Perhaps 'morbidity'? Or, "...process may put some women at risk of experiencing severe symptoms that could greatly affect quality of life." 5. In line 27, please change "menopause is an ongoing major health issue" to "has the potential to be an ongoing..." 6. Re line 30, You had no mention of incidence rates. I would either cut this part of the statement out or actually add some incidence rates. Alternately, state, "Due to considerable negative effects..." 7. In page 3, line 9, do you really want to throw this negative effect of decreased sexual desire in with its positive effects? 8. In page 4, line 3 re types of studies, it is not clear. You may want to consider some variation of this: "Only randomized controlled clinical trials conducted between 200-2015 will be included in this review. This includes cluster and crossover, blinded and non blinded designs. Quasi experimental (studies without controls) and observational studies, as well as case reports will be excluded." Also, there is no mention of whether studies conducted in various languages will be included or excluded. 9. Page 4, line 10 re participants, it appears that you are only interested in reported symptom experience without confirming any official state of menopause such as elevated FSH or menstrual irregularities? Perhaps you need to clarify this. 10. Re line 12, Stating "at least one vasomotor symptom" seems a bit vague. Perhaps you would want to state, "...and who reported a minimum of some hot flashes or night sweats that caused discomfort." 11. Re line 27, So you are eliminating all studies who reported any loss to follow up? This may be quite restrictive. You may want to consider a maximum attrition rate of 20% or even if you set that at 10%, you would be able to include more studies without introducing too much bias. Or perhaps clarify what you mean by a "whole course of the intervention" 12. Re line 43, A few questions regarding inclusion and exclusion
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	<p>criteria. Will you include non blinded studies? Are you concerned with methods of allocation concealment in your studies that you choose?</p> <p>13. Re line 48, Re outcome, did you want to clarify this further? E.g., changes in frequency, or intensity of symptoms? Will you include different outcome measurements? ORs? HRs? etc.</p> <p>14. Re page 5, line 8, databases, might you consider CINAHL?</p> <p>15. Re line 25, search terms, might you consider MeSH terms?</p> <p>16. Re page 7, line 16 re data synthesis, In regards to quantitative analysis, there is no mention of random vs fixed effects model to be used. Also, have you considered the Q statistic to test for heterogeneity? Or the I square if the sample is too small?</p> <p>17. Re lines 24-27 , the sentence, "the findings..." is a little confusing. Could you make that more clear?</p> <p>18. Re line 31 in dissemination, it is the first mention of postmenopausal women. Please keep in mind that women who are in menopausal transition experience most of the symptoms. I would keep it consistent and adhere to menopausal women and not 'post menopausal'</p> <p>The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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VERSION 1 – AUTHOR RESPONSE

Dear Reviewers; Thanks a lot for your professorial comments. Revised manuscript is replaced according to your order.

Correspondence, Nasibeh Roozbeh

Reply to the reviewers' comments

- Please include an 'Article summary' section consisting of the heading: 'Strengths and limitations of this study', and containing up to five short bullet points, no longer than one sentence each, that relate specifically to the methods of the study reported. They should not include the results of the study and should be placed after the abstract.

- Systematic review and meta-analysis will offer highest level of evidence for informed decisions.
- So far, no meta-analysis has been done on this topic.

One difficult step of this study is to collect all the raw data of eligible trials by systematic search, which may be the limitation of this meta-analysis.

- Please include a completed copy of the PRISMA-P reporting guidelines checklist

(<http://www.equator-network.org/reporting-guidelines/prisma-protocols/>)

included a completed copy of the PRISMA-P reporting guidelines checklist

- The aim of the study was generally written at the end of introduction subsection of abstract not in material and methods subsection.

Introduction: Menopause is a critical stage in every woman's life. Menopause can be a distressing time for women with many experiencing vasomotor symptoms(VMS). Phytoestrogens potentially exert various favorable effects in postmenopausal women, especially alleviating VMS. The plant of Hop(Humulus lupulus L.) contains 8-prenylnaringenin (8-PN) as the most powerful phytoestrogen known to date. Hop is eight times stronger than any other herbal estrogens. The aim of the proposed study is a comprehensive systematic and meta-analysis survey of the effects of hop in the management of menopausal vasomotor symptoms.

- PICOS, search strategy, keywords for search, time limits, the method for assessing the included studies and meta-analysis if possible should be reported in Methods and analysis subsection of abstract shortly.

Due to the limited number of words in the abstract .the main points mentioned.

Methods: Only randomized controlled clinical trials conducted between 2000-2015 will be included in this review. This includes cluster and crossover, blinded and non blinded designs. Quasi experimental and observational studies, as well as case reports will be excluded. The studies will be selected if their participants Aged 40-60 years with elevated FSH or menstrual irregularities or both and who reported a minimum of some hot flashes or night sweats that caused discomfort. 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. Our key words will be Hop, Humulus, menopause, vasomotor, Hot Flashes, phytoestrogen . Qualitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review. 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.

- The number of hot flashes should be assessed as secondary outcome

The number of hot flashes is one of the items in Green climacteric scale .it will be assessed as secondary outcome.

- Why RevMan software won't use for data analysis as specific software for systematic reviews.

Quantitative data will, where possible, be pooled in statistical meta-analysis using Rev Man software

- It is better that subgroup meta-analysis is conducted based on menopausal status including premenopause and postmenopause

We will also consider subgroup meta-analysis such as menopausal status including premenopause and postmenopause.

-There are a number of language and grammar problems with this protocol that require editing. It was revised.

-Several references are incomplete or improperly formatted -1, 2,3, 4, 7, 12, 13, 20, 22. Some of the references may not be accessible to international readers. There may be more recent, up to date references on patient attitudes toward menopause, hormone therapy and alternative treatments that you might cite. We recently did a review of botanical therapies (for the North American Menopause Society), and could only identify 2 adequate trials of hops. I hope your 'hunting' is more successful.

1-Yazdkhasti M, Simbar M, Abdi F. Empowerment and Coping Strategies in Menopause Women: A Review. Iranian Red Crescent Medical Journal. 2015;17(3) : e18944.

2-Nosek M, Kennedy HP, Gudmundsdottir M. Distress During the Menopause Transition. Sage Open. 2012;2(3):2158244012455178.

3- Harris MT. Menopause: the need for a paradigm shift from disease to women's health. PhD thesis, Southern Cross University, Lismore, NSW.2013.

4-Rubinstein, Helena. The meanings of menopause: identifying the bio-psycho-social predictors of the propensity for treatment at menopause.Lucy Cavendish College, The University of Cambridge. 2013.

7-Crowe, Brandi. The Effects of Yoga Participation on Symptoms Associated with Menopause: A Mixed Methods Study.Clemson University. 2013. All Dissertations. Paper 1241.

12- Mascitelli L, Goldstein MR. Menopause, estrogen, statins, and the immune system. Maturitas. 2011;68(2):197.

13- Teekachunhatean S, Mattawanon N, Khunamornpong S. Short-Term Isoflavone Intervention in the Treatment of Severe Vasomotor Symptoms after Surgical Menopause: A Case Report and Literature Review. Case reports in obstetrics and gynecology. 2015;2015:962740.

20- Aghamiri V, Mirghafourvand M, Mohammad-Alizadeh-Charandabi S, 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. 2015:1-6.

1. I would like to address a few grammatical concerns throughout the protocol. The most efficient manner to do this would be for the authors to review the pdf that I have uploaded. I had added suggestions using the annotation feature.

It was revised.

2. There was a mentioning of conducting a quantitative analysis of pooled data from chosen studies which qualifies this study to be a meta-analysis. It also appears that the researchers will be doing a qualitative analysis of the synthesized results. If this is the case, I would suggest to at least mention meta-analysis earlier perhaps even in the title of the article or at least in the purpose statement.

-“Protocol for Systematic Review: Hop (*Humulus Lupulus L.*) for Menopausal Vasomotor Symptoms” was changed to “Protocol for Systematic Review and meta-analysis: Hop (*Humulus Lupulus L.*) for Menopausal Vasomotor Symptoms

3. In page 1, line 43 in the abstract, it is stated that "hop is 8 times stronger than other herbal estrogens." This needs to be clarified. Eight times stronger than any other herbal estrogen? Than the highest herbal estrogen after hop? It is just not clear.

-Hop is eight times stronger than any other herbal estrogens

4. In page 2, line 18, I would stay away from the word, 'disease'. Perhaps 'morbidity'? Or, "...process may put some women at risk of experiencing severe symptoms that could greatly affect quality of life."

-process may put some women at risk of experiencing severe symptoms that could greatly affect quality of life

5. In line 27, please change "menopause is an ongoing major health issue" to "has the potential to be an ongoing..."

-menopause has the potential to be an ongoing major health issue

6. Re line 30, You had no mention of incidence rates. I would either cut this part of the statement out or actually add some incidence rates. Alternately, state, "Due to considerable negative effects..."

-Due to considerable negative effects of menopausal symptoms

7. In page 3, line 9, do you really want to throw this negative effect of decreased sexual desire in with its positive effects?

-Due to its potent phytoestrogenic compounds and humulene, tannin, beta-myrcene, pectin, potassium, and flavonoid contents along with its ability to create estrogenic, sedative, hypnotic, antipyretic, anti-inflammatory, and antiseptic effects

8. In page 4, line 3 re types of studies, it is not clear. You may want to consider some variation of this: "Only randomized controlled clinical trials conducted between 2000-2015 will be included in this review. This includes cluster and crossover, blinded and non blinded designs. Quasi experimental (studies without controls) and observational studies, as well as case reports will be excluded." Also, there is no mention of whether studies conducted in various languages will be included or excluded.

-Only randomized controlled clinical trials conducted between 2000-2015 will be included in this review. This includes cluster and crossover, blinded and non blinded designs. Quasi experimental (studies without controls) and observational studies, as well as case reports will be excluded, studies conducted in various languages will be included .

9. Page 4, line 10 re participants, it appears that you are only interested in reported symptom experience without confirming any official state of menopause such as elevated FSH or menstrual irregularities? Perhaps you need to clarify this.

-aged 40-60 years with elevated FSH or menstrual irregularities or both and experienced at least one menopausal vasomotor symptom.

10. Re line 12, Stating "at least one vasomotor symptom" seems a bit vague. Perhaps you would want

to state, "...and who reported a minimum of some hot flashes or night sweats that caused discomfort." "At least one vasomotor symptom" was changed to "... and who reported a minimum of some hot flashes or night sweats that caused discomfort".

11. Re line 27, So you are eliminating all studies who reported any loss to follow up? This may be quite restrictive. You may want to consider a maximum attrition rate of 20% or even if you set that at 10%, you would be able to include more studies without introducing too much bias. Or perhaps clarify what you mean by a "whole course of the intervention"
--"Completed the whole course of the intervention" was changed to "At least 80% of participants completed the whole course of the intervention".

12. Re line 43, A few questions regarding inclusion and exclusion criteria. Will you include non blinded studies? Are you concerned with methods of allocation concealment in your studies that you choose?
-Studies which scored over 15 on the CONSORT checklist will be included

13. Re line 48, Re outcome, did you want to clarify this further? E.g., changes in frequency, or intensity of symptoms? Will you include different outcome measurements? ORs? HRs? etc.
-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 based on the Greene Climacteric Scale, Cooperman's index, Menopause Rating Scale (MRS), or visual analogue scale (VAS).

14. Re page 5, line 8, databases, might you consider CINAHL?
-The Cochrane Central Register of Controlled Trials.

15. Re line 25, search terms, might you consider MeSH terms?
-Search terms were changed to "Hop, Humulus, menopause, vasomotor, Hot Flashes, phytoestrogen"

16. Re page 7, line 16 re data synthesis, In regards to quantitative analysis, there is no mention of random vs fixed effects model to be used. Also, have you considered the Q statistic to test for heterogeneity? Or the I square if the sample is too small?

-Two models of meta-analysis were conducted 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 estimated the between-study heterogeneity in all of the eligible comparisons using the chi-square-based Q statistic.

17. Re lines 24-27, the sentence, "the findings..." is a little confusing. Could you make that more clear?

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.

18. Re line 31 in dissemination, it is the first mention of postmenopausal women. Please keep in mind that women who are in menopausal transition experience most of the symptoms. I would keep it consistent and adhere to menopausal women and not 'post menopausal'

-Information on experiences of menopausal women involved in previous studies may also help in future research

VERSION 2 – REVIEW

REVIEWER	Marcianna Nosek University of San Francisco School of Nursing and Health Professions United States
REVIEW RETURNED	24-Feb-2016

GENERAL COMMENTS	<p>Improvements are great!</p> <p>I gave some grammatical feedback in the first portion, but then noticed that the second part of the document contained the edited draft with highlights. Please review the first portion for edit suggestions in abstract</p> <p>Please include night sweats in your key words.</p> <p>In Introduction/background, you should say, "the aim of this study is to conduct a comprehensive..."</p> <p>In Method section (in abstract),</p> <p>Why are you saying, Qualitative papers? I think you could skip the word qualitative and just say, "Papers..." Or maybe you are trying to say, "Papers selected for retrieval will be assessed qualitatively by"</p> <p>remove the comma after 'any disagreements'</p> <p>Under types of studies, you mentioned various languages. I still think you need to specify which languages you will be willing to read and if they are not in your native tongue or a language that you are proficient in, will there be a translator? This is still too vague to say, 'various languages'.</p> <p>Under search strategies, I still think it would be wise, (if you have access) to include CINAHL—the databse that includes nursing research.</p> <p>In Introduction, I still think you should eliminate the fact that hops decreases sexual desire. Even if this is true, and you want to mention it, you should not place it in a list of benefits. Unless you mean it increases sexual desire and this is a typo. You say, you removed the decreased sexual desire, but I do not see that it is removed.</p> <p>Under Ethics and Dissemination, I think you should add at the end, "... study and healthcare providers when offering treatment for women with vasomotor symptoms." –or something of that nature.</p> <p>Reference #2 Nosek... title needs to be "Distress during the menopausal transition: A rich contextual analysis of midlife women's narratives."</p> <p>The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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VERSION 2 – AUTHOR RESPONSE

Improvements are great!

I gave some grammatical feedback in the first portion, but then noticed that the second part of the document contained the edited draft with highlights. Please review the first portion for edit suggestions in abstract.

*It was revised.

Please include night sweats in your key words.

*Keywords: Hop, Humulus, menopause, vasomotor, Hot Flashes, Night sweats

In Introduction/background, you should say, "the aim of this study is to conduct a comprehensive..."

*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

In Method section (in abstract),

-Why are you saying, Qualitative papers? I think you could skip the word qualitative and just say, "Papers..." Or maybe you are trying to say, "Papers selected for retrieval will be assessed qualitatively by"

*Prior to their inclusion in the review, the selected papers will be assessed by two independent reviewers for methodological validity

-remove the comma after 'any disagreements'

*Any disagreements will be resolved through a third reviewer.

Under types of studies, you mentioned various languages. I still think you need to specify which languages you will be willing to read and if they are not in your native tongue or a language that you are proficient in, will there be a translator? This is still too vague to say, 'various languages'.

*No particular language criterion will be defined either directly during the database search or indirectly during the evaluation of studies' reference lists.

-Under search strategies, I still think it would be wise, (if you have access) to include CINAHL—the database that includes nursing research.

*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 present)
- EMBASE (via Scopus, from 2000 to the present)
- PsycINFO
- Scopus
- ProQuest
- Google scholar
- CINAHL(via EBSCO)

-In Introduction, I still think you should eliminate the fact that hops decreases sexual desire. Even if this is true, and you want to mention it, you should not place it in a list of benefits. Unless you mean it

increases sexual desire and this is a typo. You say, you removed the decreased sexual desire, but I do not see that it is removed.

*Due to its potent phytoestrogenic compounds and humulene, tannin, beta-myrcene, pectin, potassium, and flavonoid contents along with its ability to create estrogenic, sedative, hypnotic, antipyretic, anti-inflammatory, and antiseptic effects

-Under Ethics and Dissemination, I think you should add at the end, "... study and healthcare providers when offering treatment for women with vasomotor symptoms." –or something of that nature.

*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

-Reference #2 Nosek... title needs to be "Distress during the menopausal transition: A rich contextual analysis of midlife women's narratives."

*.Nosek M, Kennedy HP, Gudmundsdottir M. Distress During the Menopause Transition. A Rich Contextual Analysis of Midlife Women's Narratives. Sage Open. 2012;2(3):2158244012455178.