Author’s response to reviews

Title: Rhodiola rosea for physical and mental fatigue: a systematic review

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Author’s response to reviews: see over
Dear Editorial team,

Re: Rhodiola rosea for physical and mental fatigue: a systematic review; MS: 1730938200582055

Thank you for the opportunity to address reviewers’ comments. We have revised our manuscript and are now resubmitting it for consideration in BMC.

Below, please find our detailed response to the reviewers’ comments. In addition when reviewing our manuscript we identified some additional necessary editing. These changes are listed after the detailed response to the reviewers’ comments.

We would be pleased to answer any questions you may have, and look forward to your response.

Regards,

Sunita Vohra MD FRCPS MSc

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Reviewer Malinee Laopaiboon’s comments and authors’ responses:

The paper is interesting but some main concerns are as followings.

1. It is unclear what is the main finding of this review and where is the review discussion.

   Response: The main findings of the review are reported in results section on page # 8. The discussion and conclusion section are added on page # 16 and 17 respectively.

2. The authors should have discussion. The section should be started with review finding interpretation, follow by agreement with others, strength and weakness of the findings, applicability and implication in clinical practice and future research.

   Response: Discussion section has been added on page # 16.

3. Sequence of the results is difficult to follow. No any treatment effect magnitude and its precision are presented. It should be presented as

   3.1) search results with some explanation of excluded papers at each screening step before having the 11 final included studies.
   3.2) description of included trial characteristics and their risk of bias result
   3.3) then effects of R. rosea for each comparison should be presented in summary statistics as mentioned in the analysis plan if possible.

   Response: We have clarified the methods and results. The description of included studies can be find in Table 1, and risk of bias results are available in Figure 1 (in the upload files section), text summary in provided on page #9. The text summary of risk of bias is moved from page # 16 to page # 9.

   Unfortunately due to heterogeneity in the intervention and outcome measurement we were not able to complete our analysis as planned.

   Since the search strategy was developed for a larger review of all rhodiola rosea indications, as now indicated in the text, a flow diagram is difficult to generate as numbers represent a larger body of literature. Numbers for the first level of title/abstract screening are particularly difficult to ascertain since they would represent a larger body of literature given the extended scope of the initial review. However the search strategy and inclusion/exclusion criteria are provided and our methods can be replicated.

4. In background
   The information of Active Constituents does not provide any benefit to the paper rationale.

   Response: Given the controversy about potential effectiveness of natural products, we prefer to retain information relating to their biologic plausibility/mechanism of action.
Minor points in Methods

5. Authors report "Study design: any experimental clinical study" in the inclusion criteria. But they report "....to identify clinical studies, experimental or observational,......" in abstract. They are not consistency.

Response: This terminology has been changed to promote clarity (page # 2 abstract, and page # 6 methods).

6. A typo in the analysis plan, ....potssssible
Response: Changed to possible, page # 8 line 17.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer Myeong Soo Lee's comments and authors responses:

This is an interesting review of R. rosea for physical and mental fatigue. The authors tried to analysis this topic comprehensively with unbiased methods. I found the used ways of analysis is too complicate to know the fact easily. The authors missed the research design, type of population, definition of outcomes, etc. The combining the evidence of mixture and single herb maybe not good and this should be analysis separately.

I commented the details as followings.

- Major Compulsory Revisions

Abstract
- Are there any differences between clinical studies and experimental?

Response: We have changed the term to clinical trials (RCTs, CCTs), page # 2 line 14-15, and page # 6 line 7.
Our systematic review was limited to clinical (i.e. human) trial data page # 6 line 8. We did not include any observational studies not did we include any basic science (animal) research.

- The conclusion should be changed according to suggested analysis

Response: We were unable to perform the planned analysis due to variability in outcome measurement and R.rosea preparations. Our discussion reflects this. We have clarified
Methods

Search strategy

1. The detailed search strategy should be noted as supplement. I’d like to know the author just searched the databases with the terms only. Did the authors not use the term ‘fatigue’? Please clarify this.

Response: Detailed search strategy is attached to the manuscript (Appendix), we suggest it is made available on request from corresponding author. We did not use the term fatigue, as we found that including this term would have resulted in a narrow search, and we would have missed relevant studies. This finding was evident during screening of title, abstract and keywords; majority of included studies did not report the term fatigue as a keyword, or in their title or abstract.

2. Is the term ‘experimental clinical study’ right? The term ‘any clinical or non-clinical’ maybe changed another words.

Response: Changed to clinical trial (RCT, CCT); page # 2 line 4, and page # 6 line 1.

3. The authors included the intervention as R. rosea as part of the intervention e.g. herbal remedy. If they did, is it possible to know the sole effects of R. rosea from the whole effects?

Response: It is not possible to know the sole effect of R.rosea from combination interventions. However our goal was to be comprehensive in our approach, and these studies were included in case they provided interesting hypothesis generating questions for future research.

4. The definition of ‘metal fatigue’ and ‘physical fatigue’ should be done.

This has been added on page # 6 line 8-14.

“Fatigue can be described as a pervasive sense of tiredness or lack of energy that is not related exclusively to exertion. Fatigue can result due to excess physical or mental activity, sleep deprivation, and poor diet or range of medical conditions including infection, and cardiovascular, metabolic, connective tissue and endocrine disorders (13). Division of mental and physical fatigue is arbitrary and often the two cannot be differentiated (13, 14, 15). As such, studies describing physical or mental fatigue were both eligible for inclusion.”

5. Risk of bias. The paragraph ‘In the first three...low risk of bias’ was old method (2008). Please update the content with new method (2011).

Response: The risk of bias tool has not been changed, but we prefer and cite what was available during the time of our study and what accurately reflects our methods.

Response: Changed to possible, page 8 line 6.

Results

7. The search flow chart should be added.

Response: Since the search strategy was developed for a larger review of all rhodiola rosea indications, as now indicated in the text, a flow diagram is difficult to generate as numbers represent a larger body of literature. Numbers for the first level of title/abstract screening are particularly difficult to ascertain since they would represent a larger body of literature given the extended scope of the initial review. However the search strategy and inclusion/exclusion criteria are provided and our methods can be replicated.

Following text is added to the methods section (search strategy):

“This systematic review stemmed from a larger review prepared for the Government of Alberta in 2007 for all potential indications of Rhodiola rosea. This review includes a subset of those studies examining R. rosea for fatigue, page# 5 line 14-16.” “The detailed strategy for all databases can be found in the Appendix, page# 6 line 2.”

8. The main limitation of this review is lack of clear definition of physical fatigue and mental fatigue. These should be defined and analysis the results according to the definition. I’d like to recommend summarizing the results with 2 outcomes, physical fatigue and mental fatigue. Although the authors summarize the results of each study in details, it is hard to know the details of the included studies such as outcomes (detailed measurement for physical and mental fatigue, their results). How’s about to summarize the outcomes such as outcome 1 for physical fatigue, outcome 2 for physical fatigue, and outcome 3 for mental fatigue, etc.

Response: We have defined these terms, and our inclusion/exclusion criteria regarding these outcomes (page #6).

In our results we have grouped studies as those reporting on physical, and mental fatigue. Studies in the physical fatigue section are further classified based on single or combined Rhodiola rosea preparations.

We however, acknowledge that the distinction of mental or physical fatigue is arbitrary and often the two cannot be differentiated (Demerlier 2003 ref # 13, Sharpe M 2011 ref # 14, Sharpe MC 1991 ref # 15).

9. I’d like to suggest that the authors analysis the included studies according to their research design-For example, R. rosea vs. control A, R. rosea vs. control B, R. rosea + treatment A vs. control A etc. I think we cannot conclude the evidence without sorting out the results according to study design, type of control. The type
of intervention is also important. We cannot combine the evidence from the results of mixture and those of single compound. The target population are also considered when the authors analysis the results.

**Response:** We agree with reviewer, however the literature in the field does not allow such. We have sorted the results in Table1, and in the text according to the type of control.

10. I think the description of each study is too wordy. The table contains much of information and the text maybe need to shorten.

**Response:** This has been shortened. As suggested by the reviewer, we have deleted information that is presented in Table 1. Some of the information is not deleted, it is moved to comply with reviewers suggestion, to organize results by Rhodiola single versus combined intervention. Table1 is also reorganized for consistency.

11. The discussion section should be separated from results section.

**Response:** Discussion section is added. We found that some of the text in our results section in the original manuscript was our analysis of the results of primary studies. We moved that text to the discussion section.

12. Please add some sentence for the authors’ conclusion for the current evidence of R. rosea for physical and mental fatigue.

**Response:** Done.

"**Conclusion**

The current evidence for efficacy of R. rosea is contradictory and inconclusive due to methodological limitations of clinical trials. Methodologically rigorous RCTs must be designed to overcome these serious threats to internal validity. Such studies will help inform policy-makers, health care providers, and the public about the efficacy R. rosea supplementation for physical and mental performance."

13. I cannot find the legends of figures.

**Response:** Figure 1, is uploaded in the upload section of manuscript submission, which shows result of risk of bias.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests.
Additional editing by authors during revisions:

1) Revision of authorship: the order of the authorship has been revised, Larrisa Shamseer is now second author, and Sana Ishaque is the first author.

2) Abstract

a. Sentence changed (previous version: Two reviewers independently screened literature identified in the search and extracted data and assessed risk of bias for included studies.) to Two reviewers independently screened the identified literature, extracted data and assessed risk of bias for included studies.

b. Result section

— “Two hundred and six articles were identified from the search of which 11 met inclusion criteria for this review” is changed to “of 206 articles identified in the search, 11 met inclusion criteria for this review.”

— “Ten were described as randomized controlled trials (RCTs) and one as a controlled clinical trial” is changed to “Ten were described as RCTs and one as a CCT.”

— Two of six trials examining physical fatigue in healthy populations report R. rosea to be effective and three in five RCTs evaluating R. rosea for mental fatigue attribute efficacy to the herb” is changed to “Two of six trials examining physical fatigue in healthy populations report R. rosea to be effective as did three of five RCTs evaluating R. rosea for mental fatigue.”

— “All of the included studies exhibit either a high risk of bias in one way or another or have reporting flaws that hinder assessment of their true validity (unclear risk of bias)” is changed to “All of the included studies exhibit either a high risk of bias or have reporting flaws that hinder assessment of their true validity (unclear risk of bias).”

c. Conclusion— “A well-designed RCT that minimizes bias is needed to determine true efficacy of R. rosea for fatigue” is changed to “A rigorously-designed well reported RCT that minimizes bias is needed to determine true efficacy of R. rosea for fatigue.”

3) Methods section (page # 5-8):

a. Search strategy

— Sentence deleted, page# 6 line 1-2 “No search filters were used.”
— Word deleted, page # 5 line 18 “collectively”

b. Inclusion criteria page # 6

— “Criteria required to include a study in the review are as follows: Study design: any experimental clinical study
Population: any clinical or non-clinical population

Intervention: Rhodiola rosea (must be at least one of the ingredients) alone or in combination with other compounds

Control: Any comparator was considered

Outcomes: 1) Mental fatigue, measured using any fatigue assessment instrument (validated or not) and 2) Physical fatigue, measured by bicycle ergometer tests or any other physical tests.

Changed to:

“The inclusion criteria for included studies were as follows: (i) study design: any clinical trial; (ii) population: any clinical human population; (iii) intervention: Rhodiola rosea alone or in combination with other compounds; (iv) control: any comparator was considered eligible; (v) outcomes: mental or physical fatigue measured by any means. Where validated instruments were used, this information was collected.”

c. Data extraction items
   — Word “was” replaced with “were,” page #7 line 17

d. Risk of bias assessment
   — Spelling of “randomisation” is changed to “randomization,” page #8 line 5.
   — Word added “and” page #8 line 8.

e. Analysis plan
   — Word added: “to” page #8 line 17.
   — Word deleted: “intervention” page #8 line 17

4) Results (page #9-20)
a. Description of included studies
   — Word added: “unique” page #9 line 3
   — Word deleted “and” page #9 line 10

b. Risk of bias
   — Moved and wording slightly changed to comply with reviewers’ comments.

c. Physical fatigue
   — Order reorganized and wording shortened to comply with reviewers’ comments

d. Mental fatigue
   — Reorganized and shortened to comply with reviews’ comments.
e. Discussion, conclusion, acknowledgements, Table1 and bibliography
   — Revised to comply with reviewers’ comments, and for consistency
   with the rest of the manuscript