Author’s response to reviews

Title: Twelve Chinese herbal preparations for the treatment of depression or depressive symptoms in cancer patients: a systematic review and meta-analysis of randomized controlled trials

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Author’s response to reviews:

Manuscript number: BCAM-D-18-00641

Manuscript title: “Chinese herbal medicine for the treatment of depression or depressive symptoms in cancer patients: a systematic review and meta-analysis of randomized controlled trials”

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Dear Dr. Adelaida M Castro-Sánchez,

We appreciate your critical comments on our manuscript (BCAM-D-18-00641). We also wish to take this opportunity to thank the reviewers for their constructive comments and valuable recommendations. Based on your and the other reviewers’ suggestions, we carefully revised the manuscript. The point-by-point responses to all comments are provided below, and the corresponding revisions are in the body of manuscript.

We look forward to hearing a favorable decision from you soon. Thank you again for your time and consideration.

Sincerely,

Menglin Li, on behalf of all authors

Responses to the Editor’s comments:

Editor’s comments:

Your manuscript can be accept for publish in BMC Complementary & Alternative Medicine following comments to authors made by the reviewers.

Responses:

We appreciate your efforts to arrange a timely review of our manuscript; thank you very much. We have carefully evaluated the reviewers’ thoughtful suggestions and critical comments, responded to these suggestions point by point, and revised the manuscript accordingly.
As you recommended, we have reread the information regarding editorial policies and made minor revisions to the manuscript (please see the Declarations section, lines 443-482, pages 21-23). We have also asked American Journal Experts for help with English language editing. In addition, we found several typing mistakes in the manuscript and have corrected each of them. These additional amendments are as follows:

1. Replacing "psychological treatments" with "antidepressants" (Abstract section, line 48, page 3)

2. Replacing "P=0.02" with "P=0.03" (Abstract section, line 56, page 4)

3. Replacing "P=0.0003" with "P=0.01" (Results section, line 255, page 13)

4. Adding "P=0.01" (Results section, line 284, page 14)

5. Replacing "P=0.008" with "P=0.02" (Results section, line 319, page 16)

We hope that our responses are sufficient to render our manuscript suitable for publication in BMC Complementary and Alternative Medicine. Thank you again for considering our submission.

Below, we address the issues raised in the reviewers’ comments.

Responses to Reviewer 1 (Abdurachman Abdurachman, Ph.D):

Reviewer’s comments:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs,
supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors.

Please omitted: Systematic review, Meta-analysis from Keywords

Responses:

Thank you for the comments; they were crucial for improving our paper. According to your suggestion, we have omitted "Systematic review" and "Meta-analysis" from Keywords (Keywords section, line 65, page 4).

Responses to Reviewer 2 (A.H.M. Khurshid Alam, Ph.D):

1. Reviewer’s comments:

The author has performed a huge computer based study. I appreciate their works though I am not clear why the author used the term Chinese herbal medicine (CHM) for this study. Does it mean all kind of CHM that are used in china has been included in this study?

Response:

Thank you for your comments. The term Chinese herbal medicine (CHM) used in this study includes single herbs, herbal products extracted from natural herbs, herbal formulae, and Chinese proprietary medicines approved by the China State Food and Drug Administration (Methods section, lines 129-131, page 7). Thus, unapproved Chinese proprietary medicines and non-herbal forms of Chinese medicine (e.g., acupuncture) were excluded from our study. In addition, we established other restrictions in terms of patients, outcome measurements and type of studies (Methods section, lines 118-140, pages 6-7). Although 2696 references were identified at first, only 18 studies fulfilled the inclusion criteria and were included in this review. In total, these
trials tested 12 different types of CHMs, including 11 types of herbal formulae and one Chinese proprietary medicine.

2. Reviewer’s comments:

Another concern is that there are a lot of bias, such as wrong information regarding age, sex type of disease and also stages of cancer, may happen such type of study. How did the author overcome those bias?

Response:

Thank you for your comments.

First, I must apologize for my carelessness. There were two typing mistakes in Table 1: Characteristics of the included randomized controlled trials (Row 2, column 3, page 31 and Row 8, column 3, page 31). We have corrected the errors by replacing "T: 4.1±6.3" with "T: 64.1±6.3" and by replacing "C: 53.4±16.8" with "C: 52.6±15.7".

As you might have noticed, the quality of the trials included in our review was generally low. Most of these trials were characterized by poor methodological quality and inadequate reporting. These flaws are potential risk factors that may induce bias in the results of our study. To overcome the bias produced by incorrect information reported in the trials, we checked every record very carefully and contacted the authors if necessary. We discovered no obvious mistakes during the checking process. What we did notice is that many trials did not provide comprehensive and transparent reporting. We tried to contact the authors by email or by telephone; however, only one author responded to us, and she could not provide useful information since “she was not familiar with the details of the study design”. Although she promised to call me back, she has not answered my phone calls since then.

The corresponding amendments are listed below.
1. An explanation was added to the Methods section: “Given that many of the studies might have been conducted without registration, we checked their Methods and Results sections to assess reporting bias. In addition, we contacted the authors of assessed trials for clarification if necessary.” (lines 183-185, page 9).

2. The results of these contacts with the authors were reported: “Unfortunately, we could not obtain additional useful information by contacting the authors.” (Results section, lines 242-243, page 12).

We admit that the high risk of bias made the results of our study uncertain. However, we have made every effort to address these issues, and we have made some suggestions regarding how to improve the quality of clinical trials (Discussion section, lines 402-415, pages 19-20). We sincerely hope that you can understand the situation we faced. Thank you again for your time and consideration.

3. Reviewer’s comments:

Some minor corrections are also need. These are as follows:

page 4, lines 70-76, author need to rearrange the sentence as simple and petite form so that general reader can understand it clearly. Author need to give attention such type of sentences through out the manuscript.

Response:

Thank you for your comments and recommendations. We have asked American Journal Experts for help with English language editing. With the assistance of a native English speaking editor, we have made several corrections. The main amendments are listed below:

1.
Original version:

“Due to their reactions to their cancer diagnosis, the suffering of unpleasant symptoms related to cancer, their concerns about disease progression, and the physiological effects of certain anticancer treatments, cancer patients might be vulnerable to depression or other depressive conditions; the prevalence of depression and other depressive conditions is estimated to be 16.5% in palliative care settings and 16.3% in non-palliative care settings.”

Revised version:

“Despite these gains in cancer treatment, long-term behavioral co-morbidities, such as depression or other depressive conditions, are prominent. Reactions to the cancer diagnosis, unpleasant symptoms related to cancer, concerns about disease progression, and the physiological effects of certain anticancer treatments can all increase patients’ susceptibility to depressive symptoms. According to a meta-analysis of 94 interview-based studies, the estimated prevalence of depression and other depressive conditions was 16.5% in palliative care settings and 16.3% in non-palliative care settings.” (Background section, lines 69-76, page 4).

2.

Original version:

“Each included trial was independently assessed for the risk of bias using the criteria described in the Cochrane Handbook version 5.1.0 by the authors, with any disagreements resolved by discussion with a third party.”

Revised version:

“Each included trial was independently assessed for the risk of bias using the criteria described in the Cochrane Handbook version 5.1.0. The assessments were performed by the authors, with any disagreements resolved by discussion with a third party.”(Methods section, lines 177-179, page 9).

3.

Original version:
“In total, the included trials tested 12 different types of herbal medicines, among which Xiao Yao decoction or its modifications were the most frequently used, accounting for 22.2% of the total number of formulae tested.”

Revised version:

“In total, the included trials tested 12 different types of herbal medicines. Among these, Xiao Yao decoction or its modifications were the most frequently used, accounting for 22.2% of the total number of formulae tested.” (Results section, lines 215-217, page 11).

4.

Original version:

“In conclusion, the evidence indicated that treatment with CHM could alleviate depressive symptoms alone, as well as develop synergistic effects with antidepressants or psychological treatments.”

Revised version:

“In conclusion, the evidence indicated that treatment with CHM could alleviate depressive symptoms when used alone and could have synergistic effects when combined with antidepressants or psychological treatments.” (Conclusions section, lines 418-420, page 20).

4. Reviewer’s comments:

Page 7, line 108-111, Author need to incorporate references (Although clinical studies regarding the use of CHM for depression or depressive symptoms in cancer patients.........................)

Can check the manuscript by a native English speaker.
Response:

Thank you for your comments. We have incorporated several references for this sentence (Background section, line 111, page 6).

Once again, thank you very much for your comments and suggestions.