Author’s response to reviews

Title: Safety classification of herbal medicines used among pregnant women in Asian Countries: A Systematic Review

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Author’s response to reviews:

Dear Editor,

Thank you very much for the comprehensive and useful review of the paper. The suggested revisions have made in the revised manuscript and highlighted in Red color. Point-by-point response to the reviewers’ comments is given below.

Reviewer reports:

Reviewer #1:

Comment:
In the title please consider rephrasing the word "concerns" since there is little evidence about the negative effect of herbal remedies in pregnancy
Response:

The title is changed in the revised version (page 1, line 1).

Comment:

By reading the Aims, the reader gets the impression that the literature review has been done on prospective cohort or case-control studies that assessed pregnancy outcomes following in utero exposure to herbal remedies. However, later on in the paper, it becomes evident that the paper had two distinct aims: first, to systematically review the literature to obtain information about the most commonly used herbs in pregnancy in the Asian countries; second, to assess the safety of these common herbs using three references sources. Please consider structuring the Aims and the Methods section accordingly to enhance clarity.

Response:

The Aims (page 4, lines 71-84) and Methods (page 6, lines 94-100) are restructured in the revised version.

Comment:

Please rephrase the aim according to my previous comment, since this paper was not a systematic review of the literature on prospective and/or case-control studies assessing the safety of herbal remedies. In the conclusions the authors state that none of the reviewed studies assessed adverse effects of herbal remedies in pregnancy; I feel this is not surprising since the authors only reviewed cross-sectional studies, which cannot assess any measure of negative effect of herbs on maternal-fetal health.

Response:

The Background (page 2, lines 30-33) and Conclusions (page 2, lines 46-50) of the Abstract have been revised.
Comment:

Background: Line 64-67: would it possible to indicate what herbal remedy/remedies were found to increase the risk for SGA and miscarriage?

Response:

The suggested description has been added in the revised version (page 4, lines 68-70).

Comment:

I feel the Methods section should be better organized in light of my first general comment. Please consider removing or shortening the text from line 85 to 90 since this goes beyond the scope of the investigation. The authors should consider to describe in a better way why and for what purpose they chose to restrict the review to cross-sectional studies.

Response:

The unnecessary description has been removed and the suggested description has been added in the revised version (page 6, lines 94-100).

Comment:

The author also assessed the quality of the cross-sectional studies included, however there is no information on how these studies defined a herbal modality. Was the definition comparable across studies? How did the authors ensure that all these studies used same definition of herbal remedy?

Response:

The description regarding definition of the herbal medicines used in the reviewed studies has been added in the revised version (page 8-9, lines 157-161).
Comment:

Line 94: please indicate whether two or more independent persons did the literature search.

Response:

The suggested description has been added in the revised version (page 6, line 102).

Comment:

The section on the Safety Documentation of Identified Herbs should be more systematically described. First, the authors should describe why and how these three references sources were chosen to assess the safety of herbal remedies. These sources may be out of date given their publication dates (2004 and 2007). In a previous study (Kennedy et al., 2016) classifying the safety of herbal remedies in pregnancy in a European, American and Australian population the following sources were used: the textbooks "The Essential Guide to Herbal Safety", "Herbal Medicines in Pregnancy & Lactation", "Botanical Safety Handbook", and "Botanical Medicine for Women's Health", with addition of the Natural Medicines database. If a particular herbal medicine was not listed in the above mentioned reference sources, additional sources were used; Handbook of Medicinal Herbs and PDR for Herbal Medicines. Could any of these sources be relevant for the current study?

Response:

The suggestion section has been revised (page 6-7, lines 112-130).

Comment:

Please consider using PubMed/EMBASE to search for safety studies on herbs rather than Google Scholar. The way these search were conducted should also be described in a more appropriate way.
Response:

As suggested, PubMed/EMBASE (page 7, lines 123-125) was used instead of Google Scholar and the search strategy is presented in Additional file 1 as Table S2.

Comment:

The authors should consider stating what criteria were applied when discordant information was given in the sources on the same herb. Was any of the reference sources used as primary?

Response:

The suggested statement has been included in the revised version (page 7, lines 119-122).

Comment:

The authors should also consider describing what it is defined by the letter classification A, B, etc. in the Methods (and not only as footnote in the Tables). If this letter system is derived from the FDA risk categorization, this should be clearly stated. However the FDA has since 2016 a new classification system for medication exposures in pregnancy, since the letter system was obsolete and not informative.

It is unclear to the reader on what ground the final "potentially harmful" classification was based; did it consist of any letter category other than A? If this is the case, I feel it will produce misleading results, particularly in relation to category B. Beyond, as stated above, the letter risk categorization is not so informative in terms of what is known on the safety of medication exposures in pregnancy.
Response:

The ABC letter classification was not derived from the FDA risk categorization. In order to remove the confusion, the letter classification has been deleted in the revised version. Instead, based on a recently published study (page 7, lines 128-130), the description of each classification category is presented in the Table 1.

Comment:

It would be relevant to provide information on the plant part, type of extract, dose form, dosage etc. if that was available from the reviewed studies. This information should also be considered in terms of safety assessment of herbs. Same comment applies to the timing of use of the assessed herbs in pregnancy. The risk for congenital anomaly, for instance, may not be relevant when the herb is taken in the third trimester.

Response:

The suggested information was missing in the reviewed studies and it is described as one of the limitations in the revised version (page 13, lines 263-266).

Comment:

The authors classified 18 out of 31 herbs as potentially harmful. I find this proportion quite high. I feel this is a consequence of the reference sources used. For instance, in the study by Kennedy et al. (2016), "peppermint" and "chamomile" were classified as safe herbs in pregnancy when the reference sources listed earlier were used. Could the author expand their safety assessment using more reference sources, such as text books specifically on herbal exposures in pregnancy?

Response:

As suggested, the safety assessment was expanded using more reference sources (Methods: page 6-7, lines 112-130). As a result, all the herbal medicines were categorized again as shown in Table 5.
Reviewer #2:

Comment:
You said that Peppermint, aniseed and olibanum were the most frequently used and were among the modalities classified as potentially harmful to use in pregnancy but these plants in normal dose not harmful only in large doses and if the pregnant women took them for treatment of heartburn or spasm are not harmful as well as many of prescribing heartburn drugs for pregnant women contain peppermint kindly clarify this point.

Response:
Thanks for highlighting this issue. As suggested by the Reviewer 1, the safety assessment was expanded using more reference sources (Methods: page 6-7, lines 112-130). As a result, all the herbal medicines were categorized again as shown in Table 5. Moreover, the description regarding normal dose is added in the revised version (page 12, lines 224-225).

Comment:
Also the references style is not fit for this journal for example the journal names must be in abbreviated form, look at this journal endnote style or at the last published papers in this journal.

Response:
As suggested, the reference style is revised according to this journal.

Comment:
Also look at the attached requested corrections
Response:

The suggested minor corrections are also made in the revised version.

Reviewer #3:

Comment:

The results of the study is interesting but more standard searching methodology and reporting formats are necessary. For example, PRISMA for systematic reviews, Newcastle Assessment for quality of the studies, FDA or EU categories of the drugs for pregnancy, etc.

Response:

The necessary description regarding standard methodological formats used in the study is presented in the revised version (page 5, lines 86-89).

As far as the FDA or EU categorization of the drugs, the Reviewer 1 suggested that ABC categorization may produce misleading results. Therefore, based on a previous study, which used combination of standard mechanisms for categorization of drugs, the herbal medicines were categorized again. The necessary description is given in the revised version (page 7, lines 128-130).

Comment:

"herbal medicine" and "herbal modalities" had been sued in the title, abstract and main text. To avoid confusion and misunderstanding, it is better to sue "herbs" only.

Response:

Thanks for the comment. Because herbal medicines may include individual herb or mixture of different herbs, it would also be confusing to use term “herb” only. Therefore, we preferred to
use term “herbal medicine(s)” throughout the paper. This description is given in the revised version (page 7, lines 131-133).

Comment:
For the frequency of the herbs used, please use % instead of exact numbers.

Response:
The suggested information is added in Table 4 in revised version.

Comment:
In abstract, no adverse effects has been identified. please include the information in Result section, rather than conclusion.

Response:
Thanks for the comment. As suggested by the Reviewer 1 & 2, Results and Conclusion of the Abstract have been revised (page 2, lines 39-50).

Comment:
Table 2, please include the study location, source of study subjects, etc.

Response:
The suggested information has been added in now the Table 3 of revised version.
Comment:
If possible, please indicate which stage of pregnancy or gestational period the herbs were used during pregnancy in Table 3.

Response:
Thanks for the comment. This information was available only for three studies and it is added in now the Table 4 of revised version. Moreover, this limitation has also been stated (Discussion: page 13, lines 265-266).

Comment:
Table 4, please indicate the documentation of safety were from human or animal studies?

Response:
Thanks for the comment. The suggested information is given in now the Table 5 of revised version.

Comment:
Figure 1, please state the reason of excluded from title or abstract.

Response:
Thanks for the comment. The reason has been stated in the revised Figure 1.

Comment:
Figure 2-4, please combine
Response:

As suggested, the information is combined in now the Figure 2.