Author’s response to reviews

Title: Network Pharmacology Approach to Uncover the Mechanism Governing the Effect of Radix Achyranthis Bidentatae on Osteoarthritis

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Author’s response to reviews:

List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Network Pharmacology Approach on the Mechanism of RAB in Osteoarthritis” (ID: BCAM-D-19-01738). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

The responds to the reviewer’s comments and the main corrections in the paper are as following:

Reviewer #1:
1. Do not use abbreviation in the title.
Response: Thank you. As Reviewer suggested that abbreviation should not be used in the title. We have revised.
2. Roadmap of the study should be provided.
Response: Considering the reviewer's suggestions, we have added Roadmap of the study. This is really a good suggestion and makes the process of our work clearer. The specific information is shown in Fig.1.

3. There are some typo errors.
Response: Thank you. We are very sorry for our incorrect writing. We have revised the typo error in the article.

4. The discussion focused mainly of RA and ignored the RAB.
Response: Thanks for your comment. We discussed RAB further during the discussion.

5. Section of the introduction should be extended.
Response: Thank you. We supplemented the presentation.
1. Complement the introduction of OA, such as epidemiological studies of OA.
2. Background knowledge of RAB and the mechanism by which RAB plays a role in OA.
3. The background knowledge of network pharmacology was supplemented, and the superiority of Chinese medicine was studied through network pharmacology.

Reviewer #2:
Main comments:
1. The Introduction is very short. There is not enough background knowledge currently known about RAB other than it is the most frequently used than other herbs for treating OA. The authors need to provide more comprehensive background about the RAB, to the level of currently known in the literature. The authors claimed, "the mechanism of RAB in OA is still unclear."; however, the authors should also provide what's currently known or proposed in the published literatures about the potential mechanisms of RAB. The same thing applies to the "network pharmacology", for which more details are needed.
Response: Thank you very much for your careful review, which has benefited us a lot. First of all, we supplement the background knowledge of RAB. Further, according to the reviewers' suggestions, we have supplemented the potential mechanism of RAB in the treatment of OA. And the relevant content of network pharmacology is further supplemented.

2. It is not clear how comprehensive and relevant to the collected genes from GeneCard and OMI with respect to OA. Besides, the scope of "OA-related" needs to be clearly defined. It is also not clear how they were actually collected. More details are needed, and a complete table (supplementary table) would be needed to list all the collected genes along with their detailed information, the method of collection, and the link to the source pages.
Response: Thank you. We expanded the search scope and carried out a comprehensive collection of OA genes. " OA relate "is our writing error and does not express the meaning clearly. What we want to say is that the genes collected are related to OA. We have problems in language expression. The extended search enriches our disease target database. Thanks to your careful review. In addition, more detailed supplementary forms have been uploaded.
3. Response to comment: What was the rationale of selecting the top eight targets as the most important targets?
Response: Thank you for your review. We initially selected the top eight targets as important targets based solely on the Degree value. The reviewer's reply made us realize that this was inappropriate. To find the most important targets, we chose more parameters. Get parameters through Cytoscape plugin CytoNCA. Parameters include, DC, BC, CC, EC, NC, and LAC. A node with high DC, BC, CC, EC, NC and LAC values means that it plays a very important role in the network. In the end we selected 7 targets including MAPK8, IL6, VEGFA, EGFR, MYC, CCND1, CASP3. Many thanks to the reviewers for making our research more scientific.

4. Response to comment: The authors claimed that the larger the degree, the more likely this target will become a key target for compounds. This statement needs to be justified. And there are other measures of node importance such as betweenness, closeness, eigen vector and etc. Why was only the network degree used in the study?
Response: Thanks to the reviewers for their attention. In network, we built the target-compounds network. In addition, we no longer use degree as a filtering parameter. Instead, we build PPI network to obtain key targets. Just as we responded to the third comment.

5. Response to comment: There is no statistical evaluation of the resulting network. How significant the constructed network is different from random networks? Like the significance of node significance needs to be evaluated using random models and compared against those from the constructed network.
The suggestions of the reviewers provide a good point for our future research. In fact, we did not complete the current study. After understanding, we found that it is an indispensable work to predict the disease of drug treatment through the method of network pharmacology prediction. Through the integration of network search algorithm, data standardization algorithm, biological activity prediction algorithm and related software, the network prediction model can be established, which can quickly and stably screen out the target or target combination or subnet with strong structure and function correlation, and carry out the research of network pharmacology. Common methods include least square, partial least square, Boolean network, linear modeling, weighted matrix models, Bayesian network, rbfnetwork, random forest, random walk calculation Method (random walk), price algorithm and differential equation. We do our best to achieve this. But it's a great pity that we didn't finish the work. Our next work will focus on this research and improve our research. Thank you very much for the reviewer's opinion, which is very helpful to our research.
Thank you. In terms of statistical evaluation of significance, we referred to previous relevant literature (Methods section eg. References 16, 18, 21-22) when conducting the tests. We are not aware of random models/networks approach but would be happy to consider revising if the reviewer can provide specific referencing literature.

6. Response to comment: Why was the docking analysis limited to certain compounds and targets? This needs to be extended to all pairs.
Response: Thanks to the reviewers for their attention. We docked all compounds and key targets.
7. The writing needs to be substantially improved. Using a professional language editing service is highly recommended.
Response: Thank you. We have engaged a native speaker to polish the professional presentation and the language. If the editor strongly recommend the use of professional editorial service, we would be happy to accept the suggestion.

Minor comments:
1. Response to comment: The authors better not capitalize "Network Pharmacology".
Response: According to reviewers' comments, we have been revised.

2. Response to comment: I would recommend the authors to consider having a workflow (diagram) to illustrate the overall approach.
Response: We used workflow (diagram) for job description.

3. Response to comment: The definition of 'interaction' in this study needs to be clearly defined.
Response: The reviewer's question pointed out the inadequacy of our research. We specifically point out the definition of 'interaction'.

4. Response to comment: Acronyms must be defined before being used.
Response: We checked and revised the full text of acronyms.

5. Response to comment: Table 2 Potential targets information of RAB for OA is not informative. Instead of just item numbers, including other information, such as protein name and IDs and OMIM ID, is highly recommended.
Response: We have added more detailed information. Including: Gene Symbol, OMIM ID and Description.

6. Response to comment: Term selection better be consistent throughout the manuscript. E.g. sides vs edges.
Response: We are very sorry for our incorrect writing. We proofread the terminology of the whole paper.

7. Response to comment: Most figures are missing legends and of low-quality. They are not readable.
Response: We add legends to figure 1-7. In addition, the image quality has been improved.

8. Response to comment: References do not follow the style of BCAM.
Response: For references, we used the style of BCAM.

9. Response to comment: Lines 242 - 244. It would be better to give the actual Figure number (network).
Response: We have uploaded the detailed information as supplementary materials.

10. Response to comment: Multiple paragraphs include only one sentence.
Response: We have revised the sentence of the whole paper.
11. Response to comment: It is not clearly justified why the Protein-Protein interaction networks among the targets are important.
Response: This question has important value to improve our work. This problem involves a lot of knowledge. As for the answer to this question, we have consulted the literature, and based on our own understanding, we have given our reply. Protein protein interaction (PPI) is the basis of cell function and plays an important role in regulating physiological and pathological state of the body. Protein interaction network (PIN) is a network constructed by protein interaction information. Network nodes usually represent protein, network connecting lines represent protein protein interaction, and node size, color, connection length and thickness represent topological parameters of node network. In the target, protein interaction is of great significance to explore the possible mechanism of traditional Chinese medicine in the treatment of diseases. Through the construction of protein network, we can directly see the relationship between the targets. It is significant to explain the complexity and diversity of traditional Chinese medicine in human body. Of course, the above is just our brief explanation. The action of traditional Chinese medicine on human body is complex, which needs further study.

12. Response to comment: The complete compound - target pair information needs to be provided as Supplementary Table.
Response: We supplemented the information and uploaded it as Supplementary Table.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.
We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions.