Author’s response to reviews

Title: Investigating the multi-target pharmacological mechanism of danhong injection acting on unstable angina by combined network pharmacology and molecular docking

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Author’s response to reviews:

Dear Prof.:

Thank you very much for your critical comments on our manuscript and recognition in traditional Chinese medicine. We have carefully corrected our submission, and amended manuscript were resubmitted. A point to point response was answered below:

Editor Comments:

Thanks for the reviewers' insightful comments. Please revise the manuscript carefully according to the comments. The similarity score of your ms is 30%, which must be decreased after revision.
Answer: Thank you for your comment. We have revised the manuscript carefully according to the comments. In addition, we have modified some sentences in the manuscript, hoping to decrease the similarity score. We hope that it will meet your criteria.

Reviewer 1:

1. Line 98, the word "Structure" in "Identification of DHI Compound Structures" could be removed due to just the identification of compounds.

Answer: Thank you for your suggestion. We have already removed the word "Structure" in "Identification of DHI Compound Structures" and marked them with red. We hope that it will meet your criteria.

2. Line 101, "After deleting duplicate data, a total of 12 major compounds were collected as candidate compounds" could be moved to the Results section. Additionally, what is the criteria for determining these 12 compounds as major components?

Answer: Thank you for your suggestion. We have already moved "After deleting duplicate data, a total of 12 major compounds were collected as candidate compounds" to the Results section and marked them with red. We hope that it will meet your criteria.

The criteria for determining these 12 compounds as major components as follows: (1) Qualitative and quantitative analysis of DHI was performed by liquid chromatography coupled with orbitrap mass spectrometry; (2) Quantitative analysis method validation was in accordance with ICH guidelines; (3) There are more literature reports; (4) The compounds have high content and biological activity.

3. Lines 110-111, "After supplementing and eliminating the targets obtained in the above three databases, a total of 372 compound-prediction targets were identified." should belong to Results and could be move to the Results section.

Answer: Thank you for your suggestion. We have already moved "After supplementing and eliminating the targets obtained in the above three databases, a total of 372 compound-prediction targets were identified." to the Results section and marked them with red. We hope that it will meet your criteria.

4. Line 136, what does "The putative UA/compound targets" refer to? Does it indicate the common targets between UA and the targets predicted by compounds?

Answer: Thank you for your comment. "The putative UA/compound targets" refer to the common targets between UA and the targets predicted by compounds.

5. Lines 155 and 156, it is necessary to briefly explain the meaning of these parameter settings.
Answer: Thank you for your suggestion. MCODE algorithms can find dense regions of interaction in PPI networks based on complex connection data [1]. In addition, we identified the dense regions according to the default parameters of MCODE (Degree Cutoff=2; Node Score Cutoff=0.2; K-Core=2; Max. Depth=100) [2], and analyzed the most important functions of the hub genes in each significant module. We marked them with red in manuscript. We hope that it will meet your criteria.


6. Line 159, what is the role of Functional Enrichment Analysis could be briefly introduced?

Answer: Thank you for your comment. Through enrichment analysis of gene functions, this study is expected to find biological pathways that play a key role in the biological process, so as to better reveal and understand the potential molecular mechanism of DHI in treating UA [1]. In this study, the R 3.6.1 software with the Bioconductor package was used to analyze the GO function and KEGG pathway of the main target genes of DHI in the treatment of UA.


7. Lines 180-181, what is the screening criteria for 12 compounds?

Answer: Thank you for your comment. The screening criteria for 12 compounds as major components as follows: (1) Qualitative and quantitative analysis of DHI was performed by liquid chromatography coupled with orbitrap mass spectrometry; (2) Quantitative analysis method validation was in accordance with ICH guidelines; (3) There are more literature reports; (4) The compounds are high in content and biological activity.

8. Line 182, what is the method used to predict the targets with these compounds?

Answer: Thank you for your comment. In this study, the SuperPred (http://prediction.charite.de/), SwissTargetPrediction (http://www.swisstargetprediction.ch/) and BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm/) were adopted to find potential targets of compounds. The method is mentioned in Screening Compound Targets for DHI section.

9. Lines 198-199, "According to average degree value &gt; 10, average betweenness &gt; 0.024 and average closeness &gt; 0.44," what are real meaning of average degree value, average betweenness, and average closeness? Are the meanings of degree value, betweenness and closeness greater than their averages?
Answer: Thank you for your comment. The “degree” is regarded as the number of edges connected to it. The “betweenness” indicates the amount of shortest paths that go through a given node. Besides, the “closeness” emblematises the inverse of the sum of the distances from one node to the other. If the degree value, betweenness and closeness of the points are all greater than their mean value, it indicates that they are relatively important in this network [1].


10. Line 215, the authors performed GO and KEGG analysis on the PPI and 3 modules, but only listed the results separately, which was relatively scattered, and did not integrate the results. It is necessary to clarify which processes the overall effect of DHI is.

Answer: Thank you for your suggestion. We have already added the processes that is the overall effect of DHI and marked them with red. We hope that it will meet your criteria.

11. Line 246, how high value of binding affinity can be considered as a large binding force?

Answer: Thank you for your comment. Studies have shown that the smaller the binding affinity value, the better the binding stability [1, 2]. But through our literature review, we didn't find how high value of binding affinity can be considered as a large binding force. After reflection, we found that the Line 246 statement was not cautious enough, so we deleted it. We hope that it will meet your criteria.


12. Line 260, what is the relationship between chagas disease (American trypanosomiasis) and UA?

Answer: Thank you for your comment. It is difficult to propose a satisfactory explanation for the relationship between chagas disease (American trypanosomiasis) and UA based solely on the data in this study. According to the data from this study, it is shown that key targets of UA can be enriched in the chagas disease (American trypanosomiasis) pathway.

However, Bestetti's report indicated that chagasic patients may develop UA. What’s more, there was no difference in the incidence of unstable angina before acute myocardial infarction when chagisic was compared with non-chagisic patients [1].
Reviewer 2:

1. Can all the 12 chemical components mentioned in the manuscript be detected in Danhong injection? In addition, are these 12 ingredients the main active substances in Danhong injection?

Answer: Thank you for your comment. All the 12 chemical components mentioned in the manuscript can be detected in Danhong injection [1]. These 12 ingredients are the main substances in Danhong injection and have biological activity. For instance, salvianolic acid B could inhibit myocardial cell apoptosis and salvianolic acid A exhibits anti-thrombotic activity [2]. Rosmarinic acid has anti-inflammatory and antioxidant activities [2]. Hydroxysafflor yellow A shows endothelium cell protection and cardiovascular effects [3]. Cytidine and uridine exhibit antihypertensive activities [4].


2. The figures are not clear. Please notice that all the figures must be submitted in high resolution (300 x 300 dpi or more) TIFF format.

Answer: Thank you for your suggestion. We have uploaded pictures with a resolution of 400dpi. We hope that it will meet your criteria.

3. It seems that there are no captions under the figures. Please add the captions for each figure.

Answer: Thank you for your suggestion. We have added the captions for each figure and marked them with red. We hope that it will meet your criteria.
4. In Table 1, the molecular formula of each compound should be provided and the resolution of the structure must be improved.

Answer: Thank you for your suggestion. We have added the molecular formula of each compound and improved the resolution of the structure in Table 1. We marked them with red. And we hope that it will meet your criteria.