Response Letter

Dear Editors and Reviewers,

Thank you for giving us the opportunity to revise our manuscript with Manuscript ID: 95055. We are grateful for the encouraging comments and constructive suggestions provided by Reviewers 1 and 2. We have addressed their questions point by point and have uploaded the revised manuscript. The revisions were made precisely in accordance with the reviewers' suggestions, and all changes have been highlighted in yellow in the revised manuscript. Additionally, the manuscript has been reviewed and edited by AJE’s language services to ensure clarity and correctness. We have exerted our best efforts to make the revisions clear and hope that the revised manuscript meets the publication standards. We kindly request that you review the revised manuscript again.

Response to the comments of Reviewers

Reviewer #1:
This is a potentially significant paper. This study represents a contribution to the field of integrative pharmacology, particularly in the context of diabetic kidney disease (DKD) treatment. The authors have undertaken a heavy workload, employing a comprehensive approach that integrates network pharmacology, molecular docking technology, and molecular dynamics simulation. This rigorous methodology underscores the depth of their investigation into the material basis and mechanism of action of the Astragalus-Coptis drug pair in treating DKD. This study not only advances our understanding of the molecular mechanisms underlying the therapeutic effects of the Astragalus-Coptis drug pair but also demonstrates a novel approach that could be applied to other traditional Chinese medicine formulations. A very nice study with comprehensive set of work.

Question 1: The discussion briefly mentions the implications of the study findings, such as the identification of Quercetin as a potent active ingredient
targeting AKT1 and TNF. However, it could be expanded to include a more in-depth analysis of the potential clinical relevance and therapeutic implications of these findings. Discuss how targeting AKT1 and TNF with Quercetin may impact the pathogenesis or progression of DKD and how this could inform future research or clinical practice.

Response from the Authors: Thank you for your insightful comment and kind suggestion. Currently, there is a lack of relevant experimental studies investigating the impact of quercetin on AKT1 and TNF in DKD treatment. However, animal studies have demonstrated that quercetin improves renal function in DKD animals, reduces oxidative stress levels, and alleviates inflammatory responses in the kidneys [1]. Furthermore, a network pharmacology study predicted that the epidermal growth factor receptor (EGFR) is a potential physiological target of quercetin. This finding was confirmed by in vitro and in vivo experiments, which showed that quercetin inhibits the activation of the EGFR signaling pathway by reducing the phosphorylation of EGFR and ERK1/2, mitigating podocyte apoptosis, and improving DKD [2]. This study utilized network pharmacology, molecular docking, and molecular dynamics to predict that quercetin binds stably to AKT1 and TNF, identifying them as potential therapeutic targets. AKT1 and TNF are implicated in core pathways such as the AGE-RAGE signaling pathway in diabetic complications and the Lipid and atherosclerosis. Consequently, quercetin may modulate these core pathways by targeting AKT1 and TNF, potentially influencing advanced glycation end products and lipid metabolism, thereby enhancing the improvement of DKD. The aforementioned findings will serve as a guiding framework for future experimental validation in vitro and in vivo. The aforementioned content has been incorporated into the DISCUSSION section of the paper and is highlighted in yellow in the revised manuscript. (DISCUSSION. The sixth paragraph) Thank you once again.

Please see the reference:
Reviewer #2:
In this paper, the authors adopted a comprehensive approach integrating network pharmacology, molecular docking technology, and molecular dynamics simulation was adopted to elucidate the material basis and mechanism by which Astragalus-Coptis drug pair treats DKD. One of the strengths of this study is the clarity and coherence of the data presented. The findings are well-organized and clearly elucidate the characteristics of multiple ingredients, targets, and signaling pathways involved in the treatment of DKD with the Astragalus-Coptis drug pair. The identification of Quercetin as a potent active ingredient, specifically targeting AKT1 and TNF, is particularly noteworthy. This finding not only provides a theoretical foundation for further exploration but also offers potential therapeutic avenues for DKD treatment. Overall, this manuscript is well-organized and the topic is of great significance.

Question 1: In the method 1.2, please check the “|logFC| > 1”, is it log2FC?
Response from the Authors: Thank you for your kind suggestion. The authors are sorry for our careless mistakes. The confirmation of |log2FC| was obtained through a comprehensive review of relevant literature and consultations with experts in the field[1]. As recommended by the reviewer, we have made the change from |logFC| to |log2FC| in the revised manuscript and highlighted the modification in yellow. (MATERIALS AND METHODS. The second paragraph)Thank you once again.
Please see the reference:


Question 2: The font in all the figures of this article needs to be adjusted and enlarged, so that readers can easily obtain the information.

Response from the Authors: Thanks very much for the good suggestion. We have adjusted and enlarged the figures involved in the paper, and made appropriate adjustments to the font size. Furthermore, we have incorporated high-definition figures related to the article into a PowerPoint file, which has been uploaded to the system, ensuring convenient access to information for readers. Thank you once again.

Question 3: In Supplementary Figure 2 A-C, please indicate the meanings represented by red and cyan.

Response from the Authors: Thanks very much for the good suggestion. The colors red and cyan both represent receptors, with A, B, and C representing AKT1, TNF, and MAPK3, respectively. The gray color represents the ligands, where A, B, and C correspond to quercetin, quercetin, and obacunone, respectively. The aforementioned modifications have been incorporated into Supplementary Figure 2 in the revised manuscript and are emphasized using yellow highlighting. Thank you once again.

We sincerely appreciate the warm and diligent work of the Editors/Reviewers and hope that the corrections will meet with your approval. Once again, thank you very much for your comments and suggestions. Please do not hesitate to contact us for further questions.
Yours sincerely,

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