

Dear Editor and Reviewers,

We highly appreciate the detailed valuable comments of the referees on our manuscript (Manuscript NO: 77131), entitled “Review of the pharmacological effects of astragaloside IV and its autophagic mechanism in association with inflammation” (by Ying Yang, Meng Hong, Wenwen Lian, Zhi Chen). Following the advice, we have made revisions in response to the very helpful and positive suggestions. As below, on behalf of my co-authors, I would like to clarify some of the points raised by the Reviewers. We have uploaded the revised manuscript in two files, a “AS-IV review. Manuscript File with Tracked Changes, WJCC” file with the changes highlighted in blue and a “AS-IV review. Revised Manuscript, WJCC” file with line numbers that has been revised but without tracked changes. And we hope the Reviewers and the Editor will be satisfied with our responses to the comments and the revisions for the original manuscript.

Thanks and Best Regards!

Yours sincerely,

Ying Yang

05/23/2022

Manuscript No. 77131

Title: “Review of the pharmacological effects of astragaloside IV and its autophagic mechanism in association with inflammation“

Authors: Ying Yang, Meng Hong, Wenwen Lian, Zhi Chen

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Response to reviewers:

General Comments:

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report.

Response: Thanks very much. We have made a point-by-point response to each of the issues raised in the peer review report.

Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: The article presented by Ying Yang and collaborates, entitled “Review of the pharmacological effects of astragaloside IV and its autophagic mechanism in association with inflammation”, is a review that aimed to summarize the structure, solubility, pharmacokinetics, toxicity, pharmacological effects, and autophagy mechanism of *Astragalus membranaceus* Bunge (AS-IV). The revision contains relevant and updated information but needs to improve the forms. It is perceived that it has been written by different authors because there is no consistency in the way of addressing proteins or genes. Little care of the formal aspect. Although it includes a table and a figure. The table is very large making it impractical and with misspellings. The same goes for the figure. **Major revision: 1.** Authors should summarize findings in separate tables by tissue for ease of reading. Table 1 is too big, it is split on different pages and it mixes fabrics: a. Protective effect of AS-IV on cardiovascular disease b. Protective effect of AS-IV on the brain and nervous

system c. Protective effect of AS-IV on lung disease d. Protective effect of AS-IV on diabetes e. Protective effect of AS-IV on organ injury f. Protective effect of AS-IV on kidney disease g. Protective effect of AS-IV on gynaecopathy h. The autophagy promotion or inhibition effects of AS-IV 2. Although it is not a systematic review, it is appropriate to put a section on material and methods explaining the inclusion and exclusion criteria, databases used in the search and keywords used, among other parameters. **Minor revision 1.** The authors write AST-IV or Astragaloside IV in different ways throughout the work. The same with LC3 II or B, P62 or H9C2. Lack of coherence, please unify terms throughout the work 2. EMT is not described

Major revision 1:

1 Authors should summarize findings in separate tables by tissue for ease of reading. Table 1 is too big, it is split on different pages and it mixes fabrics: a. Protective effect of AS-IV on cardiovascular disease b. Protective effect of AS-IV on the brain and nervous system c. Protective effect of AS-IV on lung disease d. Protective effect of AS-IV on diabetes e. Protective effect of AS-IV on organ injury f. Protective effect of AS-IV on kidney disease g. Protective effect of AS-IV on gynaecopathy h. The autophagy promotion or inhibition effects of AS-IV.

Response: According to the suggestion, Table 1 is split as Table 1-8.

Table 1. Protective effect of AS-IV on cardiovascular disease

Table 2. Protective effect of AS-IV on the brain and nervous system

Table 3. Protective effect of AS-IV on lung disease

Table 4. Protective effect of AS-IV on diabetes

Table 5. Protective effect of AS-IV on organ injury

Table 6. Protective effect of AS-IV on kidney disease

Table 7. Protective effect of AS-IV on gynaecopathy

Table 8. The autophagy promotion or inhibition effects of AS-IV

Major revision 2. Although it is not a systematic review, it is appropriate to put a section on material and methods explaining the inclusion and exclusion criteria, databases used in the search and keywords used, among other parameters.

Response: Thanks for the reviewer's suggestion, "A search strategy was performed of published studies from 2001 to present using keyword searches "(astragaloside IV) AND (inflamm*)" in Pubmed. Then we included the studies related to autophagy and excluded the studies not related to autophagy." Please see Page 2 Line 36-39.

Minor revision 1. The authors write AST-IV or Astragaloside IV in different ways throughout the work. The same with LC3 II or B, P62 or H9C2. Lack of coherence, please unify terms throughout the work.

Response: Thank the reviewer very much. AST-IV has been revised as “AS-IV” (Page 4 Line 94; Page 6 Line 115; Page 15 Line 269)”. LC3-II has been revised as “LC3 II” (Page 6 Line 113). LC3-B has been revised as “LC3 II” (Page 7 Line142; Page 10 Line 205).

Minor revision 2. EMT is not described.

Response: Thank the reviewer very much. Please see Page 8 Line 155-156.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: 1. Need Abbreviation list 2. Please describe new (or suggested) pathway you might find from this literature review. 3. The explanation in discussion was unclear & conclusion was not related with discussion.

Major revision 1. Need Abbreviation list

Response: The abbreviation list is shown in Page18 Line342-358 in the review and also shown as followed.

Traditional Chinese medicine (TCM)

Astragaloside IV (AS-IV)

Cardiovascular diseases (CVDs)

Parkinson's disease (PD)

ischaemia/reperfusion (I/R)

middle cerebral artery occlusion (MCAO)

oxygen and glucose deprivation/reoxygenation (OGD/R)

non-small cell lung cancer (NSCLC)

mammalian target of the rapamycin (mTOR)

acute respiratory distress syndrome (ARDS)

diabetic peripheral neuropathy (DPN)

chronic glomerulonephritis (CGN)

mesangial cell (MC)

triple-negative breast cancer (TNBC)

3-methyladenine (3-MA)

vulvar squamous cell carcinoma (VSCC)

Graves' orbitopathy (GO)

Major revision 2. Please describe new (or suggested) pathway you might find from this literature review.

Response: Thanks for your suggestion. Please see Page 17 Line 331-333.

Major revision 3. The explanation in discussion was unclear & conclusion was not related with discussion.

Response: Thanks for your suggestion. Please see the last paragraph Page 17 Line 334-336.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript is comprehensive, and the role of AS-IV in the diseases of a certain class of system should be schematically shown the mechanism separately.

Response: Thanks for your suggestion. Please see “Major revision in the 1st point of Reviewer 1”. Please also see Table 8, this table individually lists ‘The autophagy promotion or inhibition effects of AS-IV’ in various diseases and their mechanism.