Author’s response to reviews

Title: Inhibition of Airway Remodeling and Inflammatory Response by Icariin in Asthma

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Author’s response to reviews:

We thank the reviewers for the time spent on our paper and insightful comments which have helped to increase the rigor of our study. In response to these comments we offer a point by point rebuttal as detailed below:

Robin., Ph.D. (Reviewer 1)

Comment 1. The title of the manuscript needs some change. In title instead of writing "role" authors may use more appropriate scientific words.
Response: We very much appreciate the reviewer’s comments. In response to reviewer’s comments, we changed our title to "Inhibition of Airway Remodeling and Inflammatory Response by Icariin in Asthma".

Comment 2. Please insert page numbers in the manuscript pages as it is difficult to describe the section which needs improvement.
Response: This is a great point. In response to reviewer’s comments, we have inserted page numbers in the manuscript pages to make it easier for reviewers to identify the sections which need improvement.

Comment 3. There are many spacing, punctuation and grammatical errors in the manuscript which
needs lot of improvements for more clarity in sentences.
Response: We thank the reviewer for the careful review of our manuscript. Language and grammar errors have been carefully checked following the reviewer's suggestions. The spacing, punctuation and grammatical errors in the manuscript have been removed. We now resubmit our revised manuscript as a letter to the editor according to editor and reviewers' comments.

Comment 4. In abstract there are incomplete phrases like "western analysis", which may be more appropriately modified as "western blot analysis" or "protein immunoblotting".
Response: We very much appreciate your comment. We have replaced "western analysis" to "western blot analysis" following your suggestion (Abstract section, line 20, page 2, highlight in yellow).

Comment 5. In the method section authors may include the separate section for the "chemicals and reagents used" describing their sources.
Response: Thank you for your valuable advice. A separate section to describe the sources of "chemicals and reagents used" has been added in method section (Methods section, line 6-34, page 6, highlight in yellow).

Comment 6. There are spacing errors while displaying units after values. In the "analysis of BALF" section under methods, the milliliter unit was displayed as "mL" while in other sections milliliter was displayed as "ml". Please be consistent with the accurate display of all measuring units throughout the manuscript.
Response: We apologize for this overview. All measuring units throughout the manuscript have been checked and the milliliter unit was uniformly displayed as "ml" (Methods section, line 39, page 8, highlight in yellow).

Comment 7. The authors should cite the reference for the phrase "Overall, the previous data indicated............... mechanism remain unclear" (line 4-7) under discussion section.
Response: This phrase is a conclusion of our above results, with the aim of drawing a discussion of the mechanism of anti-remodeling of icarrin. Besides, we have revised this sentence more accessibly (Discussion section, line 45-50, page 15, highlight in yellow).

Comment 8. Please rewrite the sentence "The study of Bo Lan.etc indicates that ET-1 is responsible for increased proliferation and contraction of human ASMC after incubation with conditioned medium" in discussion section with more clarity with proper citation to the respective authors.
Response: Thank you. The sentence has been reformulated as follows: "The study of Lan, B.etc indicates that mechanical compression of bronchial epithelial cells contributes to proliferation and basal contraction of ASMC and that augmented proliferation and contraction depends on epithelial cell-derived ET-1." And the citation (ref.No.45) has been added (Discussion section, line 45-53, page 16, highlight in yellow).

Comment 9. While writing the manuscript please avoid the phrases like "we tested", "we examined", "we found" etc.
Response: This is a good comment. We have checked through the manuscript and tried to avoid the use of these phrases.

Comment 10. In conclusion section the authors may name the proliferation-related factors and proliferation-related signaling pathways discussed in the manuscript relevant to this study.
Response: Thank you for pointing this out. In response to this comment, we have detailed the proliferation-related factors as TGF-β1, VEGF, IL-13 and ET-1, and proliferation-related signaling
pathway as MAPK/Erk signaling pathway (Conclusion section, line 48-50, page 17, highlight in yellow).

Comment 11. In acknowledgement section please acknowledge the institution, funding sources etc., instead of writing "not applicable".
Response: Thank you. We have expressed our acknowledgement in this section (Acknowledgements section, line 4-12, page 19, highlight in yellow).

Tetsuhiro Yoshino, M.D., Ph.D. (Reviewer 2)

Comment : First of all, I believe a reasoning part for this study should be placed in the introduction section. Authors address the reasoning in the discussion section in current version of their draft; "Years of clinical researches have shown that Epimedium harbor the ability of anti-inflammatory, anti-oxidant and anti-allergic, which are benefit to protect lung tissue and relieve asthma[39-41]." If they could, I hope authors would collect more previous articles about this topic. Otherwise, this topic, Icariin for a treatment of asthma, could sound eccentric for readers. Additionally, as I read only titles of these references, ref. No.41 sounds irrelevant for current topic. Next, I hope authors use DXM in figure 1. In current version, hexadecadrol, a synonym of DXM, is used in the figure. Last, it is very difficult to comprehend the figures. Could you upload figures with high-resolution? I think the label of vertical axis of Figure 2 (C) is Wai/Pbm, possibly.

Response: We would like to thank you for the efforts in giving these valuable comments to our paper. 1) The reasoning part of this study was placed in the introduction section (Introduction section, line 37-59, page 5, highlight in yellow). 2) We apologize for placing the references No.39-41 in the wrong position. Actually, the correct insertion position of the references is "Years of clinical researches have shown that Epimedium harbor the ability of anti-inflammatory, anti-oxidant and anti-allergic[39-41], which are benefit to protect lung tissue and relieve asthma." Additionally, we have revised this part to avoid ambiguity and moved this part to introduction section after thorough deliberation (Introduction section, line 45-59, page 4, and line 1-12, page 5, highlight in yellow). More previous articles were collected to support and detail the topic of "ICA has the ability of anti-inflammatory, anti-oxidant and anti-allergic" (Introduction section, the original ref.No.39-41 were the current ref.No.23-25, and the added references were ref.No.19-32). 3) Reference No.41 (current No.25) was cited to demonstrate that ICA has the potential of antioxidation. Other references related to the topic of "icarrin harbors the ability of antioxidation" were added in the manuscript to further support this opinion (ref.No.26-32). 4) "hexadecadrol" has been changed to "DXM" in figure 1. 5) We now upload figures with high-resolution as suggested by the reviewer. The low-resolution figures that are difficult to comprehend in PDF are because all the materials are compressed when they are created in PDF. 6) The label of vertical axis of Figure 2 (C) is indeed Wai/Pbm, and high-resolution figure 2 was uploaded for more accessibly.

We now resubmit our revised manuscript as a letter to the editor according to editor and reviewers’ comments.