November 27, 2018

Dear Reviewer 2,

Thank you very much for your kind comments and review of our previous manuscript entitled by “Jowiseungchungtang inhibits amyloid-β aggregation and amyloid-β-mediated pathology in 5XFAD mice”.

We are resubmitting the revised manuscript and a detailed account of how we have responded to the reviewer. We also appreciate for the reviewer’s comment. Please find our enclosed responses to the reviewer’s comments.

We sincerely hope that our revised manuscript will satisfy the reviewers. We would be grateful for your consideration of this manuscript for publication in the International Journal of Molecular Sciences.

All the best,

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It has been reviewed by experts in the field and we request that you make major revisions before it is processed further.

Please revise the manuscript according to the reviewers’ comments and upload the revised file within 10 days. Use the version of your manuscript found at the above link for your revisions, as the editorial office may have made formatting changes to your original submission. Any revisions should be clearly highlighted, for example using the “Track Changes” function in Microsoft Word, so that changes are easily visible to the editors and reviewers. Please provide a cover letter to explain point-by-point the details of the revisions in the manuscript and your responses to the reviewers’ comments. Please include in your rebuttal if you found it impossible to address certain comments. The revised version will be inspected by the editors and reviewers.

We sincerely appreciate this opportunity to revise our work and resubmit this manuscript. We also appreciate for the detailed comment from the reviewer and have addressed the response as described below. In the revised manuscript, red letters are used to show the changed (or added, or removed) data and expressions. The following are responses to reviewer’s comments.

[Reviewer 2]
This is a promising approach of AD’s treatment. This article demonstrated how JWS can overcome AD pathologies. This work is perfect in its current form.

[1] However, for additional evidence of the effects of JWS on AD, I would suggest to study the signaling pathways affected by JWS. Moreover, and taking into account that JWS is composed by 14 herbs, I would try each herb individually in order to know if one or two induce these effects.

Response: We appreciate for the reviewer’s comments. We fully agree with what the reviewer interested. The JWS, consisting of 14 herbs have a lot of various bioactive components, and it has variety of effects on multiple targets. Moreover, the purpose of this study was to identify the effects of JWS as a standardized formula, not as separate ingredients. Thus, we were confirming only general effects of JWS. In addition, we also addressed some possible mechanisms of herbs such as Polygalae Radix, Schisandraceae Fructus and Acori Graminei Rhizoma among the herbs that make up the JWS. As presented in the discussion, not only did the 14 herbs (and bioactivity components present in each herb) that make up the JWS individually have a therapeutic effect on Aβ-mediated neuropathology, but also might interact with each other to create complementary or synergistic therapeutic effects. We attempted to demonstrate the effectiveness of combination therapy on Aβ-mediated neuropathology by administration of known herbal formula JSW, to animal model of AD. The JWS significantly improved the Aβ-mediated neuropathologies compared to the control group. Nonetheless, we respect what the reviewer concern. Thus, we addressed the limitation of the study and suggestion regarding this issue in revised manuscript (line: 260-263).