Response to Reviewer

Dear Reviewer,

Thank you for providing this opportunity to revise our manuscript for publication. We have carefully revised the manuscript, taking into account all valuable comments and constructive suggestions from the reviewers. The revised points, including the added figure and rephrased part, were reflected in the text of the final revised manuscript. These revisions were highlighted in blue in the marked copy of the revised manuscript and in this document containing our responses to reviewers' comments. We have prepared this response document as a separate file, which will be uploaded along with two versions of the revised manuscript files (version 1: revised texts were marked in blue, and version 2: changes were unmarked). Additionally, the cover letter and graphical abstract will be included in the submission.

We hope that the revised manuscript effectively addresses the queries raised by the reviewers and clarifies the flow and context of our review, making both the reviewers and readers comprehend and find interest in our work. We believe that the manuscript was substantially improved after the revision. Therefore, we hope it is accepted for publication in the *International Journal of Molecular Sciences*.

We appreciate your time and consideration of our manuscript for publication.

Yours sincerely,



Prof. Jin Hyun Lee

Reviewer #1

The manuscript "Nature-Derived Polysaccharide-Based Composite Hydrogels for Promoting Wound Healing" from Lee et al. is an interesting review on current developments on wound healing with the use of natural polysaccharide composites. Overall, the review could be a good addition for the International Journal of Molecular Sciences, although some significant points should be addressed by the authors.

Response: We are grateful to the reviewer's positive assessment and truly appreciate your valuable time and insightful and keen comments. They have enhanced the content of this manuscript.

Comment 1. Firstly, there should be a general reformatting of the manuscript regarding the English language. In some areas there the meaning is difficult to decipher.
Such as:
Line 37 "tissue regeneration as a barrier"
Lines 36-56 please rewrite the wound healing procedure more clearly and with more details: " :
Lines 80-84 please check the phrasing:
Line 113 "variety of research" please rephrase.
Lines 119-128 please make the paragraph more clear.
Line 145 "The representative reserve" please rephrase.
Lines 239-240 please improve the phrasing.
Line 475 "can cause the risk of side effects, including fibrosis, bone loss" . Rephrase this
Line 497 "Specifically, we focused on preparing the composite hydrogel systems" Rewrite this sentence. You are describing the composite hydrogel systems in this review, you have not prepared and conducted the experiments.

Answer: We thank you for your kind and careful comments. In response to your comments, we carefully rephrased and rewrote all the parts you pointed out. Also, the manuscript has been revised by a professional English editor. Thank you.

Comment 2. Line 76 "hydrophilic components". Please define what are these components.

Answer: We thank you for your comment. To clarify the term, we changed it to "hydrophilic molecules".

Comment 3. Line 93 please add the corresponding reference.

Answer: Based on your suggestion, we added the corresponding reference.

Comment 4. One or two additional pictures with schematics describing the mechanisms of wound healing for one or two mentioned polysaccharide composites would be a very good addition.

Answer: Thank you for your thoughtful suggestion. Figures 1 and 3 already present the wound-healing mechanisms for all the polysaccharide composite hydrogels.

Comment 5. "The yellow stars: reinforcements (particles, fibers, non-woven and woven fabrics, and foams) and therapeutic agents." what you are describing is unclear.

Answer: Thank you for your comment. In response, we have revised the description in Figure 2 to explain the addition of reinforcements and therapeutic agents in a hydrogel form to fabricate the composite hydrogels.

Comment 6. Please also elaborate more when describing the improvements of adding composite in the polysaccharide hydrogels. For example, for the starch based hydrogel (CMS@CuO hydrogel) you mention that it results in advanced wound healing performance. It would be better to give to the point quick explanations such as statistics of healing improvement or information on successful in-vivo experiments. Please also do that for the other polysaccharide examples.

Answer: I appreciate your comment. Actually, we considered the article length; thus, many properties of each system were mentioned in short. However, based on your comments, we have provided additional explanations regarding the wound-healing performance of most of the composite hydrogel systems discussed.

Comment 7. Lines 243-251 this research refers more to Osteogenic and cartilage differentiation which is more towards the tissue regeneration application while the other examples you are giving are focusing more on wound healing. Either remove this application or convey your message better.

Answer: According to your thankful comment, we removed the application and added another glycogen-based composite hydrogel system. Thank you again.

Comment 8. The numbers in chemical compounds should be in subscript or superscript format. Examples are MnO2 or HA-NH2 in lines 460 and 459.

Answer: According to your careful comment, we corrected the numbers in chemical compounds in the right format. Thank you again.

Comment 9. Lines 467-468 “The H2O2 produced from GOx-MnO2 generated Mn2+ also contributed to improved MRI performance”. Elaborate more on how MRI performance was improved.

Answer: Based on your insightful comment, we have revised that part to clarify how MRI performance was enhanced. Thank you.