Dear Editor,

Dear Reviewers,

We gratefully thank the editor and all reviewers for their time spend making their constructive remarks and useful suggestions, which has significantly raised the quality of the manuscript and has enable us to improve the manuscript. Each suggested revision and comment, brought forward by the reviewers was accurately considered.

Reviewer #1:

The present manuscript is of great relevance in the field of wound healing. The manuscript is well written and the experiments were well designed. There are some issues that must be pointed out.

Comment 1: In the characterization of exosomes derived from hUC-MSCs, it is necessary to detail the western-blot technique in detail, from protein extraction to data collection.

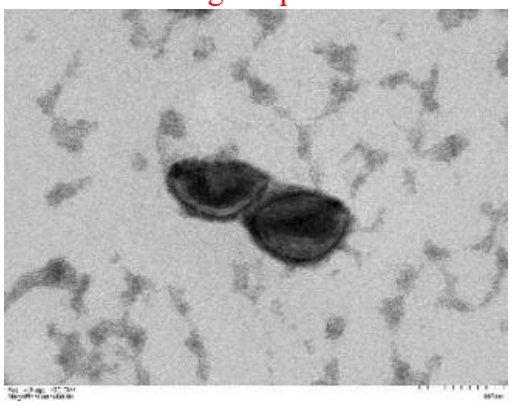
Reply 1: We gratefully appreciate for your valuable suggestion. The details of western-blot are as follows: “The protein concentration of hUC-MSC-exosomes was determined using a BCA protein quantitation kit (Zoman, Biotechnology, ZD301). After adding the required proportion of loading buffer, the sample was heated at 95°C for protein denaturation. Protein from each sample was separated on sodium dodecyl sulfate polyacrylamide gel and then transferred to PVDF membrane. After blocking with 5% skim milk for 2 h, the membranes were incubated overnight with anti-CD9 (20597-1-AP, Proteintech,), anti-Tsg101 (28283-1-AP, Proteintech), and anti-Calnexin (10427-2-AP, Proteintech) antibodies. Subsequently, the secondary antibody (SA00001-2, Proteintech) was added, followed by incubation for 1.5 h. Band visualization was achieved using chemiluminescence kit (P0018FM, Beyotime, China) to observe on the chemiluminescent image system (MiniChemi 610, Sagecreation, China)”. And We have

added the details of western-blot in the manuscripts.

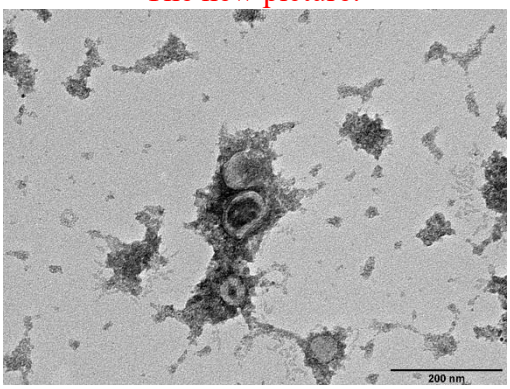
Comment 2: The morphology of exosomes by transmission electronic microscopy seems impaired, since its shape is not uniform and the membrane is not well delimited. I ask the authors to include a better image.

Reply 2: Thank you so much for your careful check. I have changed the picture into a new one as following. And we have also added a clear scale bar according to another Reviewer's suggestion.

The original picture:



The new picture:



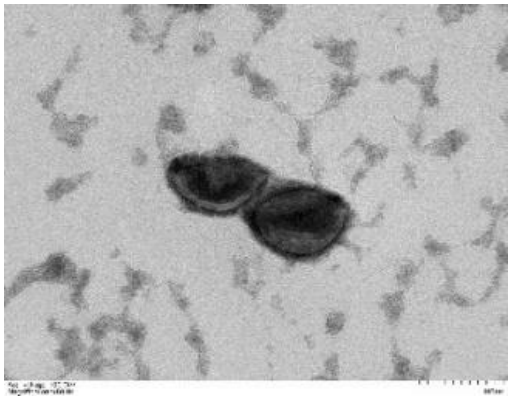
Reviewer #2:

In this study, authors used a gelatin sponge loaded with hUC-MSCs exosomes and assessed its potential as a hemostatic material and a wound healing accelerator. The study comprised in vivo and in vitro assays evaluating cytotoxicity, skin irritation, hemolysis, tissue compatibility, liver defect hemostasis, and full-thickness skin defect healing. This is a comprehensive study.

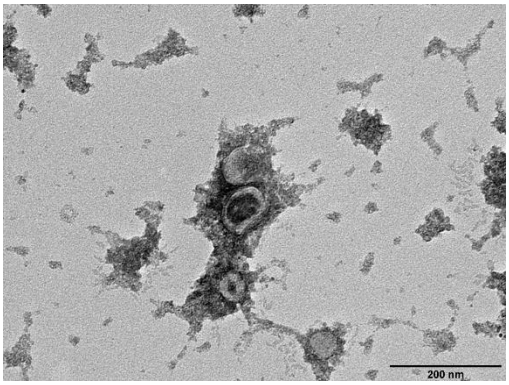
Comment 1: Please add a clear scale bar in Figure 1 A.

Reply 1: We gratefully appreciate for your valuable suggestion. Since another reviewer suggested we changed the morphology picture of exosomes by TEM because of the original one seemed impaired and the membrane was not well delimited, we have changed the Figure 1A into a new one as following, and I have added a clear scale bar in the new picture.

The original picture:



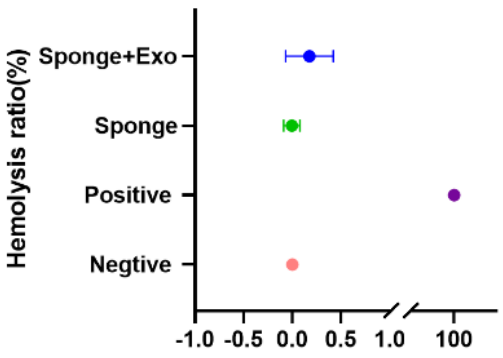
The new picture:



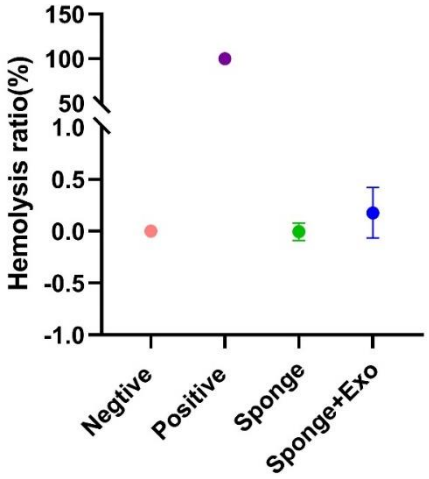
Comment 2: Please adjust the plotting method of Figure 3B (the ordinate is hemolysis rate).

Reply 2: We really appreciate your advice. We have changed the Figure 3B according to your suggestion as following, and replaced the old picture in manuscript.

The original picture:



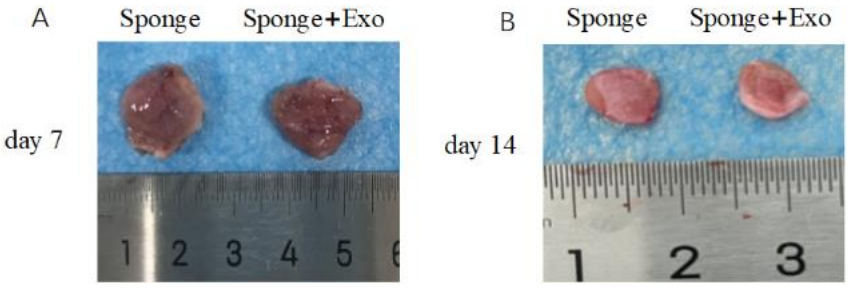
The new picture:



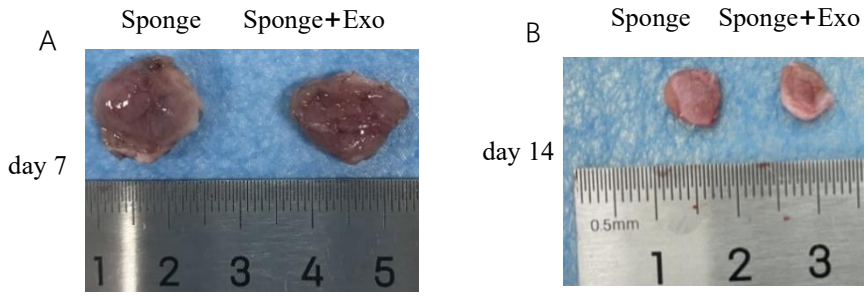
Comment 3: Try to align the scales in Figure 4A and B. Please enlarge the scale in Figure 4C or add a description.

Reply 3: We gratefully appreciate for your valuable suggestion. We have tried to align the scales in Figure 4A and B as following. Besides, I have added a description for Figure 4C with "After 7 and 14 days of implantation, there was no obvious inflammatory response was found around the tissue, and no obvious tissue fibrosis or necrosis was observed" in the manuscript. Besides, we also added "Scale bar=100 μm" for Figure 4C in the figure legend.

The original pictures:



The new pictures:



Comment 4: Please provide macroscopic images of the BCI experiment.

Reply 4: We really appreciate your suggestion. However, due to our negligence, we forgot to record the experiment process with camera. We are really sorry that we could not provide macroscopic photos of the experiment at that time. Our experiment protocol refers to the study of Yang et al. (2021) (PMID: 33496718), the experimental results are reliable. We will keep in mind to record every experiment when we perform in the

future.

Comment 5: Please use Figure 6C to clearly explain the advantages of Sponge+Exo (marking blood vessels, epithelial thickness, hair follicles, etc.).

Reply 5: We gratefully appreciate for your valuable suggestion. We have explained the advantages of Sponge+Exo with "Histopathological results showed that on day 14, sponge-loaded exosome group could see the regeneration of hair follicles and sebaceous glands better than the other two groups (Figure 6C)" in the manuscript. Besides, we have marked the hair follicles, vessels, sebaceous glands, etc. in the pictures. The pictures and legend are as following.

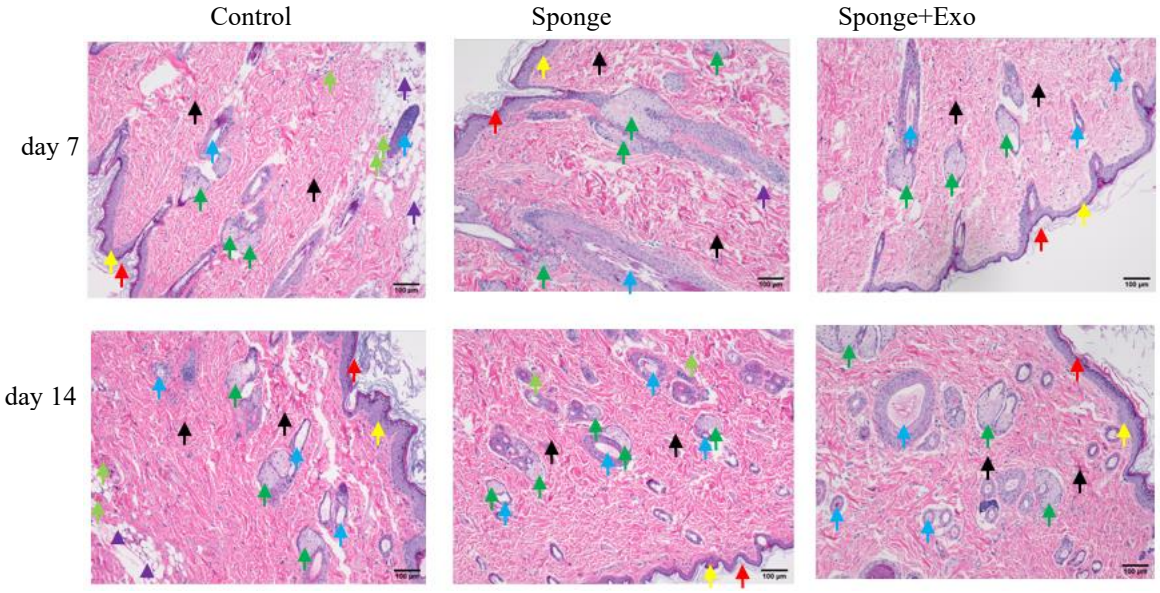
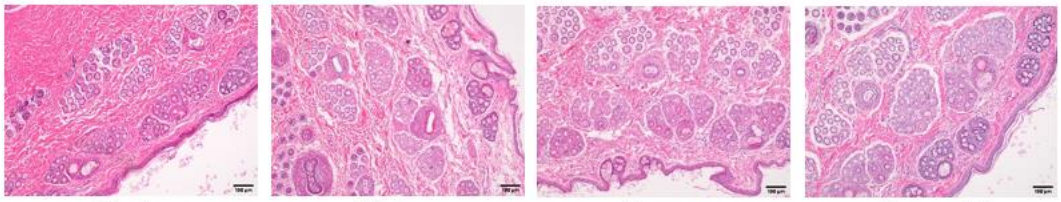


Figure 6C: HE-stained wound tissue sections as observed under a light microscope. The red arrow indicates the stratum corneum, the yellow arrow indicates the granular layer; the green arrow indicates the sebaceous gland, the blue arrow indicates the hair follicle, the black arrow indicates the collagen fibers, the light green arrow indicates the blood vessels, and the purple arrow indicates the subcutaneous fat. Scale bar=100 μm.

Comment 6. Please supplement the relevant description of H&E staining in Figure 3D and enlarge the scale.

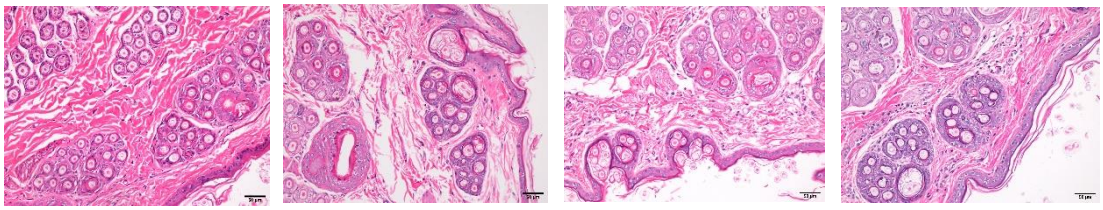
Reply 6: I have added the description of H&E staining in Figure 3D in manuscript with "All experimental rabbits had intact epidermis, with normal sebaceous glands, hair follicles, and hair structures; There were no notable pathological changes, such as inflammatory cell infiltration, tissue congestion, and edema". Besides, I have replaced the original pictures with enlarge-scaled pictures with "Scale bar=50 μm" as follows.

The original pictures:



Blank Nacl Sponge Sponge+Exo

The new pictures:



Blank NaCl Sponge Sponge+Exo

Comment 7: Related papers on this topic can be cited: https://doi.org/10.3390/molecules28114498, https://doi.org/10.1016/j.ijbiomac.2023.125754.

Reply 7: Thank you for your valuable suggestion. We have cited related these two articles in the proper place of the revised manuscript as following.

rate was calculated by photography. Formula B was used to calculate the hemolysis rate $= (OD_{sam} - OD_{neg}) \div (OD_{pos} - OD_{neg}) \times 100\%$ (1)[13]

The hemostatic capacity of the exosome-loaded gelatin sponges was evaluated using a rat hemorrhagic liver model[14]. Twelve SD rats were divided into the

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JOURNAL EDITOR-IN-CHIEF'S REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 87405

Title: Enhanced wound healing and hemostasis with exosome-loaded gelatin sponges from human umbilical cord mesenchymal stem cells

Journal Editor-in-Chief (**Associate Editor):** Shengwen Calvin Li

Country/Territory: United States

Editorial Director: Jia-Ping Yan

Date accepted review: 2023-09-13 04:22

Date reviewed: 2023-09-13 04:33

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[Y] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Rejection
[ ] Grade D: Fair		[ ] Minor revision
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Major revision

JOURNAL EDITOR-IN-CHIEF (ASSOCIATE EDITOR) COMMENTS TO AUTHORS

WPS_1673360041 请责编注意：我发给作者确认的版本中对文稿标题和简短标题进行了修改，但作者回复说不允许修改文稿标题和简短标题，我不太清楚是否是因为作者方面的原因。因为文稿标题有明显的问题，我把建议修改的文稿标题和简短标题分别附在下面，请酌情处理： 建议的文稿标题：Enhanced wound healing and hemostasis with a gelatin sponge loaded with exosomes derived from human umbilical cord mesenchymal stem cells 建议的文稿简短标题：Exosome-loaded gelatin sponge enhances wound healing' EIC: The original title emphasized the effects by placing the important phrases in the opening, which is powerful. The longer the title, the better description: which attracts the readers. So, please use the author's title.

Reply: Thanks for your comments, the title " Enhanced wound healing and hemostasis with exosome-loaded gelatin sponges from human umbilical cord mesenchymal stem cells**" is original.**