



PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 85404

Title: Injectable hydrogel made from antler mesenchyme matrix for regenerative wound healing via creating a fetal-like niche

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 03475330

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor, Surgeon

Reviewer’s Country/Territory: Japan

Author’s Country/Territory: China

Manuscript submission date: 2023-04-28

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-16 04:25

Reviewer performed review: 2023-05-16 07:57

Review time: 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Comments to the author The manuscript entitled "Injectable hydrogel made from antler mesenchyme matrix for regenerative wound healing via creating a fetal-like niche" was reviewed. The paper is theoretical and carefully written. As the author describes in this paper, wound healing is a balance between cell proliferation, extracellular matrix and growth factors. Therefore, the following questions arise. Why did the authors select only cells with high cell proliferation capacity to evaluate this hydrogel in Figure 1? Which cells are positive for Ki67 in the middle of wound healing? Even on day 30, Ki67 is positive in some cells. Are these the same in fetal tissue regeneration? Which cells are Ki67 positive on day 30 in normal wound healing? Are there no infections at the wound site in rats? Does the hydrogel stay in place when attached to the tissue? Are there any follicles in the injured area? If so, have surrounding follicles migrated to the injured area?



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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05468066

Position: Peer Reviewer

Academic degree: PhD

Professional title: Senior Lecturer, Senior Scientist

Reviewer's Country/Territory: Bangladesh

Author's Country/Territory: China

Manuscript submission date: 2023-04-28

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-24 04:59

Reviewer performed review: 2023-05-28 09:49

Review time: 4 Days and 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors have written this manuscript on a well-designed study. There are no major issues I can point to. The manuscript is suitable for publication in this well-reputed journal following checking the similarity index and other publication ethics-related points.



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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04861666

Position: Peer Reviewer

Academic degree: BSc, MSc, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: India

Author's Country/Territory: China

Manuscript submission date: 2023-04-28

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-31 00:51

Reviewer performed review: 2023-06-02 08:22

Review time: 2 Days and 7 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Scarring in wound healing poses a challenge in the clinic because it involves a complex process employing multiple factors and cells related to the microenvironment. Although synthetic hydrogels or ECM hydrogels have been tested, the outcomes have been unsatisfactory. In this study, the authors are the first to report on the role of an acellular ECM hydrogel prepared from stem cell tissue (antler reserve mesenchyme, HARM) in cutaneous wound healing. They found that there were high expression levels of IL10 and TGFβ3 in the healed skin of the HARM group compared to the control. It was also observed that the healed skin of the HARM group favored the expression of fetal wound healing genes, including collagen III and TGFβ3, but did not favor the expression of scar healing genes, including collagen I and TGFβ1, when compared with those in the N-CTRL and P-CTRL groups to varying degrees. The effects of the fetal-like wound healing niche created by HARM on the recruitment of stem cells and maintenance of plasticity were detected, as observed by significantly higher CD73 and CD90 in the HARM group compared to that of the control groups. Altogether, this novel type of hydrogel, HARM, has a better effect on wound healing and has better translational



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potential. In my opinion, the manuscript is well-planned, explained well, nicely written, and suitable for publication. Comments: I did not find any place where the authors have mentioned obtaining permission to isolate HRAM from the deer. I think it needs to be included in the manuscript somewhere. The authors should also include a few lines about the future translational scope of this research in the discussion.



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Peer-review model: Single blind

Reviewer's code: 05468264

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2023-04-28

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-31 07:38

Reviewer performed review: 2023-06-02 09:41

Review time: 2 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Correct the wrong words

- Core tip: “and thus pave the way for HARM to be developed for the clinic use.” “Pave” change to “paved”
- Histology: “The collagen fibres (blue area on micrograph) in Masson staining and the positive expression (fluorescence area on microphage) of the target genes in IF staining were analysed statistically” “Fibres” correct to “fibers” “analysed” correct to “analyzed”
- Figure 3 “the collagen fibre” correct to “fiber”. Please correct the fiber in full manuscript.
- Figure 4 the wrong word “typica”, please correct the word “The expression levels collagen I , TGFβ1, and Engrailed 1”, please add the word “of”

Correct the error sentence

- Introduction, “Healing in adult skin wounds usually results in scar formation, consisting of thick bundles of collagen fibers in the dermis, lacking functional cutaneous appendages”
- Preparation of HARM HARM was formed when 10×PBS was added into the solution and stored at 37 °C for 1 h (Figure 1a). Lyophilized-HARM (Figure 1b) were sputter-coated with a thin layer of gold before observation Above -mentioned Figure 1a and 1b should be Figure S1b and S1a.
- 3D Cell Culture and Related Assays Which cell was used to culture for 3D cell?
- Creation and treatment of Full-Thickness



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Wounds in a Rat Model

Question 1. Creation and treatment of Full-Thickness

Wounds in a Rat Model

Please add the animal groups, and the numbers of rats per

group. 2. Statistical Analysis Multi-comparisons were made using ANOVA in the package of GraphPad Prism 9.0. Please describe the analysis method of the multi-comparisons using ANOVA, ordinary one-way ANOVA or two-way ANOVA?

Dunnet's test or Tukey's test? 3. HARM Promotes the Expression of Fetal Wound

Healing-Related Genes in Rats I don't agree with the viewpoint of this sentence "The expression levels of IL10 and TGF β 3, the typical fetal wound healing-related genes"

Fernanda Rodrigues Helmo reported that TGF- β 1 and TGF- β 3 are significantly expressed in human fetal and adult skin, respectively. (Reference 24, Fetal Wound Healing Biomarkers, doi.org/10.1155/2013/567353). Whereas in fetal dermis and with

increased gestational age, TGF- β 3 presented the same pattern of expression as the epidermis. 4. Figure S1 Is the state of HARM a liquid or a semi solid at 4°C?

Is the state of HARM a solid at 37°C? Whether the basic character of hydrogel is evaluated?