Reviewer #1:
Comments:
Correct the wrong words 1. Core tip: “and thus pave the way for HARM to be developed for the clinic use.” “Pave” change to “paved” 2. 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” 3. Figure 3 “the collagen fibre” correct to “fiber”. Please correct the fiber in full manuscript. 4. Figure 4 the wrong word “typica”, please correct the word “The expression levels collagen I, TGFβ1, and Engrailed 1”, please add the word “of”.
Reply: Done.

Correct the error sentence
1.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”
Reply: The sentence has been changed to: “Healing in adult skin wounds usually results in scar formation, and scar consists of thick bundles of collagen fibers in the dermis and lacks functional cutaneous appendages”.

2. 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.
Reply: Done.

3. 3D Cell Culture and Related Assays Which cell was used to culture for 3D cell?
Reply: The cells, including HUVEC, NIH 3T3, ADSC, BMSC, ADSC, and BMSC, were used for 3D culture; and more detailed descriptions have been added in the manuscript.

4. Creation and treatment of Full-Thickness 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.
Reply: The details have been added in the manuscript: “The model rats were randomly divided into three groups (HARM, HPUB and PBS), with each group having10 rats.”

5. 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?
Reply: Significant differences were evaluated using t-test and one-way ANOVA. The difference was considered statistically significant (*$p < 0.05$), or highly significant (**$p < 0.01$, or ***$p < 0.001$).

6. 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 TGFβ3, the typical fetal wound healing-related genes” Fernanda Rodrigues Helmo reported that TGF-β1 and TGF-β3 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-β3 presented the same pattern of expression as the epidermis.
Reply: Based on our understanding to the comments from the Reviewer, we believe there is no controversy between us and the Reviewer in that fetal skin expresses higher level of TGF-β3 than that of adult skin, and vice versa in TGF-β1. The Reviewer believes that TGF-β3 has the same expression pattern between fetal dermis and epidermis. Our study did not go into that detail to separate dermis from epidermis. To soft the tone of our description, we deleted the word “typical”.

7. 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?
Reply: HARM was semi solid state at 4 ° C, and solid state at 37 ° C. Basic characteristics of the hydrogel will be evaluated in our future study.

Reviewer #2:
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.
Reply: In China, deer antler is a commercially available product, and all deer antlers used in this study were purchased from Dongao Deer Farm; and more detailed descriptions have been added in the manuscript.
The future translational scope of this research has been added and described as “Overall, we believe that our prepared hydrogels may have clinical benefits for stimulating regenerative wound healing, especially those large cutaneous wounds caused by burns, scalds, or machinery.”

Reviewer #3:
Comments: 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.
Reply: Thank you.

Reviewer #4:
Comments:
Why did the authors select only cells with high cell proliferation capacity to evaluate this hydrogel in Figure 1?
Reply: RM cells have very high proliferative potential, so their extracellular matrix will inevitably provide them with corresponding microenvironments. We believe that ECM

hydrogel prepared from RM will also play a significant role in cell migration and proliferation during wound healing. This is why we only cells with high cell proliferation capacity to evaluate this hydrogel.

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?
Reply: Some cutaneous appendage cells and vascular-related cells are positive for Ki67 on day 15. Even on day 30, Ki67 is also positive in some cutaneous appendage cells and vascular-related cells. This may be on 30 days; some cutaneous appendages and blood vessels have not yet matured, so they are still in a proliferative state. Takaya K et al.(PMID: 36140233) reported that ki67 is highly expressed in the epidermal basal layer and the base of feral wounds, which is similar to our results. Very few cells (except for red blood cells) express Ki67 on day 30 in normal wound healing.

Are there no infections at the wound site in rats?
Reply: Because the experimental rats were raised in a very hygiene environment, thus no wound infection was observed in this particular study.

Does the hydrogel stay in place when attached to the tissue?
Reply: We regularly observed whether the hydrogel stays in the wounds, and the answer is yes. We speculated that it may be caused by the adsorption of the hydrogel.

Are there any follicles in the injured area? If so, have surrounding follicles migrated to the injured area?
Reply: Through the histological results, we observed the hair follicles were mainly regenerated in the healed skin in situ and de novo, and we cannot preclude that some hair follicles may be derived from the migration from around the wound, based on the observation in the vitro experiments, that HARM can promote cell migration.