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Intradermal Hypoxia MSC Secretome Modulates Filaggrin and Loricrin in SLS-Induced Xerosis-Like Wistar Rats

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Background: Xerosis cutis is characterized by epidermal barrier dysfunction and reduced expression of filaggrin (FLG) and loricrin (LOR). Current management mainly relies on emollients and moisturizers that provide symptomatic relief without restoring the barrier. However, the effect of intradermal hypoxia-conditioned mesenchymal stem cell secretome (SH-MSCs) on these proteins remains unclear. This study evaluated the effect of intradermal SH-MSCs on *FLG* and *LOR* expression in a sodium lauryl sulfate (SLS)-induced xerosis-like Wistar rat model.

Materials and methods: Thirty male Wistar rats were randomized and divided into 6 groups. Xerosis model was prepared with topical application of 5% SLS twice daily for 9 days. Xerosis rats were treated with NaCl/100-300 µL of SH-MSC. Skin tissue was observed and documented macroscopically and dermoscopically. In addition, skin samples were collected on day 22, mRNA was isolated, *FLG* and *LOR* mRNA expression was quantified by qPCR using the 2−ΔΔCt method relative to GAPDH.

Results: SLS induced dryness, scaling, erythema, fissuring, and epidermal thickening. *LOR* expression differed significantly among groups ($F(5, 24) = 20.629$, $p<0.001$), with the lowest level in the xerosis and the highest in the 300 µL group. FLG expression also differed significantly ($F(5, 24)=18.266$, $p<0.001$). Both *FLG* and *LOR* were increased dose-dependently.

Conclusion: Intradermal SH-MSC enhanced the expression of epidermal barrier-related genes in an SLS-induced xerosis-like rat model. Under the conditions tested, the 300 µL SH-MSC dose appeared to be the most effective for modulating both *FLG* and *LOR* expression. These findings could suggest the potential relevance of hypoxia-conditioned MSC secretome as a cell-free strategy for barrier restoration.

Keywords: *xerosis cutis, sodium lauryl sulfate, hypoxia-conditioned mesenchymal stem cell secretome, intradermal injection, filaggrin, loricrin*

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Introduction

Xerosis cutis is a common dermatological condition characterized by reduced skin hydration, roughness, scaling, fissuring, and persistent pruritus, all of which substantially impair quality of life, particularly among older adults. A high prevalence of xerosis in elderly populations was reported, reaching more than half of >70 years old individuals. Xerosis is frequently associated with secondary complications such as dermatitis, skin tears, and pressure injuries.[1–3] At the molecular level, xerosis is closely related to epidermal barrier dysfunction, where reduced expression of structural proteins in the stratum corneum compromises water retention and increases trans-epidermal water loss. Among these proteins, filaggrin (FLG) plays a central role in maintaining natural moisturizing factors and corneocyte integrity, whereas loricrin (LOR) forms a major component of the cornified envelope that provides mechanical resilience and external protection. Depletion of these proteins weaken barrier homeostasis and predisposes the skin to inflammation and microbial invasion.[4-6]

Current management of xerosis primarily relies on emollients and topical moisturizers that offer symptomatic hydration but do not adequately restore the underlying structural defects of the epidermal barrier.[7] Recent regenerative approaches have shifted attention toward mesenchymal stem cell (MSC)-derived secretome and extracellular vesicles as cell-free therapeutic alternatives. These biologically active products contain growth factors, cytokines, lipids, and regulatory RNAs that promote tissue repair, immunomodulation, and barrier recovery. The MSC secretome and extracellular vesicles enhance ceramide synthesis, reduce inflammation, and improve epidermal integrity in inflammatory dermatoses such as atopic dermatitis.[8–10] Hypoxia preconditioning further augments these effects by stimulating hypoxia-inducible factor (HIF)-1α–dependent secretion of pro-regenerative and anti-inflammatory factors, thereby increasing the therapeutic potency of the secretome.[11–13] However, evidence regarding the use of hypoxia-conditioned MSC secretome specifically for xerosis-related barrier dysfunction remains scarce.[15] Moreover, direct evaluation of terminal differentiation proteins, particularly FLG and LOR, as primary outcomes is limited. Intradermal administration, which allows localized delivery closer to the dermal-epidermal interface, has not been sufficiently investigated in xerosis-like conditions induced by irritants such as sodium lauryl sulfate (SLS), a well-established model of barrier disruption.[16,17]

The effect of secretome of hypoxic mesenchymal stem cell secretome (SH-MSC) on the expression of FLG and LOR in an SLS-induced xerosis-like Wistar rat model remains unclear. Therefore, current study was performed to evaluate the expression of FLG and LOR following intradermal administration of SH-MSCs in an SLS-induced xerosis-like Wistar rat model.

Materials and methods

SH-MSC Preparation

Stock of SH-MSC as described in our previous publication was used in this study.[18] Briefly, SH-MSC as prepared as follows, MSC was cultured in serum-free complete medium in hypoxic chamber maintaining a gas mixture composed of 5% O_2, 5% CO_2, and balanced N_2 at 37°C for 24 h. After that, the medium was collected and centrifuged at 2000 rpm at 8°C for 20 min and filtered with a 0.22 μm membrane (Corning, New York City, NY, USA).

Animal Model Preparation and Treatment

Healthy male Wistar rats, 6–8 weeks, 180-200 g, were obtained and acclimatized for 7 days under standardized housing conditions (20-26°C, 12-hour light-dark cycle, adequate ventilation, and ad libitum access to water and standard pellet diet). The rats were randomized and divided into 6 groups, 5 rats per group. The 1st group was healthy rats, the 2nd group was xerosis rats treated with 300 μL of 0.9% sodium chloride (NaCl) (Cat #2B1309, Baxter Healthcare Corporation, Deerfield, IL, USA), the 3rd group was xerosis rats treated with 300 μL of 0.2 mg/mL hyaluronic acid (Cat #385908, Sigma-Aldrich, Darmstadt, Germany), the 4th group was xerosis rats treated with 300 μL of 1:3 diluted SH-MSC in 0.9% NaCl (100 μL of SH-MSC+200 μL of 0.9% NaCl), the 5th group was xerosis rats treated with 300 μL of 2:3 diluted SH-MSC (200 μL of SH-MSC+100 μL of 0.9% NaCl), and the 6th group was xerosis rats treated with 300 μL of SH-MSC.

Xerosis rats were prepared by shaving a 2 cm × 3 cm dorsal area and applying topical 5% SLS (Ca t#817034, Merck, Darmstadt, Germany) solution twice daily for 9 consecutive days to disrupt the stratum corneum barrier. On day 10, animals were randomly assigned to groups. Intradermal injections were performed for the groups

of xerosis rats (2nd, 3rd, 4th, 5th and 6th groups) at four equidistant dorsal points (75 µL per site) on day 10, 13, 16, and 19.

All procedures were performed under controlled laboratory conditions to ensure reproducibility and minimize confounding factors. The study protocol complied with institutional guidelines for animal research and received approval from the Institutional Animal Ethics Committee prior to commencement.

Macroscopic, Dermoscopic, and Histopathological Analyses

Development of xerosis-like lesions was confirmed through macroscopic observation and dermoscopic evaluation using a standardized xerosis severity scoring system adapted from a previously published method (XASI-based scoring). Observation of clinical signs including scaling, fissures, erythema, and roughness, was performed and documented. Representative samples were also examined histologically with haematoxylin–eosin staining to verify structural barrier disruption. Macroscopic, dermoscopic and histological analyses were performed by 2 blinded investigators to reduce assessment bias.

Dorsal Skin Collection and RNA Isolation

On day 22, animals were euthanized under anesthesia. Full-thickness dorsal skin samples were harvested using a sterile biopsy punch. Tissues were immediately washed with RNAse-free phosphate-buffered saline and preserved in RNA stabilization solution at −80 °C for molecular analysis.

Total RNA was extracted from skin with RNAiso Plus (Cat #9108, Takara Bio, Shiga, Japan), reverse transcribed into complementary DNA with ReverTra Ace qPCR RT Master Mix (Cat #FSQ-201, Toyobo, Osaka, Japan), and analyzed using real-time qPCR with Thunderbird SYBR qPCR Mix (Cat #QPS-201, Toyoba).

The primer sequences were as follows, FLG forward primer: 5′-AGGCCTCTGTTGAAGGTTCTG-3′; FLG reverse primer: 5′-CTAGTGCAGGCAGGG CATTAT-3′; LOR forward primer: 5′-AGTTCTCCGTGGACGCCTAT-3′; LOR reverse primer: 5′-GCACTGGAATTGGGAGGGAAT-3′; GAPDH forward primer: 5′-GAAGGT GAAGGTCGAGTC-3′; and GAPDH reverse primer: 5′-GAAGATGGTGATGGGATTTC-3′. The qPCR cycling conditions consisted of initial denaturation at 95°C for 1 min, followed by 40 cycles of denaturation at 95°C for 15 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s. Melting curve analysis was performed from 60°C to 95°C to confirm amplification specificity. Expressions of *FLG* and *LOR* mRNA were quantified relative to GAPDH using the 2−ΔΔCt method. All measurements were performed in duplicate by blinded investigators.

Results

Characterization of the SLS-Induced Xerosis-Like Skin Model

Repeated topical application of 5% SLS progressively induced xerosis-like skin changes from day 0 to day 9 (Figure 1). Macroscopic and dermoscopic documentation showed increasing surface roughness, thick scaling, erythema, and fissure formation, with the most severe phenotype observed on day 9 (Figure 1A & 1B). Histopathologic evaluation using HE staining provided additional evidence of barrier disruption in the xerosis-like group. Compared with normal control skin, which showed relatively preserved epidermal and dermal architecture, SLS-induced skin showed stratum corneum desquamation, epidermal thickening, increased granular layer prominence, abnormal keratinocyte differentiation, and irregular, thinned dermal collagen fibers. In some areas, wide intercellular clear spaces and red blood cell accumulation within the dermis were also observed, consistent with xerosis-like structural damage.

Macroscopic and Dermoscopic of Skin Surface Changes

Representative macroscopic and dermoscopic observations demonstrated progressive improvement of xerotic skin appearance following SH-MSC treatment. On days 13, 16, and 19, the 2nd group was xerosis rats treated NaCl exhibit more dryness, scaling, erythema, and skin surface roughness compared with the healthy. In contrast, treatment with HA and SH-MSC showed gradual improvement in skin surface condition over time. The SH-MSC-treated groups, particularly at higher doses (200 µL and 300 µL) demonstrated smoother skin surfaces with reduced xerotic features compared with the negative control group (Figure 2 & 3).

FLG Relative Expression

FLG relative expression was assessed across six groups. The lowest mean *FLG* relative expression was observed in the group of xerosis treated with NaCl merely (0.55±0.26),

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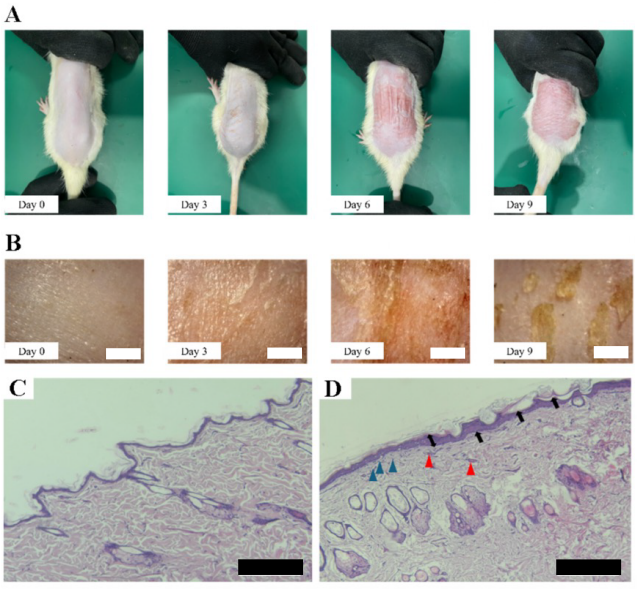


Figure 1. Macroscopic, dermoscopic, and histopathological appearances of the SLS-induced xerosis-like skin model. Macroscopic (A) and dermoscopic (B) appearances of all groups on days 0, 3, 6, and 9 were documented. White scale bar in: 2 mm. Histopathological appearances were obtained with HE staining for normal skin (C) and SLS-induced xerosis-like skin on day 9 (D). Black scale bar: 200 µm. Black arrow: stratum corneum desquamation; red arrowhead: epidermal thickening; blue arrowhead: granular layer prominence.

while the highest mean *FLG* relative expression was observed in the group of xerosis treated with 300 µL of SH-MSC (3.64±0.75) (Figure 4). Compared with the group of xerosis treated with NaCl merely, the groups of xerosis treated with 100-300 µL of SH-MSC showed significant higher FLG relative expression in dose dependent manner. Normality testing indicated normal distributions in all groups (Shapiro–Wilk $p>0.05$), whereas variance homogenity was not met (Levene $p=0.010$). One-way analysis of variance (ANOVA), followed by Tamhane's T2 post hoc test showed significant between-group differences ($F(5, 24) = 18.266$, $p<0.001$) (Table 1).

LOR Relative Expression

The lowest mean LOR relative expression was observed in the group of xerosis treated with NaCl merely (0.53±0.30), while the highest mean LOR relative expression was observed in the group of xerosis treated with 300 µL of SH-MSC (5.83±1.48) (Figure 5). Similar with the FLG, *LOR* relative expressions were significantly increased in the groups treated with 100-300 µL of SH-MSC in dose dependent manner. Normality testing indicated normal distributions in all groups (Shapiro–Wilk $p>0.05$), whereas variance homogenity was not met (Levene $p=0.021$). One-way analysis of variance (ANOVA), followed by Tamhane's T2 post hoc test showed significant between-group differences ($F(5, 24) = 20.629$, $p<0.001$) (Table 1).

Discussion

Macroscopic and dermoscopic changes confirmed that the model reproduced irritant-induced epidermal barrier damage that resembles clinical xerosis cutis. SLS acts as a surfactant that extracts stratum corneum lipids, disrupts corneocyte cohesion, and increases trans-epidermal water loss, which subsequently weakens barrier integrity and promotes inflammatory responses.[3,19,20] This biological context supports the use of the SLS model as a relevant platform for assessing barrier-repair interventions in xerosis-like injury.

Histopathological findings further supported barrier dysfunction, showing desquamation of the stratum corneum, epidermal thickening, abnormal keratinocyte differentiation, and irregular dermal collagen organization. These alterations are consistent with structural hallmarks of xerosis and irritant dermatitis, in which impaired cornification and altered epidermal maturation compromise

Table 1. Summary of inferential analyses for *LOR* and *FLG*, including one-way ANOVA results and key pairwise comparisons from Tamhane's T2 post hoc test with exact *p*-values.

Gene	One-way ANOVA	Tamhane Post-hoc Test
LOR	$F(5, 24) = 20.629$, $p<0.001$	G1 vs. G5 ($p=0.009$) G1 vs. G6 ($p=0.028$) G2 vs. G5 ($p=0.002$) G2 vs. G6 ($p=0.015$) G2 vs. G4 ($p=0.050$)
FLG	$F(5, 24) = 18.266$, $p<0.001$	G1 vs. G4 ($p=0.026$) G1 vs. G6 ($p=0.009$) G2 vs. G4 ($p=0.002$) G2 vs. G6 ($p=0.005$) G3 vs. G6 ($p=0.025$)

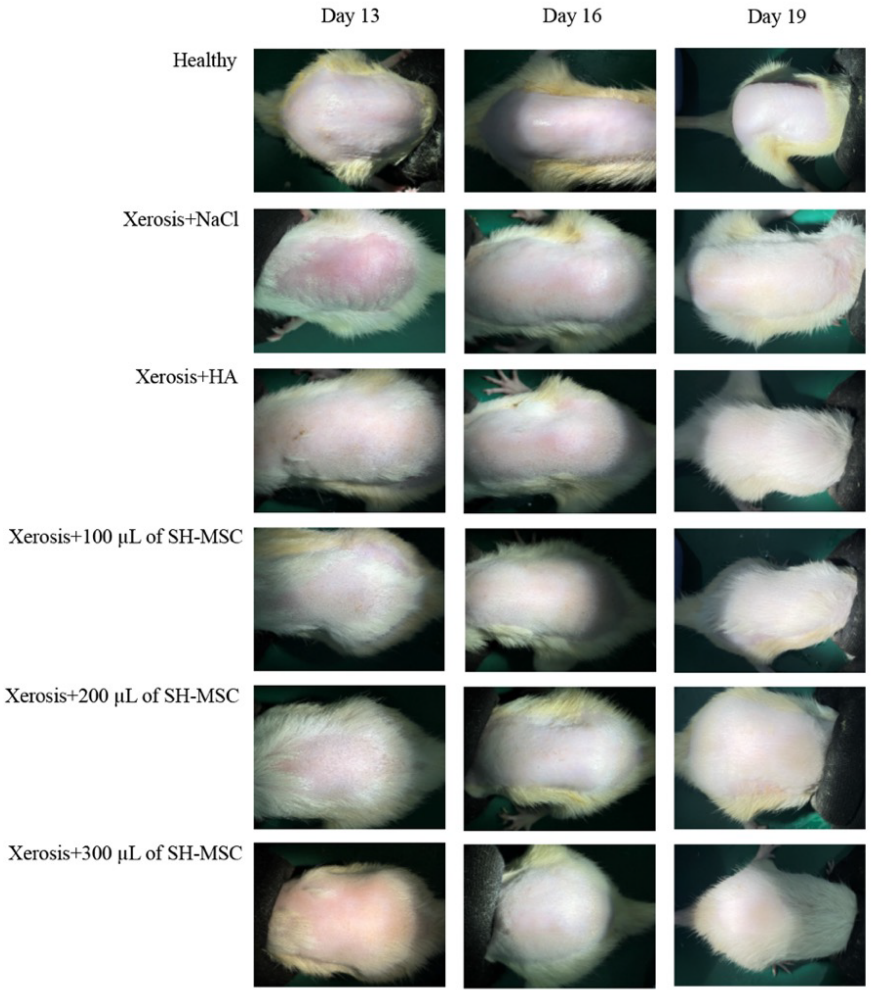


Figure 2. Representative macroscopic images of rat skin after treatment/injections. Representative images show the dorsal skin surface condition of rats in each experimental group at each observation day after treatment/injections. The images allow visual comparison of macroscopic skin changes, including dryness, scaling, erythema, and skin surface roughness, among the experimental groups.

mechanical resistance and hydration retention.[21,22] The presence of consistent tissue-level abnormalities justified the selection of terminal differentiation biomarkers as mechanistic indicators of therapeutic recovery, including FLG and LOR as core components of barrier architecture and hydration homeostasis.[1,5]

The principal finding of this study was the significant increase in *LOR* relative expression in treated groups, particularly in higher secretome dose groups, compared with the xerosis control, consistent with previous reports on the regenerative potential of MSC-derived secretome in skin repair.[14,26] LOR is a major component of the cornified envelope and plays a critical role in terminal keratinocyte differentiation and mechanical stabilization of the stratum corneum.[4] Reduced *LOR* expression has been associated with impaired barrier formation and increased susceptibility to irritants. Therefore, the marked increase in LOR expression observed after treatment suggests improved epidermal maturation and restoration of barrier structure, rather than merely superficial hydration improvement. [1,4, 27]

Prior dermatologic studies reported that MSC-conditioned media or extracellular vesicles improve epidermal regeneration, enhance lipid synthesis, and restore barrier proteins in inflammatory skin disorders, which is consistent with the present direction of effects.[28,29] The present findings therefore reinforce the positioning of hypoxia-conditioned secretome as a potent enhancer of epidermal differentiation in a xerosis-like injury setting. These results also support the broader concept that stem cell–derived bioactive products may facilitate skin repair by modulating inflammation, promoting tissue remodeling, and helping restore cutaneous homeostasis.[8,24,30]

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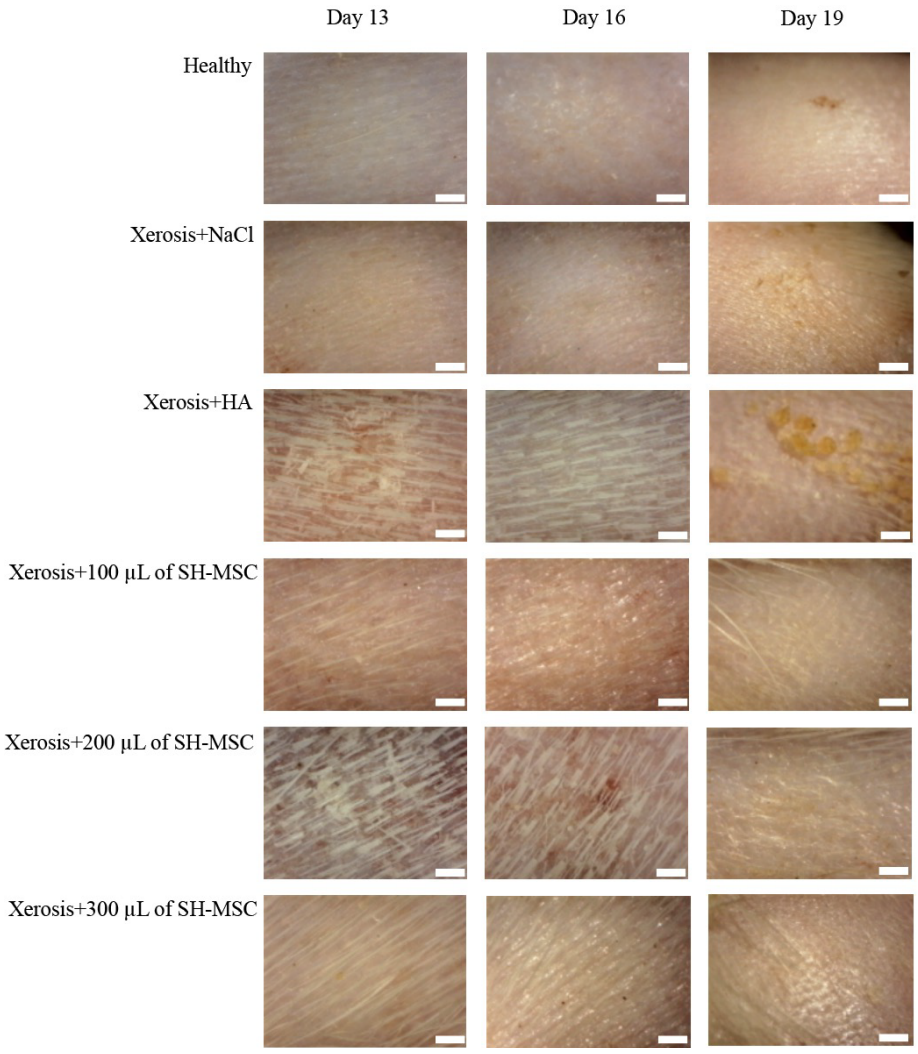


Figure 3. Representative dermoscopic skin surface images of the injection treatment groups. Dermoscopic appearances of all groups on days 13, 16, and 19 after treatment/ injection were documented. White scale bar: 2 mm.

Hypoxia preconditioning likely contributed to the observed therapeutic effect. Hypoxic culture conditions activate HIF-1α–dependent pathways and increase secretion of trophic and angiogenic mediators such as Vascular Endothelial Growth Factor (VEGF), Interleukin (IL)-10, and other regenerative cytokines. Studies have shown that SH-MSC exhibits superior regenerative and immunomodulatory properties compared with normoxic preparations.[13,31,32]

FLG also showed an increase in treatment groups compared with the xerosis control and demonstrated an upward trend across escalating secretome doses. FLG plays a central role in maintaining natural moisturizing factors, regulating stratum corneum hydration, and supporting corneocyte integrity, which makes FLG a critical molecular correlate of xerosis severity and barrier dysfunction.5,6 The improvement of FLG expression in secretome-treated groups suggests that hypoxia-conditioned secretome may contribute not only to cornified envelope reinforcement via LOR but also to restoration of hydration-related barrier biochemistry mediated by FLG-associated pathways.5,6 This combined increase of LOR and FLG supports a more comprehensive recovery of epidermal terminal differentiation and barrier homeostasis rather than a single-marker effect.1

The inclusion of HA provided an important comparator because HA is widely used to enhance hydration and support barrier function. The overall upward trends in barrier-marker expression in the secretome-treated groups, particularly at higher doses, support the interpretation that hypoxia-conditioned secretome may offer broader regenerative signaling beyond hydration support alone. A plausible biological explanation is that secretome products can simultaneously modulate inflammatory pathways and

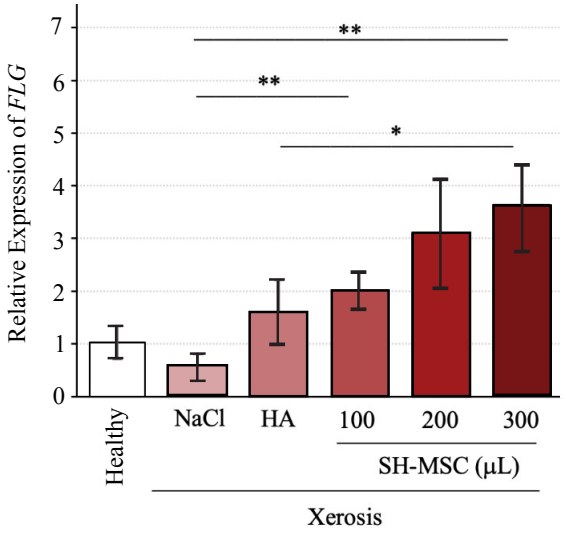


Figure 4. FLG relative expression of all groups. FLG: Filaggrin; SH-MSC: Secretome of Hypoxic Mesenchymal Stem Cell; NaCl: Sodium Chloride; HA: Hyaluronic Acid; *p<0.05; **p<0.01.

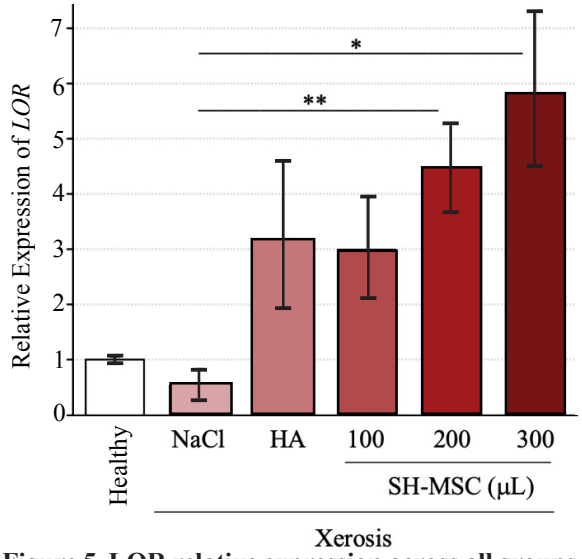


Figure 5. LOR relative expression across all groups. LOR: Loricrin; SH-MSC: Secretome of Hypoxic Mesenchymal Stem Cell; NaCl: Sodium Chloride; HA: Hyaluronic Acid; *p<0.05; **p<0.01.

keratinocyte differentiation programs, while HA primarily emphasizes hydration and extracellular matrix-related microenvironmental support.7,8 This distinction aligns with evidence that MSC-derived secretome and extracellular vesicles can reduce inflammatory signaling and improve barrier function in inflammatory dermatoses.10,28,29

Several limitations should be acknowledged. First, this study used an SLS-induced xerosis-like animal model, which may not fully replicate the biological complexity, heterogeneity, and chronic clinical course of xerosis in humans, thereby limiting direct clinical translation. Second, the outcomes were assessed at the gene expression level only, protein-level validation would provide stronger confirmation that the observed transcriptional changes were reflected at the functional protein level. Third, no direct functional barrier measurements, such as trans-epidermal water loss or skin hydration assessment, were performed, which limits interpretation of whether molecular improvement was accompanied by measurable barrier recovery. Fourth, detailed characterization of secretome composition and extracellular vesicle potency was not performed, which may influence reproducibility across batches. Therefore, future studies should incorporate protein-level validation, functional barrier measurements, standardized secretome profiling, and translational studies in more clinically relevant models to strengthen applicability to human disease.

Conclusion

Intradermal SH-MSC enhanced the expression of epidermal barrier-related genes in an SLS-induced xerosis-like rat model. Under the conditions tested, the 300 µL SH-MSC dose appeared to be the most effective for modulating both FLG and LOR expression. These findings could suggest the potential relevance of hypoxia-conditioned MSC secretome as a cell-free strategy for barrier restoration. However, further validation using protein-level and functional assessments in more clinically relevant models is still required.

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Authors' Contributions

IKAS contributed to conceptualization, study design, methodology development, data acquisition, statistical analysis, and manuscript drafting. AP contributed to research planning, experimental supervision, and interpretation

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of results. ES contributed to project supervision, critical review, and substantial revision of the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethical Statement

Ethical approval for this study was obtained from the Bioethics Committee for Medical/Health Research, Faculty of Medicine, Universitas Islam Sultan Agung Semarang (approval number: No. 25/I/2026/Komisi Bioetik).

Conflict of Interest

The authors declare that there are no conflicts of interest related to this study.

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