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ORIGINAL ARTICLE

Hypoxic Mesenchymal Stem Cells Mitigate UVB-Induced Collagen Loss by Suppressing Interleukin-6 (IL-6) and Matrix Metalloproteinase 3 (MMP-3) in a Rat Model

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Abstract

Background/Aim: Persistent ultraviolet B (UVB) radiation exposure generates oxidative stress, facilitating proinflammatory interleukin-6 (IL-6) cytokine secretion that subsequently activates the matrix metalloproteinase 3 (MMP-3) enzyme, resulting in collagen degradation. Mesenchymal stem cells cultured under hypoxic conditions (HMSCs) demonstrate the capacity to stimulate diverse cytokines and growth factors capable of preventing collagen breakdown. This study aimed to evaluate the role of HMSCs administration on MMP-3 and IL-6 levels in a rat model exposed to UVB radiation.

Methods: This study was an experimental *in vivo* study using a post-test-only control group design with a completely randomised method. The study included male Wistar rats aged 2 to 3 months, weighing between 200 and 250 grams. Male Wistar rats were divided into 5 groups: T1 (healthy rats without UVB exposure), T2 (rats exposed to UVB without treatment), T3 (rats subjected to UVB radiation received a 200 µL subcutaneous injection of hyaluronic acid - HA), T4 (rats subjected to UVB radiation received a 2.5×10^5 HMSCs cells subcutaneously) and T5 (rats subjected to UVB radiation received a 5×10^5 HMSCs cells subcutaneously). Analysis of MMP-3 and IL-6 levels was performed using the ELISA method.

Results: Administration of HMSCs at doses of 2.5×10^5 and 5×10^5 cells significantly decreased IL-6 levels to 66.22 and 42.19 pg/mL, respectively. HMSCs administration also significantly decreased MMP-3 levels, with a dose of 5×10^5 cells reducing MMP-3 levels to 3329.00 pg/mL.

Conclusion: HMSCs improve the condition of collagen loss in the skin due to UVB radiation exposure through inhibition of IL-6 and MMP-3.

Key words: Mesenchymal stem cells, hypoxia treated; HMSCs; Interleukin-6; Matrix metalloproteinase 3; Collagen.

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Introduction

Ultraviolet B (UVB) radiation represents a significant environmental stressor that profoundly impacts skin health, triggering a cascade of molecular mechanisms that compromise skin integrity and accelerate aging.[1-3] Chronic UVB exposure increases the production of oxygen-derived

reactive molecules (ROS) and nitrogen monoxide (NO), leading to significant deterioration of collagen integrity and compromising dermal architecture. The prevalence of this issue is striking, with epidemiological data revealing that 83 % of individuals under 30 years' experience collagen reduction due to UVB exposure, manifesting as wrinkles and diminished skin elasticity.[4]

The pathogenesis of UVB-induced skin damage is complex, involving multiple interconnected cellular processes. ROS overexpression initiates signalling through the mitogen-activated protein kinase (MAPK) cellular pathway following UV exposure, prompting nuclear factor kappa-β (NF-kB) nuclear migration and the ensuing inflammatory response sequence. This activation induces transcription of critical cytokines like interleukin-6 (IL-6), IL-1, TNF-α and IFN-γ, further stimulating matrix metalloproteinases (MMPs) including MMP-3 and MMP-1.[5, 6] These enzymes suppress collagen synthesis while promoting tissue degradation, creating a destructive feedback loop that accelerates skin aging.

Current therapeutic approaches primarily focus on protective strategies and tissue repair using chemical substances like hyaluronic acid (HA).[7] However, these treatments often present limitations, including potential side effects such as allergic reactions, skin dehydration and long-term complications.[7, 8] Consequently, there is a pressing necessity for novel, biologically-based strategies capable of efficiently addressing skin damage caused by UVB exposure. Mesenchymal stem cells (MSCs) emerge as a promising alternative, particularly hypoxia-preconditioned mesenchymal stem cells (HMSCs).[9] These exceptional cells exhibit significant potential in suppressing inflammation and oxidative stress while offering minimal immunogenicity.[10, 11] Preliminary research suggests HMSCs can induce anti-inflammatory cytokines, including interleukin-10 (IL-10) and growth factors such as transforming growth factor-β (TGF-β),[12] which can potentially counteract UVB-induced skin damage.[13, 14]

Despite these promising indications, significant knowledge gaps remain regarding the precise mechanisms by which HMSCs modulate inflammatory responses in UVB-induced skin damage. Specifically, the effects of HMSCs on MMP-3 and IL-6 levels remain incompletely understood. This study addresses this critical research gap by systematically evaluating the impact of subcutaneous HMSC injections at different cellular doses on inflammatory markers and collagen dynamics in a UVB-induced collagen loss model using male Wistar rats. By elucidating the potential therapeutic mechanisms of HMSCs, this research seeks to provide novel insights into innovative, cell-based strategies for mitigating photoaging and preserving skin health. The findings may not only advance understanding of UVB-induced skin damage but also pave the way for more effective, biologically-driven interventions in dermatological and aesthetic medicine.

Methods

Study design

The experimental methodology incorporated a randomised complete design with post-intervention assessment only, including five biological replications for each experimental condition. The study involved male Wistar rats aged 2 to 3 months, with each rat weighing between 200 and 250 g. The rats were divided into five distinct groups: T1 (healthy control group without UVB irradiation), T2 (negative control group exposed to UVB and administered subcutaneous NaCl as a vehicle), T3 (positive control group exposed to UVB and treated with 200 µL of subcutaneous hyaluronic acid *Staris*), T4 (treatment group 1 exposed to UVB and receiving subcutaneous HMSCs at a concentration of 2.5×10^5 cells) and T5 (treatment group 2 exposed to UVB and administered subcutaneous HMSCs at a concentration of 5×10^5 cells). Irradiation was performed five times per week (on days 1, 2, 4, 5 and 7) for two weeks. On day 15, rats in the T4 and T5 groups received single subcutaneous injections of HMSCs at their respective predetermined cell concentrations.[15] On day 22, which is 7 days after HMSC treatment, all the rats were sacrificed. Blood samples were collected using vacutainer EDTA. Skin tissue was collected in RNA-later for qRT-PCR analysis, while other skin tissue was preserved in 4 % PFA for staining.

MSCs isolation and characterisation

Rat umbilical cords with foetuses were collected and processed under sterile conditions by transferring them to a container with 0.9 % NaCl and thoroughly washing with phosphate-buffered saline (PBS). The umbilical cords were carefully

separated from foetuses, blood vessels removed and then finely minced before being evenly distributed in a 25 cm^2 tissue culture flask. After allowing tissue adherence for 3 minutes, DMEM complete medium supplemented with bovine foetal serum was introduced. Cell cultivation occurred in controlled conditions (37 °C, 5 % CO_2 atmosphere), with cellular expansion becoming evident following a fortnight of incubation. Culture maintenance involved bi-weekly partial medium replacement and cultures were maintained until reaching 80 % confluence. Cell characterisation was performed using flow cytometry by detaching cells with *BD Accutase* cell detachment solution, washing and resuspending at 1 × 10^7 cells/mL in staining buffer. Flow cytometry reagents were prepared in 5 mL falcon tubes, with 100 µL of cell suspension added to each tube. The specimens were subjected to a 30-minute incubation period at ambient temperature under light-protected conditions, followed by two consecutive washing steps using staining buffer. Subsequently, the samples were reconstituted in 300-500 µL of the aforementioned buffer. Cells were analysed for mesenchymal stem cell marker expression, focusing on positive markers CD90, CD29 and negative markers CD45 and CD31.[16-18]

Hypoxic preconditioning of MSCs

Upon achieving 80 % confluency, MSCs were supplemented with a complete culture medium to a final volume of 10 mL and transferred to a hypoxia chamber. Oxygen concentration was regulated through nitrogen gas infusion until achieving 5 % oxygen saturation, validated via an oxygen monitoring system. Following 24-hour incubation at 37 °C under hypoxic conditions, cells were harvested and subsequently resuspended in 0.9 % NaCl solution for downstream applications.[19-21]

Collagen loss induction

Following a one-week acclimatisation period, the rats were anesthetised with a combination of ketamine (60 mg/kg of body weight) and xylazine (20 mg/kg of body weight). The dorsal area was completely shaved to expose the skin for UVB irradiation. The rats were exposed to ultraviolet radiation with a peak emission of 302 nm, using a minimal erythema dose of 160 mJ/cm^2 per session. The exposure was administered for approximately 8 minutes per session, with the UV source positioned at a distance of 20 cm from the subjects. Irradiation was performed five times per week (on days 1, 2, 4, 5 and 7) for two weeks.

Collagen analysis

Collagen analysis was performed using Masson's Trichrome staining method. The histological sections were initially subjected to deparaffinisation, followed by incubation in preheated Bouin's fixative at a temperature range of 54-64 °C for a duration of 60 minutes. Subsequently, the specimens underwent a 10-minute cooling phase and were then thoroughly rinsed under running water. The specimens were then subjected to a sequential staining protocol utilising a series of specialised reagents, including Weigert's Iron haematoxylin, Beirich scarlet/acid fuchsin solution, phosphomolybdic/phosphotungstic acid mixture and Aniline Blue. Each staining phase was conducted with precisely defined incubation periods to ensure optimal results. After a final acetic acid treatment, the slides were dehydrated and coverslips were applied. The fraction of collagen was calculated by detecting the blue area under the 400×magnification fields of each group (four files randomly in each group) using Image-Pro Plus 6.0 software

Inflammatory marker analysis

Quantitative analysis of MMP-3 and IL-6 levels was conducted under enzyme-linked immunosorbent assay (ELISA). The skin samples collected on day 22 were isolated using RIPA buffer (Sigma Aldrich) following the manufacturer's protocol to prepare for the ELISA assay. ELISA kits from Finetest® (Wuhan, China) were utilised, following the manufacturer's prescribed protocol. Absorbance was measured at 450 nm using a microplate reader.

Statistical analysis

Statistical analyses were conducted utilising SPSS software version 25.0 (IBM Corp, Armonk, NY, USA). The normality of data distribution was evaluated using the Shapiro-Wilk test. Descriptive statistics were presented as means accompanied by their respective standard deviations. Statistical comparisons between experimental groups were performed using either one-way ANOVA for parametrically distributed datasets or the Kruskal-Wallis test for nonparametric distributions. Post-hoc analyses employed Tukey's Honestly Significant Difference (HSD) test for parametric comparisons and Dunn's test for nonparametric evaluations. A probability threshold of $p < 0.05$ was applied to determine statistical significance, with all inferences calculated within a 95 % confidence interval framework.

Results

Anatomical observations on day 15 revealed that rats exposed to UVB radiation exhibited erythema and wrinkling on the dorsal skin compared to the healthy control group (Figure 1 A-B). Microscopic examination using Masson's trichrome staining for collagen was conducted on day 15 to assess UVB-induced collagen loss (Figure 1 C-D). The results demonstrated evident collagen loss in UVB-exposed rats compared to unexposed controls. In the UVB exposure groups, the percentage of collagen fibres significantly decreased to 10.23 % ± 1.78, compared to the healthy group, which had 37.89 % ± 3.56 (Figure 1E).

Umbilical cords were obtained from 19-day pregnant rats. The isolated cells were cultured in specialised medium using culture flasks. After the fourth passage and 24 hours of hypoxia treatment, the MSCs exhibited adherent growth with a characteristic spindle-shaped morphology (Figure 2A). To validate the multipotency of the hypoxia-treated mesenchymal stem cells (HMSCs), they were cultured in osteogenic and adipogenic induction media for 14 days. The osteogenic lineage commitment was verified through the detection of calcium-rich deposits, which were rendered visible via Alizarin red staining methodology (Figure 2B). The accumulation of lipid droplets demonstrated adipogenic differentiation, detected using Oil Red O staining (Figure 2C). The red coloration in both cultures indicated successful differentiation of HMSCs into osteocytes and adipocytes. Flow cytometry was used to validate the isolated HMSCs by analysing the expression of specific surface markers. The quantitative results showed positive expression of CD90 (99.98 %) and CD29 (95.25 %), while CD45 (0.12 %) and CD31 (0.05 %) were negatively expressed (Figure 2D). These findings confirm the characteristic surface marker profile of mesenchymal stem cell.

The results of IL-6 expression analysis revealed that the healthy rat group exhibited the lowest mean IL-6 levels (37.13 ± 9.40 pg/mL), followed by the T5 treatment group (UVB-irradiated rats

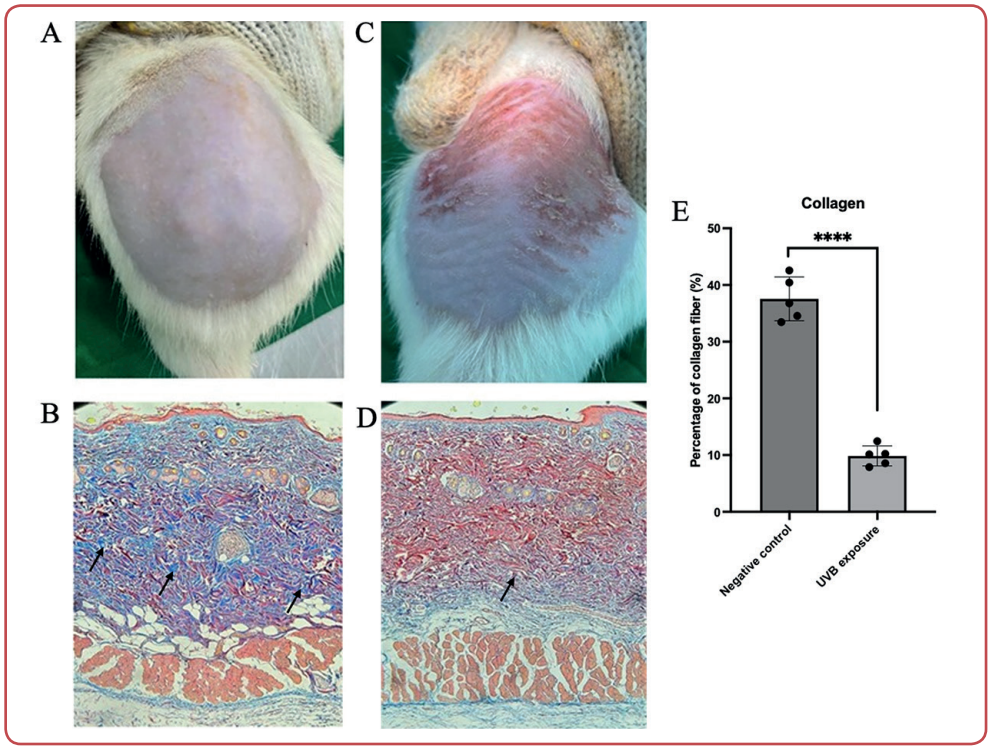

*Figure 1: The validation of collagen in rat skin: (A) Healthy rats show no redness or wrinkles on the skin. (B) UVB-exposed rats exhibit visible redness and wrinkles on the skin. (C) Masson's trichrome staining of healthy rat skin reveals blue coloration, indicating normal collagen production and (D) UVB-exposed rat skin shows red coloration in Masson's trichrome staining, indicating inhibited collagen expression. The black arrow indicates the deposition of collagen. (E) Quantitative analysis of the percentage of collagen in each group ****p < 0.001 compared to the control group, t-test study.*

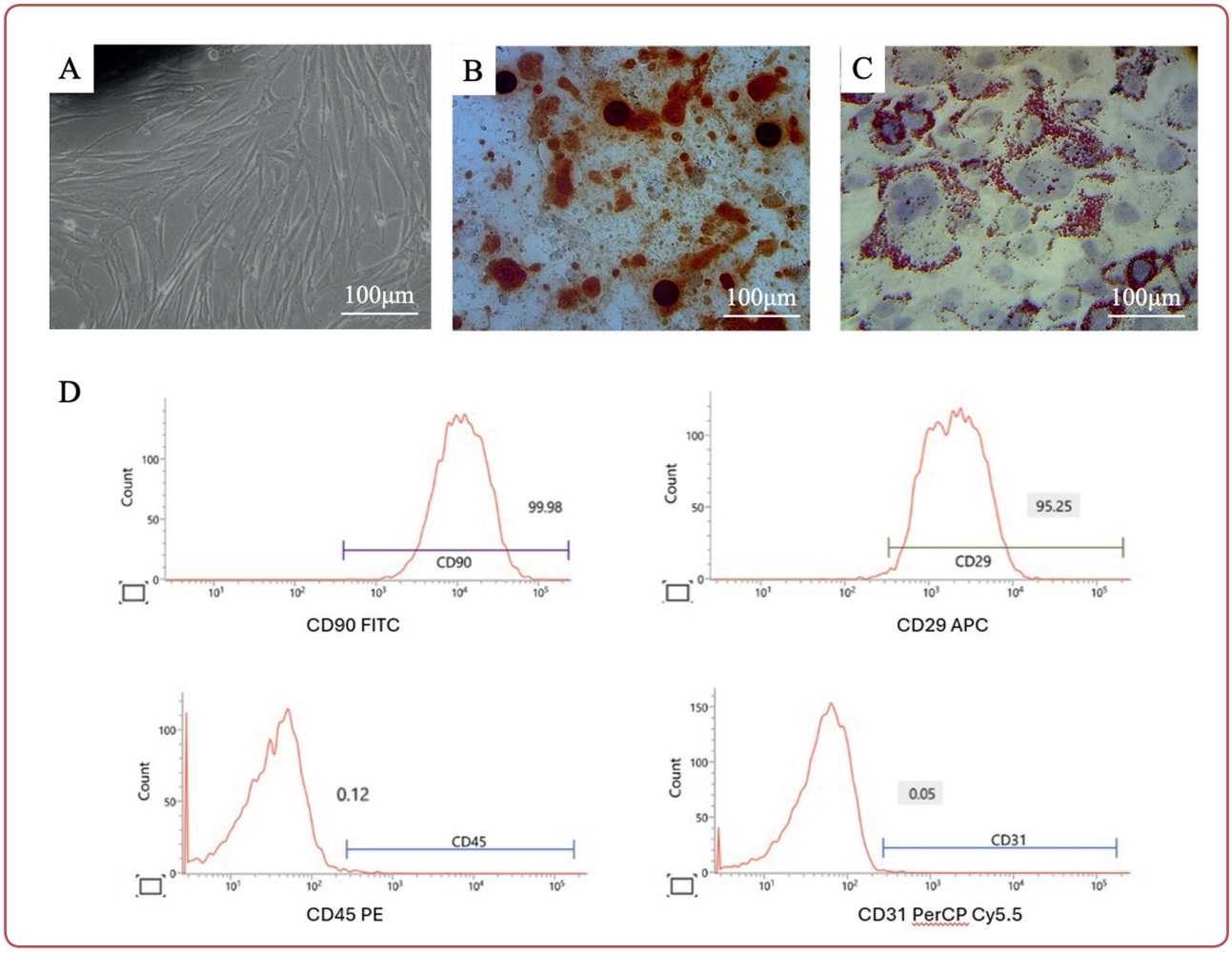

Figure 2: Validation of hypoxia-preconditioned mesenchymal stem cells (HMSCs). (A) HMSCs at passage 4 showing 80 % confluence (40x magnification) (B) Calcium deposition visualised by Alizarin Red staining (400x magnification). (C) Lipid deposition demonstrated by Oil Red O staining (400x magnification). (D) Immunophenotypic characterisation of HMSCs via flow cytometric assessment of characteristic cellular markers, including CD90+, CD29+, CD45- and CD31-.

treated with 5 × 10^5 HMSCs subcutaneously) at 42.19 ± 5.30 pg/mL and the T4 group (UVB-irradiated rats treated with 2.5 × 10^5 HMSCs subcutaneously) at 66.23 ± 17.48 pg/mL. The highest value of IL-6 level (272.02 ± 12.74 pg/mL) were detected in the untreated UVB-irradiated cohort that received only physiological saline solution (0.9 % NaCl, 200 µL) as vehicle control (Figure 3).

In a group of UVB-irradiated rats that received HA (T3 group, positive control), the level of IL-6 induced by UVB exposure was not significantly reduced compared to the group exposed to UVB only (T2 group, negative control). In contrast, HMSC significantly reduces the levels of IL-6 in UV-B irradiated rats. UV-B exposure leads to an increase in IL-6 levels, but both doses of HMSC effectively lower these levels compared to the control group that was exposed to UV-B only (T2 group). The results suggest that HMSC treatment effectively reduces IL-6 levels in UVB-irradiated rats.

The analysis of MMP-3 expression revealed that the healthy rat group exhibited the lowest mean MMP-3 levels (806.84 ± 98.82 pg/mL), followed by the T5 treatment group (UVB-irradiated rats treated with 5 × 10^5 HMSCs subcutaneously) at 3,329.00 ± 192.83 pg/mL and the T4 group (UVB-irradiated rats treated with 2.5 × 10^5 HMSCs subcutaneously) at 4,099.80 ± 269.08 pg/mL. The highest mean MMP-3 level (8,065.20 ± 384.89 pg/mL) was observed in the negative control group, which received UVB irradiation and only 200 µL of 0.9 % NaCl as a vehicle. T3 group, (positive control) showed a decrease in MMP-3 levels up to 5,492.60 ± 271.98 pg/mL compared to the T2 group (negative control) (Figure 4). These results indicate that HMSC treatment significantly reduced MMP-3 levels in UVB-irradiated rats.

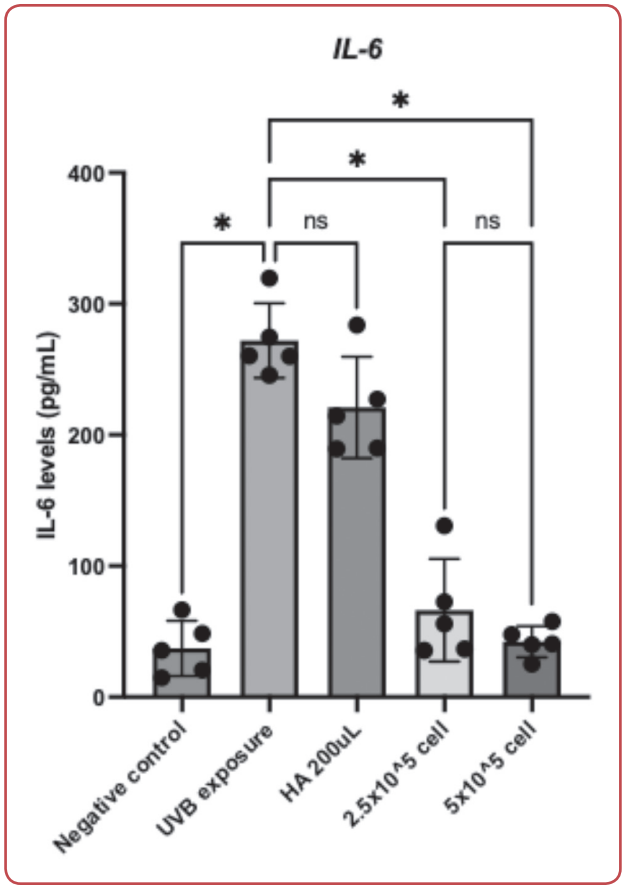

*Figure 3: Interleukin 6 (IL-6) levels in rat models of collagen loss. Data are presented as mean values from 5 animal models ± SD. * $p < 0.05$ indicates significant difference and ns $p > 0.05$ indicates no significant difference. The rats were divided into five distinct groups: T1 (healthy control group without UVB irradiation), T2 (negative control group exposed to UVB and administered subcutaneous NaCl as a vehicle), T3 (positive control group exposed to UVB and treated with 200 µL of subcutaneous hyaluronic acid - HA), T4 (treatment group 1 exposed to UVB and receiving subcutaneous HMSCs at a concentration of 2.5 × 10^5 cells) and T5 (treatment group 2 exposed to UVB and administered subcutaneous HMSCs at a concentration of 5 × 10^5 cells).*

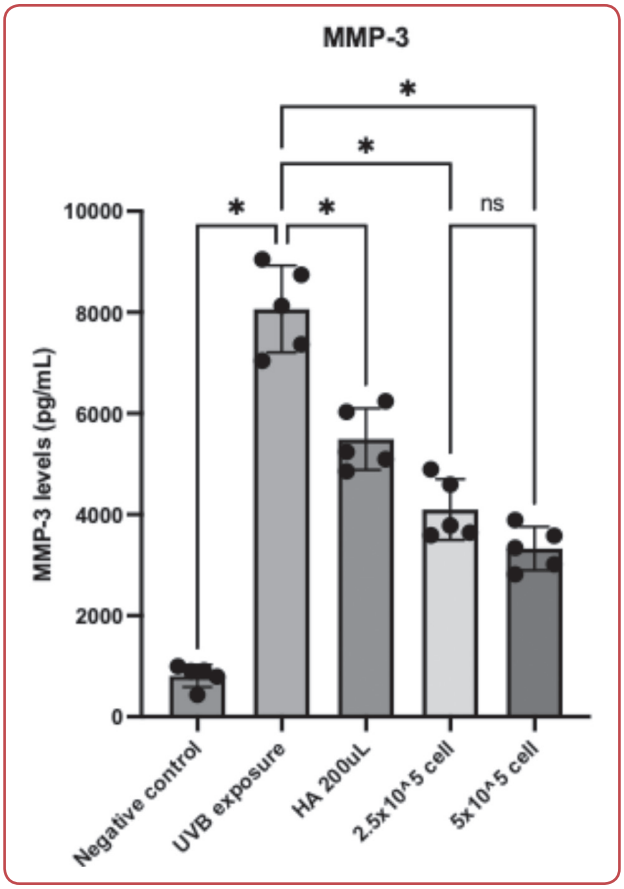

*Figure 4: Matrix metalloproteinase 3 (MMP-3) levels in rat models of collagen loss. Data are presented as mean values from 5 animal models ± SD. * $p < 0.05$ indicates significant difference and ns $p > 0.05$ indicates no significant difference. The rats were divided into five distinct groups: T1 (healthy control group without UVB irradiation), T2 (negative control group exposed to UVB and administered subcutaneous NaCl as a vehicle), T3 (positive control group exposed to UVB and treated with 200 µL of subcutaneous hyaluronic acid - HA), T4 (treatment group 1 exposed to UVB and receiving subcutaneous HMSCs at a concentration of 2.5 × 10^5 cells) and T5 (treatment group 2 exposed to UVB and administered subcutaneous HMSCs at a concentration of 5 × 10^5 cells).*

Discussion

Ultraviolet B (UVB) radiation represents a critical environmental stressor that significantly compromises skin integrity through complex molecular mechanisms of oxidative damage.[22] Presened study provides compelling evidence of the regenerative capacity of mesenchymal stem cells conditioned under low oxygen tension (HMSCs) to counteract ultraviolet B-mediated collagen destruction through regulation of inflammation and redox-sensitive signalling mechanisms. The pathogenesis of UVB-induced skin damage is characterised by a multifaceted inflammatory response initiated through the dysregulated production of oxygen-derived free radicals and non-radical reactive species.[23,24] Previous studies reported that exposure to UVB at a MED of 150 mJ/cm^2 significantly increased oxidative stress levels by raising malondialdehyde (MDA) gene expression, an oxidant enzyme, four times higher than in healthy groups.[25] UVB exposure activates the canonical NF-kB-mediated transcriptional regulation pathway, initiating a harmful molecular sequence that suppresses anti-inflammatory cytokines while simultaneously elevating pro-in-

flammatory mediators. This inflammatory environment creates a conducive milieu for sustained collagen degradation through enhanced matrix metalloproteinase (MMP) activity and reduced collagen synthesis.[26, 27]

Presented findings demonstrate a significant breakthrough in understanding how HMSCs can interrupt this inflammatory cycle. The dose of HMSCs ranging from 5×10^5 to 2.5×10^6 cells has shown beneficial effects in several disease conditions.[17, 28, 29] Since lower doses already have beneficial effects, those were used those this study. It was found that the administration of HMSCs, particularly at the 5×10^5 cell dose, resulted in remarkable reductions in both interleukin-6 (IL-6) and MMP-3 levels. This observation is pivotal, as IL-6 plays a crucial role in maintaining and expanding the process of collagen reduction in UVB-exposed skin. The mechanism underlying HMSC's therapeutic action appears to be multifaceted. By inducing anti-inflammatory cytokine IL-10 expression, HMSCs effectively suppress IL-6 levels by activating intracellular regulatory proteins, including suppressors of cytokine signalling 3 (SOCS3).[30-32] This cytokine modulation represents a sophisticated cellular response to oxidative stress, demonstrating the adaptive potential of hypoxia-preconditioned stem cells.[33, 34]

Moreover, the significant reduction in MMP-3 levels aligns with emerging research on MSC-mediated tissue regeneration. The HMSCs effectively counteract UVB-induced DNA damage by intervening in critical cellular stress response pathways.[35, 36] By stabilising hypoxia-inducible factor-1α (HIF-1α) and activating antioxidant enzymatic mechanisms, these cells create a protective microenvironment that mitigates oxidative stress and promotes cellular resilience.[37, 38] The 5×10^5 cell dose demonstrated optimal therapeutic efficacy, suggesting a critical threshold in stem cell-mediated tissue protection. This finding has significant implications for potential clinical applications, providing a more nuanced understanding of cellular dosing strategies in regenerative medicine. Presented results extend beyond immediate inflammatory suppression, highlighting the potential of HMSCs in regulating complex cellular signal transduction pathways by maintaining homeostatic equilibrium between inflammation generation and cellular detoxification systems, these cells offer a promising approach to preventing UVB-induced collagen degradation and photoaging.

Conclusion

HMSCs showed significant potential in reducing collagen loss caused by ultraviolet B exposure by effectively inhibiting inflammatory markers. Presented findings suggest that HMSCs could be a promising therapeutic approach for preventing photoaging and preserving skin integrity by lowering the levels of MMP-3 and IL-6.

Ethics

The ethics committee of the Medical Faculty, Universitas Islam Sultan Agung, Semarang, Indonesia, approved the study under decision No 398/X/024/Komisi Bioetik, dated 30 October 2024.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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