IJPST
Indonesian Journal of Pharmaceutical Science and Technology

Research Article
Vol. 13 No. 1 (2026): 32-38
https://doi.org/10.24198/ijpst.v13i1.63650

Hypoxic MSCs Reduce UV-B Collagen Loss by Modulating CD68 and TNF-α Expression

Sri Umi Ati[1*], Agung Putra[2,3,4], Titiek Sumarawati[4], Eko Setiawan[4,5], Sugeng Ibrahim[2,6], and Dodik Taskworo[7]
[1]Student of Postgraduate Biomedical Science, Universitas Islam Sultan Agung, Semarang, Indonesia
[2]Stem Cell and Cancer Research (SCCR) Laboratory, Semarang, Indonesia
[3]Department of Doctoral Biomedical Science, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, ndonesia
[4]Department of Postgraduate Biomedical Science, Universitas Islam Sultan Agung, Semarang, Indonesia
[5]Department of Surgery, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia
[6]Faculty of Medicine, Soegijapranata Catholic University, Semarang, Indonesia
[7]Neurology Department, Faculty of Medicine Diponegoro University/Dr. Kariadi Hospital, Semarang, Indonesia

Abstract
Ultraviolet-B (UV-B) radiation-induced skin photoaging is marked by collagen degradation and chronic inflammation, with limited effective treatments currently available. Hypoxic-preconditioned mesenchymal stem cells (H-MSCs) offer a novel therapeutic approach due to their immunomodulatory capabilities. This study evaluated the effects of H-MSCs at two doses (2.5×10^5 and 5×10^5 cells) on UVB-induced collagen loss, focusing on CD68 expression and TNF-α levels in a rat model. Male Wistar rats were divided into five groups: healthy controls, UV-B-exposed negative controls (saline), positive controls (hyaluronic acid), and two H-MSC-treated groups. After UV-B exposure (160 mJ/cm², five times per week for two weeks), validated H-MSCs were administered subcutaneously. Collagen content was assessed histologically, while CD68 gene expression and TNF-α levels were measured by qRT-PCR and ELISA, respectively. UVB exposure led to significant reductions in collagen and increased levels of inflammatory markers. H-MSC treatment showed dose-dependent anti-inflammatory effects, with the higher dose (5×10^5 cells) optimally reducing CD68 expression and TNF-α levels, nearly matching healthy controls. These results suggest that H-MSCs, particularly at higher doses, may be a promising therapy for UVB-induced skin damage and collagen loss.

Keywords: CD68, collagen loss, HMSCs, UVB

Article History:
Submitted 23 May 2025
Revised 20 February 2026
Accepted 21 February 2026
Published 28 February 2026

*Corresponding author:
miufk005@gmail.com

Citation:
Ati SU, Putra A, Sumarawati T, Setiawan E, Ibrahim S, Taskworo D. Hypoxic MSCs Reduce UV-B Collagen Loss by Modulating CD68 and TNF-α Expression Indonesian Journal of Pharmaceutical Science and Technology. 2026: 13 (1), 32-38.

MSC Hipoksia Mengurangi Kehilangan Kolagen akibat UV-B melalui Modulasi Ekspresi CD68 dan TNF-α

Abstrak
Penuaan kulit akibat radiasi Ultraviolet-B (UV-B) ditandai oleh degradasi kolagen dan peradangan kronis, dengan terapi efektif yang masih terbatas. Sel punca mesenkimal yang diprakondisikan dalam kondisi hipoksia (H-MSC) menawarkan pendekatan terapeutik baru melalui kemampuan imunomodulatornya. Penelitian ini mengevaluasi efek H-MSC dengan dua dosis ($2,5\times10^5$ dan 5×10^5 sel) terhadap kehilangan kolagen yang diinduksi UV-B, dengan fokus pada ekspresi CD68 dan kadar TNF-α pada model tikus. Tikus Wistar jantan dibagi menjadi lima kelompok: kontrol sehat, kontrol negatif terpapar UV-B (salin), kontrol positif (asam hialuronat), serta dua kelompok perlakuan H-MSC. Setelah paparan UV-B (160 mJ/cm², lima kali per minggu selama dua minggu), H-MSC tervalidasi diberikan secara subkutan. Kandungan kolagen dinilai secara histologis, sedangkan ekspresi gen CD68 dan kadar TNF-α diukur masing-masing menggunakan qRT-PCR dan ELISA. Paparan UV-B menyebabkan penurunan signifikan kandungan kolagen dan peningkatan penanda inflamasi. Perlakuan H-MSC menunjukkan efek antiinflamasi yang bergantung dosis, dengan dosis tinggi (5×10^5 sel) secara optimal menurunkan ekspresi CD68 dan kadar TNF-α hampir setara dengan kelompok sehat. Hasil ini menunjukkan bahwa H-MSC, terutama pada dosis lebih tinggi, berpotensi menjadi terapi yang menjanjikan untuk kerusakan kulit dan kehilangan kolagen akibat paparan UV-B.

Kata Kunci: CD68, kehilangan kolagen, HMSCs, UVB

1. Introduction

Ultraviolet B (UVB) radiation is the primary factor causing exogenous aging.[1] Chronic exposure to UVB radiation increases nitric oxide (NO) and reactive oxygen species (ROS), decreasing collagen content.[2] This continuous reduction in collagen due to UVB exposure correlates with the aging process known as photoaging, a complex skin aging issue, leading to cumulative structural and physiological changes and progressive alterations in all skin layers, particularly in light-exposed areas.[3] UVB exposure causes cellular damage that triggers macrophage (CD68) modulation as part of the immune response to clear dead and damaged cells and secrete pro-inflammatory cytokines.[4,5] Overexpression of ROS due to UVB radiation activates the mitogen-activated protein kinase (MAPK) pathway and nuclear factor kappa-β (NF-kβ), inducing transcription of pro-inflammatory cytokines such as TNF-α.[6,7] Administration of Hypoxia Mesenchymal Stem Cells (HMSCs) is known to have numerous benefits in addressing various health issues. Still, no studies have reported the effects of HMSCs on M1 macrophage profiles and TNF-α levels, particularly in collagen loss conditions.[8,9] The advantage of HMSCs over other treatments is their non-immunogenic nature and lack of side effects. Therefore, this research is crucial for further examining the effects of HMSCs on CD68 expression, an M1 macrophage marker, and TNF-α levels in male Wistar rats with UV-B-induced collagen loss.

Previous research reported that 83% of young to adult individuals experience premature aging due to UV-B exposure, resulting in wrinkles and decreased skin elasticity.[10] Clinical studies show that aging occurs in 40% of adults under 55, with moderate to severe changes.[11] Skin health issues due to UV-B exposure continue to increase annually, with a study in Australia showing 1,539 individuals aged 20-55 experiencing photoaging, with a total prevalence of 72% in men and 47% in women under 30 years old.[12,13]

Populations in tropical areas or those frequently exposed to direct sunlight have a higher risk of significant collagen degradation. This high prevalence is found across age groups, from young adults to older people. Previous studies have reported that UVB exposure causes the expression of inflammatory molecules, ultimately leading to collagen degradation.[14] UVB exposure also affects macrophage expression in skin cells.[15] Continuous macrophage infiltration eventually causes sustained damage to the dermal ECM due to the release of MMPs and ROS.[16,17]

Additionally, activated macrophages secrete pro-inflammatory molecules, causing further damage to cells and tissues. The immunomodulatory ability of hMSCs is reported to induce the release of anti-inflammatory cytokines, such as IL-10, and growth factors, including transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), Platelet-Derived Growth Factor (PDGF), and Hepatocyte Growth Factor (HGF), which can increase collagen levels.[18–20]

The role of HMSCs in regulating macrophage expression and its effect on TNF-α levels in collagen loss models has not been studied. Therefore, this research is important for identifying the role of HMSCs in regulating M1 macrophage expression, as evidenced by CD68 staining and TNF-α levels, in Wistar rats with UVB-induced collagen loss *in vivo*.

2. Materials and Method

2.1. Tools

Biosafety cabinet, CO_2 incubator (37°C, 5% CO_2), inverted microscope, refrigerated centrifuge, flow cytometer, NanoDrop spectrophotometer, real-time PCR system (Illumina), UVB lamp (302 nm, 160 mJ/cm², 20 cm distance), microtome, light microscope, analytical balance, and standard histology staining equipment.

2.2. Materials

Male Wistar rats (8–10 weeks, 200–250 g), Dulbecco's Modified Eagle Medium (DMEM, Gibco), fetal bovine serum (FBS, Gibco), penicillin–streptomycin (Gibco), phosphate-buffered saline (PBS, pH 7.4), sterile saline (NaCl 0.9%), nitrogen gas for hypoxia, hyaluronic acid, and xylazine for anesthesia, Masson's Trichrome reagents, TNF-α ELISA kit (Finetest®, Cat. ER1393), TRIzol™ Reagent (Invitrogen, Cat. 15596026), cDNA synthesis kit (Invitrogen), SYBR Green Master Mix (Illumina), and primers for CD68 and GAPDH (synthesized by IDT®).

2.3. Methods

2.3.1. Ethical Clearance Statement

All experimental procedures received approval from the Bioethics Committee of the Faculty of Medicine, Universitas Islam Sultan Agung (Approval No. 426/X/2024/Komisi Bioetik) and adhered strictly to ARRIVE 2.0 guidelines. Animals were maintained in individually ventilated cages under a controlled 12-hour light/dark cycle with unrestricted access to food and water, supplemented by environmental enrichment, and afforded 24-hour recovery intervals following UVB exposure sessions.

2.3.2. Study design

Sample size (n=5 per group, total n=25 male Wistar rats) was determined a priori via power analysis using G*Power software (version 3.1.9.7), assuming α=0.05, power=80% (1-β=0.80), and medium effect size (Cohen's d=0.5) for primary outcomes based on pilot data and prior UVB rat studies. This yielded minimum n=5/group for one way ANOVA. Justification aligns with ARRIVE 2.0 guidelines. The experimental framework followed a post-intervention assessment design with randomized group allocation. The experimental groups comprised: a healthy group, UVB exposure group, a positive control group that received standard therapy control hyaluronic acid 200 µL, and two HMSC intervention groups receiving either 2.5 × 10^5 cells or 5 × 10^5 cells.

2.3.3. Hypoxic MSCs preparation

Mesenchymal stem cells were extracted from rat umbilical tissue under aseptic conditions. The processing involved thorough PBS cleansing, vessel elimination, and tissue fragmentation before transfer to culture vessels. The growth medium consisted of DMEM enriched with antimicrobial agents and fetal bovine serum. Cultures were maintained at physiological temperature (37°C) in a CO_2-regulated environment until reaching optimal density. Using standardized staining protocols, identity verification employed flow cytometric analysis to examine characteristic markers (CD90/CD29-positive; CD45/CD31-negative). Upon achieving 80% confluence, stem cell preparations underwent hypoxic conditioning. This process involved nitrogen-mediated oxygen reduction to 5% for 24 hours, followed by cell recovery and suspension in physiological saline.

2.3.4. Collagen loss induction

Following environmental adaptation, animals underwent dorsal hair removal and anesthetic administration (ketamine 60 mg/kg combined with xylazine 20 mg/kg). UV exposure parameters included 302 nm radiation at 160 mJ/cm², delivered from a distance of 20 cm. The regimen consisted of five weekly sessions over two weeks. HMSC administration occurred on day 15 post-initiation.

2.3.5. Collagen Analysis

Tissue collagen was evaluated using Masson's Trichrome histological analysis. The procedure encompassed tissue deparaffinization, Bouin's solution treatment, and sequential application of specialized stains, including Weigert's Iron Hematoxylin, Biebrich Scarlet/Acid Fuchsin, phosphomolybdic/phosphotungstic acid, and Aniline Blue, followed by dehydration and mounting.

2.3.6. TNF-α analysis

TNF-α quantification was performed using a commercial ELISA kit (Finetest® Cat. ER1393). The protocol involved careful sample preparation and standardized immunoassay procedures, with spectrophotometric measurement at 450 nm.

2.3.7. CD68 gene expression analysis by qRT-PCR

Total RNA was isolated from rat skin tissue samples using TRIzol™ Reagent (Invitrogen, Cat. 15596026) according to the manufacturer's protocol. RNA purity and concentration were determined by the Nanodrop. For cDNA synthesis, 500 ng of total RNA was reverse-transcribed using a cDNA synthesis kit (Invitrogen) according to the provided instructions. Quantitative real-time PCR (qRT-PCR) was performed using SYBR Green Master Mix and a real-time PCR system (Illumina). The primer sequences for CD68 were forward 5'-GCTACATGGCGTCCGAGG-3' and reverse 5'-CTTCTCGGATGCCGGTGTT-3'. GAPDH was used as the housekeeping gene with the following primers: forward 5'-TGCACCACCAACTGCTTAGC-3' and reverse 5'-GGCATGGACTGTGGTCATGAG-3'. All reactions were run in triplicate. The relative expression of CD68 was calculated using the comparative Ct (ΔΔCt) method, normalized to GAPDH expression

2.3.8. Statistical analysis

Data distribution was evaluated for normality using the Shapiro-Wilk test. CD68 gene expression data demonstrated a non-normal distribution ($p<0.05$), necessitating the application of the Kruskal-Wallis test with the Mann-Whitney post hoc test. In contrast, TNF-α gene expression data met normality criteria ($p\geq0.05$), allowing one-way analysis of variance (ANOVA) followed by Tukey's post hoc analysis. Statistical significance was established at $p<0.05$. All analyses were performed using SPSS version 26.

3. Result

3.1. MSCs isolation and validation

The population utilized in this study consisted of MSCs at passage 7, characterized by their spindle-like morphology and adherence to the flask surface (Figure 1A). The osteogenic and adipogenic differentiation potential of MSCs also serves as a validation method for these cells. MSCs demonstrated the capacity to differentiate into osteogenic lineages, as evidenced by calcium deposits visualized by red staining with

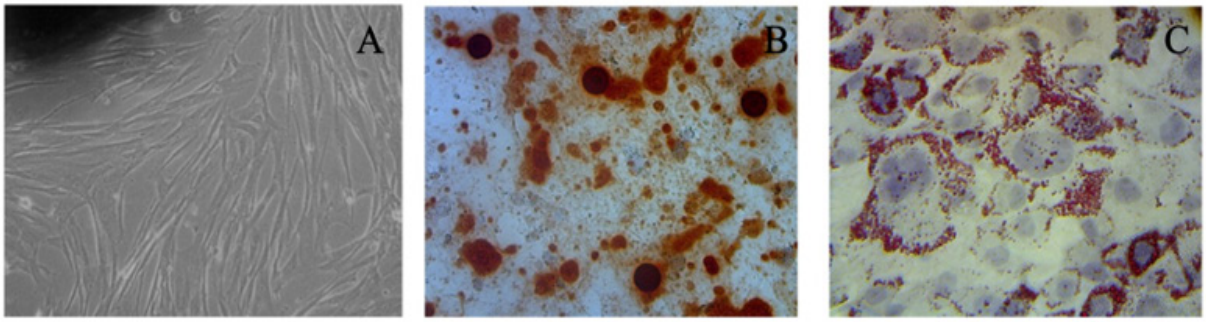

Figure 1. Microscopic observation results of MSC morphology. (A) MSCs at 80% confluence exhibiting spindle-like morphology at 40× magnification. (B) MSC differentiation assay results in osteogenic culture medium at 400× magnification. (C) MSC differentiation assay results in adipogenic culture medium at 400× magnification.

Alizarin Red (Figure 1B). Additionally, MSCs exhibited adipogenic differentiation potential, indicated by the accumulation of brown-colored lipid droplets (Figure 1C). The isolated MSCs were validated by immunophenotyping via flow cytometry, demonstrating their expression of characteristic MSC surface markers. This study showed that the MSCs used exhibited positive expression of CD90 (99.98%) and CD29 (95.25%) while displaying a negative expression of CD45 (0.12%) and CD31 (0.05%) (Figure 2).

3.2. Collagen loss validation

The collagen loss animal model was validated by observing tissue structure using Masson's trichrome staining technique. The histological profile of the non-UV-B exposed rat group consisted of epidermis, dermis, and hypodermis. The outermost layer is the epidermis, with a thin keratin spread over it. Beneath the epidermis lies the dermis, containing connective tissue with dense collagen and elastic fibers. Collagen fibers are indicated by the blue staining in Figure 3A-B, while the red coloration in the image represents keratin, cytoplasm, and muscle tissue.

The skin histology of the UV-B-exposed group showed collagen fiber denaturation, as evidenced by the predominance of red coloration in the dermis. A noticeable difference in the connective tissue and collagen structure appeared more loosely arranged in the UV-B-exposed group. UV-B exposure can alter fibroblast regulation of collagen homeostasis, leading to an imbalance between collagen synthesis and degradation.

3.3. The effect of HMSCs on TNF-α levels and CD68 gene expression

This study found that H-MSC treatment significantly decreased CD68 gene expression in the skin tissue of collagen-loss model rats in a dose-dependent manner (Figure 4A). The most pronounced reduction occurred in the group receiving 5×10^5 HMSCs in 200 µL (2.96 ± 1.02 relative expression), representing the optimal therapeutic dose. Furthermore, TNF-α levels measured by ELISA were markedly elevated following UVB irradiation (369.30 ± 57.51 pg/ml) compared with the Healthy group (66.60 ± 40.98 pg/ml; Figure 4B).

Significant changes in TNF-α levels were observed after HA and H-MSC treatments, with the H-MSC group showing a notably lower decrease. The most significant reduction in TNF-α levels was observed in the UVB-exposed group that received HMSC at a dose of 5×10^5 cells. This group had a TNF-α level of 80.50 ± 23.46 pg/ml, approaching the normal range observed in the healthy group. Notably, substantial biological variability (TNF-α SD ±40 pg/mL in controls) underscores the

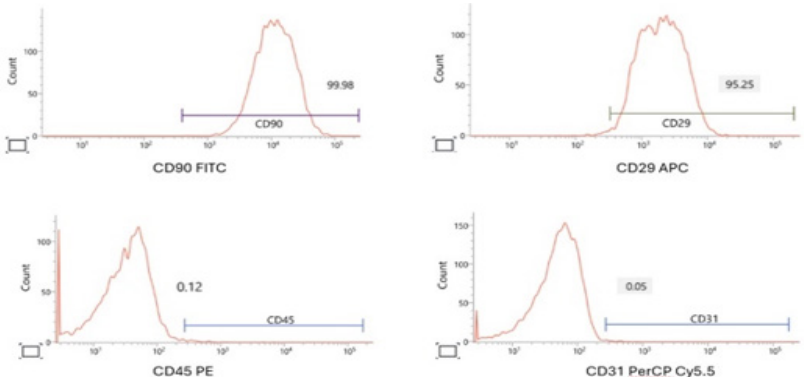

Figure 2. MSC immunophenotyping for CD90, CD29, CD45, and CD31 expression using flow cytometry analysis.

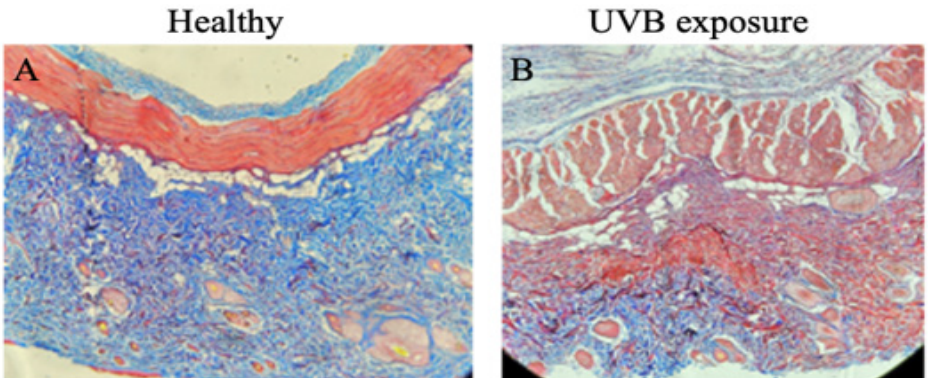

Figure 3. (A) Collagen, indicated by blue staining, is more abundant in healthy rats compared to (B) UVB-exposed rats without treatment (100× magnification).

heterogeneity of inflammatory responses in this model. In addition, spearman correlation analysis revealed a significant positive association between CD68 gene expression and TNF-α levels (r=0.72, p<0.01), supporting coordinated HMSC-mediated suppression of these inflammatory markers.

4. Discussion

UVB radiation represents a primary environmental risk factor for skin photoaging, triggering a cascade of cellular and molecular events that lead to structural and functional alterations in the skin.6 This study validated that UVB exposure successfully induced a collagen loss model, as evidenced by both physical and microscopic observations. Compared to healthy controls, the significantly elevated CD68 gene expression and TNF-α levels in UVB-exposed negative control groups align with established literature on UV-induced inflammatory responses. The inflammatory response to UVB exposure involves a complex interplay between immune cells and inflammatory mediators.[14,21] Our findings demonstrated that UVB radiation modulates M1 macrophage (CD68) infiltration, initiating a cycle of repeated immune cell recruitment with each exposure.[22,23]

This chronic inflammatory state, characterized by sustained macrophage infiltration, leads to progressive dermal extracellular matrix (ECM) degradation through the continuous release of matrix metalloproteinases (MMPs) and reactive oxygen species (ROS).[24,25]

A key finding of this study was the dose-dependent therapeutic effect of HMSC administration. Both treatment groups showed significant improvements in inflammatory markers, with the higher HMSC dose (5×10⁵ cells) demonstrating superior efficacy in

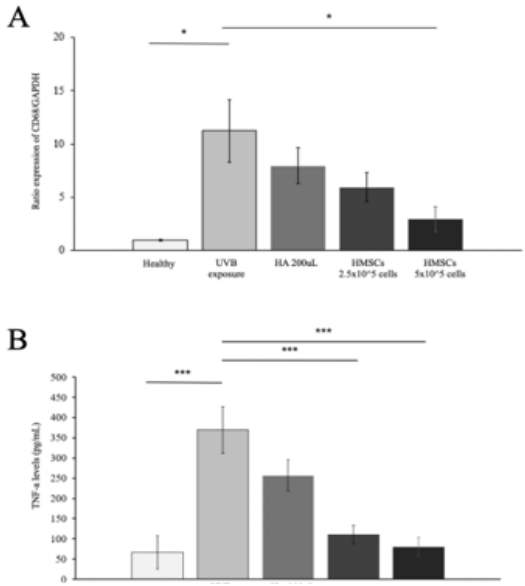

Figure 4. (A) Graph of relative CD68 expression and (B) TNF-α protein expression in skin tissue after HMSC treatment administration shows significant differences between the healthy rat group and the UVB exposure group, and between the UVB exposure group and the treatment group *(p<0.05) indicated significant differences, ***(p<0.001) indicated significant differences.

reducing CD68 gene expression and TNF-α levels. The correlation between decreased CD68 expression and reduced TNF-α levels suggests a coordinated dampening of the inflammatory response, with the HMSC 5×10^5 cells achieving results most closely approximating normal physiological conditions. HMSCs exert immunomodulatory effects by secreting extracellular vesicles that contain anti-inflammatory mediators.[26] Previous studies demonstrate HMSCs increase PGE_2, TGF-β, and IL-10 secretion, which inhibit NF-κB activation and promote macrophage repolarization from pro-inflammatory M1 (CD68+) toward anti-inflammatory M2 phenotypes, mechanisms potentially explaining our observed reductions in CD68 expression and TNF-α levels.[27,28] These paracrine effects represent plausible pathways for HMSC therapeutic activity in photoaging models. These findings have important implications for therapeutic approaches to UV-induced skin damage.

HMSCs increase PGE_2 secretion, which interacts with EP2 and EP4 receptors on macrophages, thereby inhibiting NF-κB pathway activation and reducing pro-inflammatory gene expression and macrophage polarization towards the M1 phenotype.[29,30] In addition, the decrease in M1 macrophage (CD68) expression and TNF-α inflammation by MSCs is that HMSCs enhance their anti-inflammatory capabilities by expressing high levels of TGF-β and IL-10. TGF-β, which is also secreted by HMSCs, can promote macrophage polarization towards the M2 phenotype and reduce inflammation.[31,32] On the other hand, IL-10 reduces inflammation and prevents collagen degradation via the Suppressor of Cytokine Signalling-3 (SOCS3). This occurs because IL-10 can activate STAT3 phosphorylation, leading to homodimerization and nuclear translocation, triggering the expression of STAT3-responsive genes, namely suppressor of cytokine signaling 3 (SOCS3).[33] This mechanism induces the expression of anti-inflammatory molecules that play a crucial role in regulating macrophage expression and TNF-α levels. In summary, HMSC administration effectively attenuated CD68 expression and TNF-α levels in UVB-induced photoaging, supporting its potential as an anti-inflammatory therapy for UV-damaged skin.

5. Conclusion

In conclusion, the HMSCs at 5×10^5 cells effectively attenuated UVB-induced photoaging, reducing CD68 gene expression to 2.96 ± 1.02 and TNF-α levels by 78% (80.50 ± 23.46 pg/mL vs. 369.30 ± 57.51 pg/mL in UVB controls). The significant Spearman correlation between these markers ($r=0.72$, $p<0.01$) confirms coordinated anti-inflammatory efficacy. These quantitative findings establish HMSCs as a promising therapeutic candidate for clinical management of UV-induced skin damage.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Siebenga PS, van Amerongen G, Klaassen ES, de Kam ML, Rissmann R, Groeneveld GJ. The ultraviolet B inflammation model: Postinflammatory hyperpigmentation and validation of a reduced UVB exposure paradigm for inducing hyperalgesia in healthy subjects. European Journal of Pain (United Kingdom). 2019;23(5):874-83.
2. Putri RS, Putra A, Chodidjah, et al. Clitorea ternatea flower extract induces platelet-derived growth factor (Pdgf) and gpx gene overexpression in ultraviolet (uv) b irradiationinduced collagen loss. Med Glas. 2023;20(1):15-21.
3. Chen S, He Z, Xu J. Application of adipose-derived stem cells in photoaging: basic science and literature review. Stem Cell Res Ther. 2020;11(1):1-15.
4. Subedi L, Lee TH, Wahedi HM, Baek SH, Kim SY. Resveratrol-Enriched Rice Attenuates UVB-ROS-Induced Skin Aging via Downregulation of Inflammatory Cascades. Oxid Med Cell Longev. 2017;2017.
5. Gao S, Gao S, Guo K, Chen Y, Zhao J, Jing R, et al. Keratinocyte growth factor 2 ameliorates UVB-induced skin damage via activating the AhR/nrf2 signaling pathway. Frontiers in Pharmacology. 2021; 12:655281.
6. Yang CY, Guo Y, Wu WJ, Man MQ, Tu Y, He L. UVB-Induced Secretion of IL-1 β Promotes Melanogenesis by Upregulating TYR/TRP-1 Expression In Vitro. Biomed Res Int. 2022; 2022(1):8230646.
7. Mayasari YI, Subchan P, Putra A, Chodijah C, Hussana A, Sumarawati T, et al. Secretome hypoxia mesenchymal stem cells inhibited ultraviolet radiation by inhibiting interleukin-6 through nuclear factor-kappa beta pathway in hyperpigmentation animal models. Open Access Macedonian Journal of Medical Sciences. 2023;11(B):188-94.
8. Munir D, Nasution IP, Restimulia L, Putra A, Amalina ND. The role of mesenchymal stem cells in allergic rhinitis and its relationship with IL-10, plasma cells and regulatory T cells. Med Glas. 2023;20(2):175-80.
9. Daryanti E, Putra A, Sumarawati T, Amalina ND, Prasetio A, Sidiq HA. The Comparison of Normoxic and Hypoxic Mesenchymal Stem Cells in Regulating Platelet-derived Growth Factors and Collagen Serial Levels in Skin Excision Animal Models. Open Access Maced J Med Sci. 2023;11(A):181-7.
10. Padhi S, Sarangi R, Ramdas A, Ravichandran K, Varghese RG, Alexander T, et al. Cutaneous hyperpigmentation in megaloblastic anemia: A five year retrospective review. Mediterranean Journal of Hematology and Infectious Diseases. 2016;8(1): e2016021.
11. Zhang S, Duan E. Fighting against Skin Aging: The Way from Bench to Bedside. Cell Transplant. 2018;27(5):729-738.

12. Dodig S, Čepelak I, Pavić I. Hallmarks of senescence and aging. Biochem Med (Zagreb). 2019;29(3):1-15.
13. Helfrich YR, Sachs DL, Voorhees JJ. Overview of skin aging and photoaging. Dermatology nursing / Dermatology Nurses' Association. 2008;20(3).
14. Hu L, Nomura S, Sato Y, Takagi K, Ishii T, Honma Y, et al. Anti-inflammatory effects of differential molecular weight Hyaluronic acids on UVB-induced calprotectin-mediated keratinocyte inflammation. Journal of dermatological science. 2022;107(1):24-31.
15. Orecchioni M, Ghosheh Y, Pramod AB, Ley K. Macrophage polarization: Different gene signatures in M1(Lps+) vs. Classically and M2(LPS-) vs. Alternatively activated macrophages. Front Immunol. 2019;10(5):1-14.
16. Zhang QZ, Su WR, Shi SH, Wilder-Smith P, Xiang AP, Wong A, et al. Human gingiva-derived mesenchymal stem cells elicit polarization of m2 macrophages and enhance cutaneous wound healing. Stem cells. 2010;28(10):1856-68.
17. Horiba S, Kawamoto M, Tobita R, Kami R, Ogura Y, Hosoi J. M1/M2 Macrophage Skewing is Related to Reduction in Types I, V, and VI Collagens with Aging in Sun-Exposed Human Skin. JID Innov. 2023;3(6).
18. Kusumo MH, Husain SA, Amalina ND. Secretome MSCs restore α-smooth muscle actin protein tissue expression in croton oil-induced hemorrhoid rats. International Journal of Cell and Biomedical Science. 2023;2(4):139-46.
19. Restimulia L, Ilyas S, Munir D, Putra A, Madiadipoera T, Farhat F, et al. The CD4+ CD25+ FoxP3+ regulatory T cells regulated by MSCs suppress plasma cells in a mouse model of allergic rhinitis. Medical Archives. 2021;75(4):256.
20. Prajoko YW, Putra A, Dirja BT, Muhar AM, Amalina ND. The Ameliorating Effects of MSCs in Controlling Treg-mediated B-Cell Depletion by Indoleamine 2, 3-dioxygenase Induction in PBMC of SLE Patients. Open Access Maced J Med Sci. 2022;10:6-11.
21. Hussaana A, Suparmi, Murti HA. Protective effect of bixin isolated from Bixa orellana L. Seeds on UVB-induced inflammation and immunosuppression of the skin. Bangladesh Journal of Medical Science. 2019;18(1):107-11.
22. Liu YC, Zou XB, Chai YF, Yao YM. Macrophage polarization in inflammatory diseases. Int J Biol Sci. 2014;10(5):520-529.
23. Chen L, Tredget EE, Wu PYG, Wu Y, Wu Y. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. PLoS One. 2008;3(4).
24. Lee YR, Noh EM, Han JH, Kim JM, Hwang JK, Hwang BM, et al. Brazilin inhibits UVB-induced MMP-1/3 expressions and secretions by suppressing the NF-κB pathway in human dermal fibroblasts. European Journal of Pharmacology. 2012;674(2-3):80-6.
25. Zukhiroh Z, Putra A, Chodidjah C, Sumarawati T, Subchan P, Trisnadi S, et al. Effect of secretome-hypoxia mesenchymal stem cells on regulating SOD and MMP-1 mRNA expressions in skin hyperpigmentation rats. Open Access Macedonian Journal of Medical Sciences. 2022;10(A):1-7.
26. Weiss ARR, Dahlke MH. Immunomodulation by Mesenchymal Stem Cells (MSCs): Mechanisms of action of living, apoptotic, and dead MSCs. Front Immunol. 2019;10:1191.
27. He X, Dong Z, Cao Y, Wang H, Liu S, Liao L, et al. MSC-derived exosome promotes M2 polarization and enhances cutaneous wound healing. Stem cells international. 2019;2019(1):7132708.
28. Darlan DM, Munir D, Putra A, Jusuf NK. MSCs-released TGFβ1 generate CD4+CD25+Foxp3+ in T-reg cells of human SLE PBMC. Journal of the Formosan Medical Association. 2021;120(1):602-8.
29. Liu F, Qiu H, Xue M, Zhang S, Zhang X, Xu J, et al. MSC-secreted TGF-β regulates lipopolysaccharide-stimulated macrophage M2-like polarization via the Akt/FoxO1 pathway. Stem cell research & therapy. 2019;10(1):345.
30. Zhao G, Liu F, Liu Z, Zuo K, Wang B, Zhang Y, et al. MSC-derived exosomes attenuate cell death through suppressing AIF nucleus translocation and enhance cutaneous wound healing. Stem cell research & therapy. 2020;11(1):174.
31. Kuntardjo N, Dharmana E, Chodidjah C, Nasihun TR, Putra A. TNF-α-Activated MSC-CM Topical Gel Effective in Increasing PDGF Level, Fibroblast Density, and Wound Healing Process Compared to Subcutaneous Injection Combination. Majalah Kedokteran Bandung. 2019;51(1):1-6.
32. Liang W, Chen X, Zhang S, Fang J, Chen M, Xu Y, et al. Mesenchymal stem cells as a double-edged sword in tumor growth: focusing on MSC-derived cytokines. Cellular & Molecular Biology Letters. 2021;26(1):3.
33. Putra A, Ridwan FB, Putridewi AI, Kustiyah AR, Wirastuti K, Sadyah NA, et al. The role of TNF-α induced MSCs on suppressive inflammation by increasing TGF-β and IL-10. Open access Macedonian journal of medical sciences. 2018;6(10):1779.