Molecular and Cellular Biomedical Sciences, Vol.9 No.3, November 2025, p.124-78
Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v9i3.647

RESEARCH ARTICLE

MCBS
Mol Cell Biomed Sci. 2025; 9(3): 141-8
DOI: 10.21705/mcbs.v9i3.647

Exosomes from Hypoxic Mesenchymal Stem Cells Enhance TGF-α Expression and Promote Collagen Regeneration in Wistar Rats with Collagen Loss

Ade Ifalliah Putri Kusumawardani[1], Prasetyowati-Subchan[1], Titiek Sumarawati[1], Eko Setiawan[1,2]

[1]*Department of Biomedical Science, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia*
[2]*Department of Surgery, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia*

Background: Ultraviolet B (UVB) exposure triggers reactive oxygen species (ROS) formation, inhibits procollagen synthesis via the transforming growth factor-beta (TGF-β)/Smad pathway, and leads to collagen loss. Exosomes derived from hypoxia-conditioned mesenchymal stem cells (EH-MSCs) are more effective than those from normoxic MSCs due to their higher content of miRNAs and cytokines with anti-inflammatory and regenerative properties. This study aims to evaluate the effect of EH-MSC injection on TGF-β levels and collagen density in Wistar male rats with UVB-induced collagen loss.
Materials and methods: This *in vivo* experimental study used a post-test only control group design with 30 rats, divided into five groups: Healthy group, 0.9% NaCl-treated group, hyaluronic acid (HA)-treated group, 200 µL EH-MSC-treated group, and 300 µL EH-MSC-treated group. TGF-β levels were analyzed using ELISA, while collagen density was assessed with Masson trichrome staining.
Results: Highest mean TGF-β levels were observed in the 300 µL EH-MSC-treated group (155.56±99.84 pg/mL), while the highest collagen density was found in the Healthy group (23.07±1.81 pg/mL). Mann-Whitney test indicated a significant increase (p=0.008) in TGF-β levels in treatment groups compared to the 0.9% NaCl-treated group. Post Hoc LSD Tamhane test for collagen density also showed a significant increase (p=0.000) in treatment groups compared to the 0.9% NaCl-treated group.
Conclusion: EH-MSC injection significantly increased TGF-β levels and collagen density, indicating its potential for promoting skin repair in UVB-induced collagen loss.

Keywords: *EH-MSC, collagen loss, TGF-β, collagen density*

Introduction

Ultraviolet B (UVB) light, a component of sunlight, contributes to skin wrinkles by reducing collagen. High radiation levels trigger reactive oxygen species (ROS) formation, leading to oxidative stress, inflammation, and activation of pro-inflammatory cytokines via pathways such as NF-kB, HIF-1α, Nrf2, and AP-1.[1] UVB exposure

Submission: January 30, 2025
Last Revision: April 11, 2025
Accepted for Publication: April 17, 2025

Corresponding Author:
Ade Ifalliah Putri Kusumawardani
Department of Biomedical Science, Faculty of Medicine
Universitas Islam Sultan Agung
Terboyo Kulon, Semarang 50112, Indonesia
e-mail: adeifalliah@gmail.com

Cell and Biopharmaceutical Institute

also activates mitogen-activated protein kinase (MAPK) signaling, stimulating AP-1 and increasing matrix metalloproteinase (MMP) expression (*e.g.*, MMP-1, MMP-3, MMP-9), which degrades collagen.[2] This results in decreased type I procollagen, a key structural skin protein regulated by transforming growth factor beta (TGF-β).[3] UVB inhibits procollagen synthesis by downregulating the TGF-β/Smad pathway, where TGF-β binds to its receptors and initiates gene transcription via Smad2/Smad3 phosphorylation.

Exosome -based mesenchymal stem cell (E-MSC) therapy has emerged as a promising strategy to counteract collagen degradation. Studies suggest that subcutaneous injection of 100μL E-MSC prevents pro-inflammatory mediator release, making it a potential treatment for photoaged skin.[4] Populations in tropical regions, such as Indonesia, face a higher risk of collagen depletion due to UV exposure.[5] A common therapy for collagen loss is hyaluronic acid (HA) injection, which enhances hydration and skin volume.[6] However, HA is metabolized within months and does not address the underlying structural damage.[7,8]

Exosome from hypoxia-conditioned mesenchymal stem cells (EH-MSC) therapy offers a more comprehensive approach by stimulating collagen synthesis via the TGF-β/Smad pathway and inhibiting MMP activity. Additionally, EH-MSC enhances anti-inflammatory and regenerative effects through increased secretion of miRNA and cytokines under hypoxic conditions. MSCs can differentiate into fibroblasts, which produce collagen. Exosomes, extracellular vesicles released by MSCs, contain microRNA (miRNA) and cytokines that modulate inflammation.[9,10] For example, miR-1246 enhances TGF-β regulation in response to ROS, while IL-10 suppresses NF-κB to reduce inflammation and collagen degradation.

Adipose-derived stem cell (ADSC) exosomes activate the TGF-β/Smad pathway, increasing type I procollagen expression.[11] They also contain growth factors like epidermal growth factor (EGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), supporting collagen synthesis, angiogenesis, and tissue repair. EH-MSC therapy, derived from MSCs cultured under hypoxic conditions, amplifies growth factor secretion, promoting tissue regeneration. Additionally, EH-MSCs increase TGF-β levels, inhibiting MMP activity and further preventing collagen degradation.[11]

Recent findings indicate that exosomes can be stored at -20°C for up to six months without losing biochemical activity.[12] However, cryopreservation at -80°C or in liquid nitrogen (-196°C) is recommended for long-term stability. Standardizing exosome isolation methods and ensuring quality control parameters such as protein concentration and microbiological purity are essential for clinical applications.

Research on exosomes-based therapies in Indonesia remains limited, particularly in dermatology. A multidisciplinary approach involving cell biology, dermatology, biotechnology, and clinical medicine is necessary to optimize their therapeutic potential. Based on this background, the present study aims to evaluate the effect of EH-MSC administration on TGF-β levels and collagen density in UVB-induced collagen loss.

Materials and methods

Study Design

This research was an *in vivo* experimental design utilizing a post-test-only control group framework to evaluate the effect of exosomes derived from hypoxic mesenchymal stem cells (EH-MSCs) on transforming growth factor-beta (TGF-β) levels and collagen density in male Wistar rats with UVB-induced collagen degradation. The experimental protocol received ethical clearance from the Bioethics Commission for Medical and Health Research of the Faculty of Medicine, Universitas Islam Sultan Agung, Semarang (Approval No. 480/XI/2024/Komisi Bioetik). All procedures were conducted according to the ethical principles articulated in the Declaration of Helsinki and the Indonesian National Guidelines for Health Research Ethics issued by the Ministry of Health in 2004.

Animal Treatment

Thirthy male Wistar rats, aged 10 weeks and weighing approximately 220 grams, were utilized in this study. The animals were randomly assigned into five groups as follows: healthy control group with no UVB exposure (healthy group), UVB-exposed group receiving a subcutaneous injection of 200 μL 0.9% sodium chloride solution (0.9% NaCl-treated group), UVB-exposed group receiving a subcutaneous injection of 200 μL hyaluronic acid (HA-treated group), UVB-exposed group administered 200 μL of EH-MSCs subcutaneously (200 μL EH-MSC group), and UVB-exposed group administered 300 μL of EH-MSCs subcutaneously (300 μL EH-MSC group).

Before the intervention, all animals underwent a 7-day acclimatization period. During this phase, rats were

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v9i3.647

maintained at a controlled ambient temperature of 23°C with a 12-hour light/dark photoperiod to support circadian rhythm stability. Each rat was housed individually in sanitized, ventilated cages designed to minimize microbial contamination. Animals were provided unrestricted access to standard pellet feed and potable water to ensure nutritional adequacy. Throughout the acclimatization and experimental phases, the health status of the rats was monitored daily. Any animal showing signs of illness or physiological distress was excluded from the study.

EH-MSC Isolation and Preparation

MSCs were isolated from the umbilical cords of 21-day pregnant rats and cultured in a medium containing Dulbecco's modified eagle medium (DMEM), fetal bovine serum (FBS), antibiotics, and antifungals. Once the culture reached 80% confluency, the MSCs were conditioned under hypoxic conditions with 5% oxygen for 24 hours. Microscopic observation after the fourth passage showed that the cultured MSCs adhered to the bottom of the flask and exhibited a spindle-like morphology. The culture medium containing exosomes was then collected and filtered using a tangential flow filtration (TFF) system equipped with a 100-500 kDa sterile hollow fiber polyether-sulfone membrane. To minimize variability and preserve exosome integrity, flow rate and pressure were maintained consistently throughout the filtration process.

The filtered exosomes were washed twice with phosphate-buffered saline (PBS) to remove residual culture medium and free proteins, ensuring purity and uniformity of the isolated exosomes. Exosome validation was conducted using flow cytometry to confirm the presence of specific surface markers $CD63^+$ and $CD9^+$, indicative of exosomes derived from MSCs. To ensure specificity and accuracy, the flow cytometry analysis included several controls: Positive controls, using standard exosomes known to express CD63 and CD9; Negative controls, using medium without exosomes; Isotype controls, to exclude non-specific antibody binding; and compensation controls, applied to correct for spectral overlap between fluorochromes Additionally, fluorescent calibration beads were used as standards for size and fluorescence intensity, providing a reference for quantifying exosome marker expression and validating the presence of properly sized vesicles.

Treatment Administration and ELISA analysis

Before UVB irradiation, a 2 × 3 cm area on the dorsal region of each rat was carefully shaved to ensure consistent and unobstructed exposure. The UVB-exposed groups were subjected to irradiation using a calibrated UVB lamp (Philips TL 20W/12 RS SLV, Koninklijke Philips N.V., Amsterdam, Netherlands), emitting at a peak wavelength of 302 nm and delivering an energy dose of 150 mJ/cm². The irradiation protocol was administered five times per week over two consecutive weeks. On day 22, following the completion of the UVB exposure regimen, each experimental group received the designated treatment via subcutaneous injection precisely at the previously irradiated site.

To evaluate the therapeutic efficacy of the interventions, serum levels of transforming growth factor-beta 1 (TGF-β1) were quantitatively assessed using a high-sensitivity sandwich enzyme-linked immunosorbent assay (ELISA), performed by the manufacturer's instructions. The assay utilized the Rat TGF-β1 ELISA Kit (E-EL-R0052, Elabscience, Houston, TX, USA), and optical density was recorded at 450 nm using a microplate spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). For collagen analysis, skin tissue homogenates were prepared using radioimmunoprecipitation assay (RIPA) buffer, followed by centrifugation at 12,000 × g for 10 minutes at 4°C to obtain the supernatant for subsequent analysis.

Sample Collection and Analysis

On day 29, all animals were euthanized by cervical dislocation in compliance with institutional ethical protocols. Skin specimens were collected from the dorsal treatment area using a sterile 6 mm biopsy punch. Each specimen was longitudinally divided into two equal portions. One portion was immediately fixed in 10% neutral-buffered formalin for histopathological examination, while the remaining portion was preserved in RNAlater™ stabilization solution (Invitrogen, Carlsbad, CA, USA) and stored at -80°C for subsequent molecular and biochemical analyses.

Histological Analysis

Formalin-fixed tissue samples were processed through a standard paraffin-embedding protocol, sectioned at a thickness of 4 μm using a microtome, and stained with Masson's trichrome to visualize and assess dermal collagen fiber density. Quantitative image analysis of collagen distribution and density was performed using ImageJ software (National Institutes of Health, Bethesda, MD, USA). For TGF-β1 analysis, tissue homogenates preserved in RIPA buffer were subjected to ELISA as previously described, and absorbance was measured at 450 nm to determine cytokine concentration.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean±standard deviation (SD). The Shapiro–Wilk test was used to assess normality, and Levene's test was applied to evaluate the homogeneity of variances. If both assumptions were met, intergroup comparisons were conducted using a one-way analysis of variance (ANOVA), followed by the least significant difference (LSD) post hoc test for pairwise comparisons. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Hypoxia-Cultured MSCs Exhibited Spindle Morphology and Expressed Characteristic Surface Markers

After reaching 80% confluence by the fourth passage, microscopic observation revealed that the cultured MSCs adhered to the bottom of the flask and exhibited a spindle-like morphology (Figure 1).

Flow cytometry analysis confirmed the expression of characteristic MSC surface markers. MSCs highly expressed CD90 (99.8%) and CD29 (97.7%), and showed low expression of hematopoietic and endothelial markers CD45 (1.9%) and CD31 (3.7%) (Figure 2).

MSCs Successfully Differentiated into Osteocytes and Adipocytes

The differentiation potential of MSCs was evaluated by culturing the cells in osteogenic and adipogenic media. Successful differentiation into osteocytes and adipocytes was confirmed by the presence of calcium and lipid deposits, stained red with Alizarin Red and Oil Red O (Figure 3).

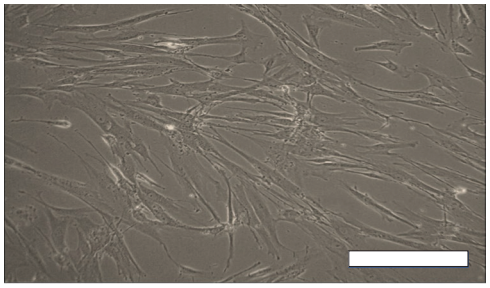

Figure 1. MSCs at 80% confluence displayed a spindle-like cell morphology at 100x magnification. White bar: 100 µm.

Hypoxic Conditions Enhanced MSCs Differentiation and Exosome Isolation

MSCs were incubated under hypoxic conditions (5% oxygen) for 24 hours within a hypoxia chamber. The exosomes were isolated from the culture medium using the TFF method (100-500 kDa). The flow cytometry analysis validated the exosome content, confirming the expression of $CD63^+$ and $CD9^+$ exosome markers. The peak event in the flow cytometry results occurred at 10^3, with 0.75 µg/100 µL or 7.5 ng/µL of exosome (Figure 4).

UVB Exposure Decreased Collagen Density and Enhanced Wrinkle Formation in Rats

Macroscopic examination revealed more pronounced wrinkles in the UVB-induced rats compared to the non-exposed control group. To further validate collagen depletion, Masson's trichrome staining was performed. The results showed a decrease in collagen density and a more disorganized collagen structure in the UVB-exposed rats compared to the control group (Figure 5).

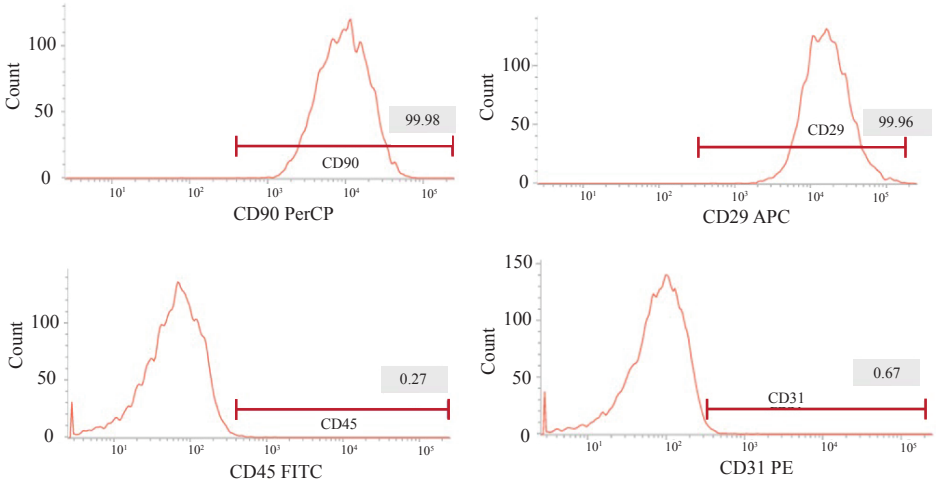

Figure 2. MSCs expressed high levels of CD90 and CD29, and low levels of CD45 and CD31.

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v9i3.647

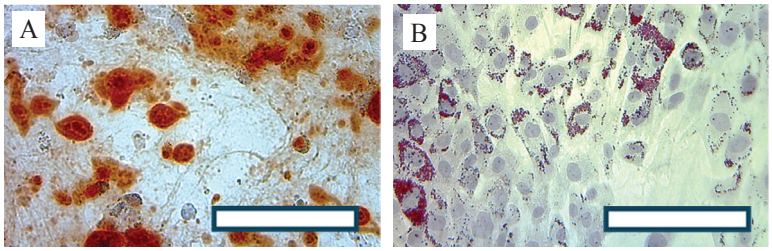

Figure 3. MSCs differentiated into osteocytes and adipocytes. A: Osteogenic differentiation was confirmed by calcium deposits presence, stained with Alizarin Red. B: Adipogenic differentiation was confirmed by lipid droplets presence, stained with Oil Red O. White bar: 25 µm.

EH-MSC Injections Increased TGF-β Levels and Collagen Density in UVB-Induced Rats

Statistical analysis showed that the lowest mean TGF-β levels was found in the 0.9% NaCl-treated group, followed by the Healthy group and the HA-treated group. The highest TGF-β levels were observed in the 200 µL and 300 µL EH-MSC-treated groups.

Due to violations of normality and homogeneity (Shapiro-Wilk and Levene's tests, $p<0.05$), the Kruskal-Wallis test was applied and showed a statistically significant difference in TGF-β levels among all groups ($p=0.001$). Pairwise comparisons using the Mann-Whitney test confirmed that both EH-MSC-treated groups (200 µL and 300 µL) had significantly higher TGF-β levels than the other groups ($p<0.05$) (Figure 6).

In terms of collagen density, the lowest values were recorded in the 0.9% NaCl-treated group, followed by the 300 µL and 200 µL EH-MSC-treated groups. The highest collagen densities were observed in the Healthy and HA-treated groups (Figure 7). Since the data met the assumptions for normality and homogeneity ($p>0.05$), one-way ANOVA was used, revealing significant differences among groups ($p=0.000$). Post hoc LSD analysis indicated that collagen density in the HA-treated and 200 µL EH-MSC-treated groups was significantly higher than in the 0.9% NaCl-treated group ($p<0.05$). These findings suggest that 200 µL of EH-MSC was more effective than 300 µL in promoting collagen regeneration in UVB-induced rats.

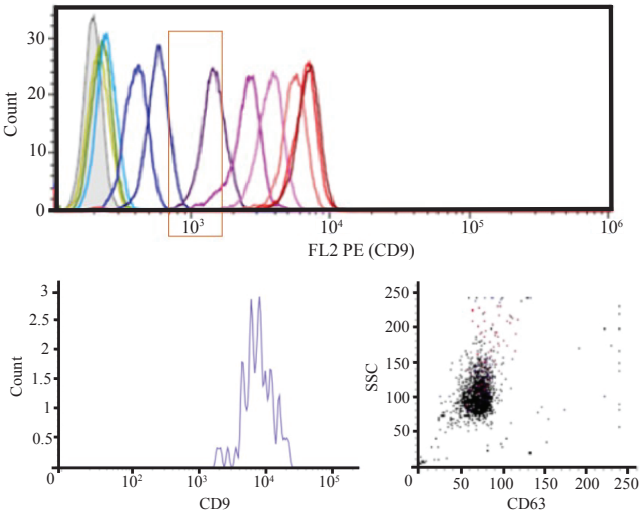

Figure 4. Flow cytometry analysis confirmed the presence of CD63⁺ and CD9⁺ exosome markers.

Discussion

The findings showed that both doses of Eh-MSC injection subcutaneously increased TGF-β levels and collagen density. The increased TGF-β may be an initial response, while collagen regeneration may require more time to become significant. However, the significantly increased TGF-β suggests that subcutaneous injection of Eh-MSCs may have potential as an effective anti-inflammatory and antioxidant agent in UVB-exposed skin. Exosomes from MSCs have become an interesting subject of research in regenerative therapy due to their potential in stimulating tissue regeneration and regulating immune response.[13] Recent studies have demonstrated that hypoxic preconditioning of MSC enhances their therapeutical potential. This approach leads to the release of exosomes with improved biological functions, thereby augmenting tissue regeneration capabilities. Additionally, hypoxia influences the size, quantity, and cargo of exosomes, affecting their functional properties.[14]

Among the components contained in these exosomes, miRNAs, growth factors, and cytokines is a significant factor in mediating the effects of the anti-inflammatory and immunomodulatory effects of MSCs.[15] Meanwhile, growth factors in exosomes, such as epidermal growth factor (EGF) or fibroblast growth factor (FGF), can stimulate the proliferation and differentiation of target cells, as well as affect signal pathways involved in immune responses.[16]

TGF-β has a close relationship with collagen density, as TGF-β is a key regulator in the process of collagen synthesis and extracellular matrix remodeling in the skin.

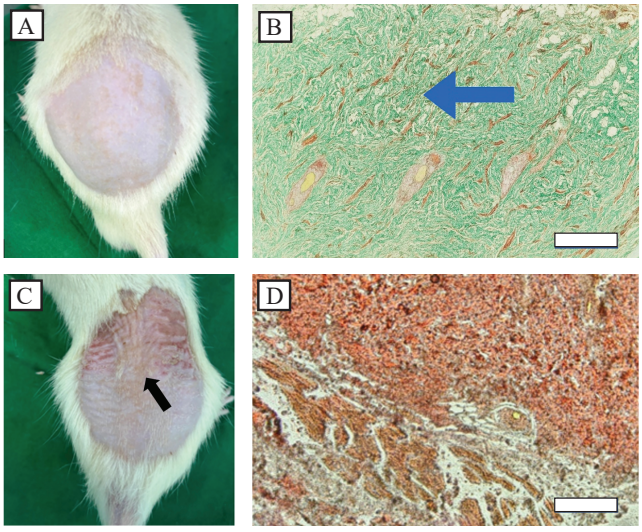

Figure 5. Collagen loss validation in UVB-induced rats. A: Healthy rats exhibited no visible wrinkles. B: Collagen tissue in healthy rats appeared dense and well-organized in the dermal layer, as indicated by the blue arrow. C: UVB-induced rats exhibited obvious wrinkles. D: Collagen tissue in UVB-induced rats showed reduced density and disorganization. White bar: 50 µm.

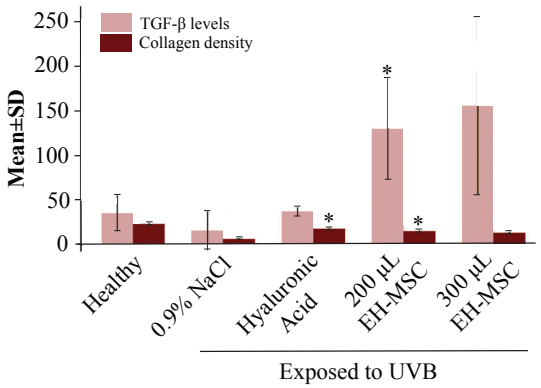

Figure 6. EH-MSC Treatment Increased TGF-β Levels and Collagen Density. Bar chart shows the effects of EH-MSC on TGF-β levels and collagen density across experimental groups. Asterisks (*) indicate significant increases in TGF-β levels (p<0.05, Mann-Whitney test) and collagen density (p<0.05, LSD post hoc test).

The formation of TGF-β in UV-exposed and exosome-injected skin depends on the skin condition, the extent of UV damage, and the mechanism of action of the exosome. Exosomes contain biomolecules such as RNA, proteins, and other growth factors that can increase TGF-β levels. The initial formation of TGF-β after exosome injection can occur within 1 to 7 days, while the long-term effects within 1 to 3 months can reach optimal levels, support more consistent collagen production, and increase collagen density.[17] UV exposure can damage collagen through activation of MMP enzymes that destroy collagen and oxidative stress that accelerates skin aging. Under optimal conditions, collagen density formation after exosome injection can be seen in 2 to 4 weeks and reaches its peak in 3 to 6 months.[18]

This study showed that TGF-β levels were significantly increased compared to the healthy group, negative control group, and positive control group. At high levels, TGF-β often reversibly inhibits cell proliferation, but EH-MSCs not only express TGF-β receptors on their cell surface but can also remain quiescent for several months. It means EH-MSCs can re-enter the cell cycle in response to certain conditions, which is different from cell aging and cell differentiation in general. The ability of TGF-β to balance active cell proliferation and reversible cell cycle is important to maintain the ability of EH-MSCs to respond quickly to changes in tissue physiology. TGF-β signaling pathways control biological processes across a broad spectrum from immune system homeostasis to self-renewal.[19] The results of this study are in line with previous research that states MSC exosome therapeutics and modes of action relevant to regeneration diseases, as well as quality control measures needed for the development of exosome-derived therapies.[20] Other studies have also suggested that MSC exosomes may contain miRNAs that inhibit NFkB activation. In addition, through NFkB regulation, exosomes can also affect CD86 gene expression and lead to decreased M1 macrophage activation so that M2 increases in macrophages.[21]

In this study, collagen density did not increase compared to the healthy group and the positive control group. EH-MSCs play an important role in the repair of UVB-damaged skin tissue. They contain various growth factors such as vascular endothelial growth factor (VEGF), TGF-β, and hepatocyte growth factor (HGF) that promote angiogenesis, cell regeneration, and extracellular matrix repair. These factors help repair collagen damage and promote the skin regeneration process, which is crucial for restoring the skin's structural integrity after UVB exposure. Exosomes also contribute to reducing the inflammatory response exacerbated by tissue degradation by repairing collagen and extracellular matrix damage.[22] In collagen density, it was found that the 200 µL EH-MSC is better than

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v9i3.647

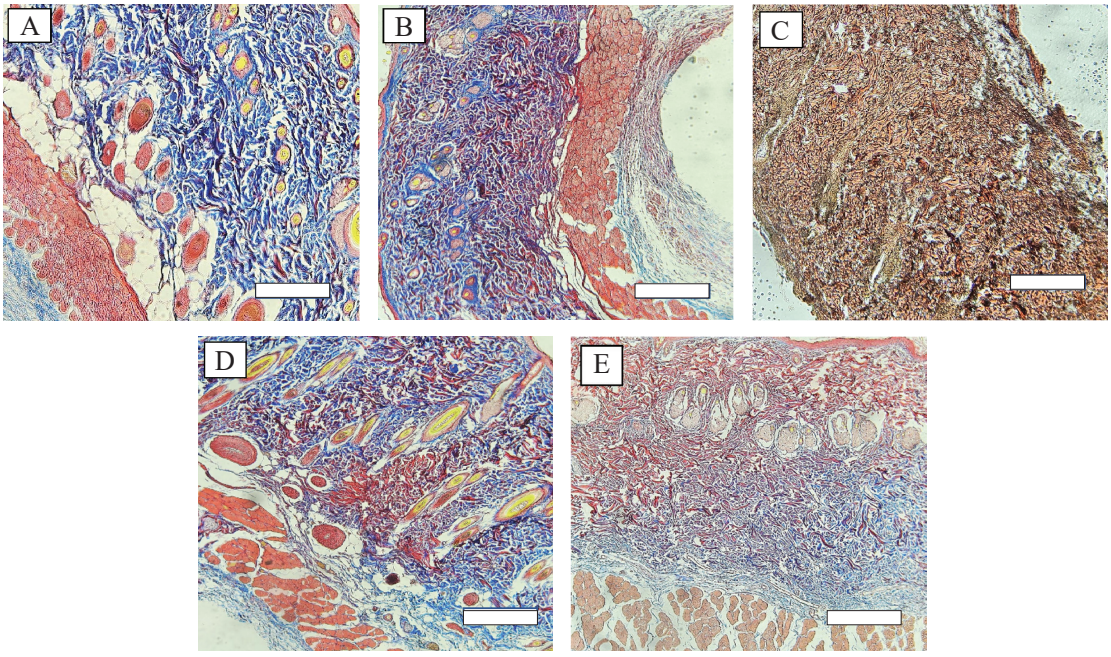

Figure 7. The 200 µL EH-MSC-treated group enhanced collagen density in UVB-Induced Rats. Representative histological images showing collagen density (blue) in Healthy group (A), 0.9% NaCl-treated group (B), HA-treated group (C), 200 µL EH-MSC-treated group (D), and 300 µL EH-MSC-treated group (E). Increased collagen density was observed in groups 200 µL and 300 µL EH-MSC-treated group compared to group B, with denser collagen fibers in the 200 µL EH-MSC-treated group than in the 300 µL EH-MSC-treated group. White bar: 50 µm.

300 µL, it can be caused by several factors. Fibroblasts have a limited capacity to receive and respond to biomolecules delivered by exosomes, when the amount is excessive, the effectiveness can decrease. The collagen matrix in the skin is also influential as it requires a balance between production and degradation. a high dose of EH-MSC can disrupt this balance by triggering compensatory mechanisms.[13,23]

The results of this study are not in line with previous research which says that overall MSC-derived exosomes are a promising cell base in the skin regeneration process[24], therefore more research is needed to further explore the potential use of exosomes with a longer period with the right dose.

A notable limitation of the study is the absence of an analysis of the exosome content, which could significantly impact collagen density outcomes. Understanding the specific cargo withing exosomes, such as miRNAs and proteins, is crucial, as these components play pivotal roles in mediating anti-inflammatory and immunomodulatory effects. For instance, exosomes derived from hypoxic endothelial cells have been found to contain increased levels of certain proteins, like Lysyl oxidase-like 2, which are associated with collagen cross-linking and stabilization.[25] Another limitation of the study is that it only analyzed EH-MSCs in terms of TGF-β levels and collagen density. Additionally, the results showed that a dose of 200 µL of EH-MSC demonstrated higher collagen density compared to a dose of 300 µL. Therefore, to better understand the effects, future studies should evaluate a range of concentrations and employ more precise dosing strategies.

Conclusion

EH-MSCs significantly increased TGF-β levels and improved collagen density in UVB-induced collagen loss in rats. These findings highlight the potential of EH-MSCs as a promising therapeutic strategy for promoting skin regeneration and repair.

Authors' Contributions

AIPK, PS, TS, and ES were involved in concepting and planning the research and performing the data acquisition/collection. AIPK calculated the experimental data and performed the analysis. AIPK, PS, TS, and ES drafted the

manuscript and designed the figures. AIPK also aided in interpreting the results. AIPK, PS, TS, and ES contributed to the critical revision of the manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest or competing interests related to the content of this manuscript.

References

1. Ansary TM, Hossain MR, Kamiya K, Komine M, Ohtsuki M. Inflammatory molecules associated with ultraviolet radiation-mediated skin aging. Int J Mol Sci. 2021; 22(8): 3974. doi: 10.3390/ijms22083974.
2. Kartika R, Wibowo H. Impaired function of regulatory t cells in type 2 diabetes mellitus. Mol Cell Biomed Sci. 2020; 4(1): 1-9.
3. Quan T, He T, Kang S, Voorhees JJ, Fisher GJ. Solar ultraviolet irradiation reduces collagen in photoaged human skin by blocking transforming growth factor-β type II receptor/Smad signaling. Am J Pathol. 2004; 165(3): 741-51.
4. Park AY, Lee JO, Jang Y, Kim YJ, Lee JM, Kim SY, *et al*. Exosomes derived from human dermal fibroblasts protect against UVB-induced skin photoaging. Int J Mol Med. 2023; 52(6): 120. doi: 10.3892/ijmm.2023.5323.
5. Dewiastuti M, Hasanah IF. Pengaruh faktor-faktor risiko penuaan dini di kulit pada remaja wanita usia 18-21 tahun. J Profesi Med J Kedokt dan Kesehat. 2017; 10(1): 21-25.
6. Sugianto M, Achadiyani A, Nugraha GI. Antioxidant effects of red fruit oil on MMP-1 gene expression and malondialdehyde levels on skin exposed to UVB rays. Mol Cell Biomed Sci. 2019; 3(2): 100-6.
7. Guo J, Fang W, Wang F. Injectable fillers: Current status, physicochemical properties, function mechanism, and perspectives. RSC Adv. 2023; 13(34): 23841-58.
8. Valentina I, Achadiyani A, Adi SS, Lesmana R, Farenia R. Effect of Lactobacillus reuteri administration on wrinkle formation and type I procollagen levels in UVB-exposed male Balb/c Mice (Mus musculus). Mol Cell Biomed Sci. 2020; 4(3): 113-20.
9. Zhao Q, Ren H, Han Z. Mesenchymal stem cells: Immunomodulatory capability and clinical potential in immune diseases. J Cell Immunother. 2016; 2(1): 3-20.
10. Beegle J, Lakatos K, Kalomoiris S, Stewart H, Isseroff RR, Nolta JA, *et al*. Hypoxic preconditioning of mesenchymal stromal cells induces metabolic changes, enhances survival, and promotes cell retention in vivo. Stem Cells. 2015; 33(6): 1818-28.
11. Gao W, Wang X, Si Y, Pang J, Liu H, Li S, *et al*. Exosome derived from ADSCs attenuates ultraviolet B-mediated photoaging in human dermal fibroblasts. Photochem Photobiol. 2021; 97(4): 795-804.
12. Wu JY, Wu SN, Zhang LP, Zhao XS, Li Y, Yang QY, *et al*. Stem cell-derived exosomes: A new method for reversing skin aging. Tissue Eng Regen Med. 2022; 19(5): 961-8.
13. Hu JC, Zheng CX, Sui BD, Liu WJ, Jin Y. Mesenchymal stem cell-derived exosomes: A novel and potential remedy for cutaneous wound healing and regeneration. World J Stem Cells. 2022; 14(5): 318-29.
14. Zhuo H, Chen Y and Zhao G (2024) Advances in application of hypoxia-preconditioned mesenchymal stem cell-derived exosomes. Front. Cell Dev. Biol. 2024; 12: 1446050. doi: 10.3389/fcell.2024.1446050.
15. Cai J, Wu J, Wang J, Li Y, Hu X, Luo S, *et al*. Extracellular vesicles derived from different sources of mesenchymal stem cells: therapeutic effects and translational potential. Cell Biosci. 2020; 10(69): 1-14.
16. Aheget H, Mazini L, Martin F, Belqat B, Marchal JA, Benabdellah K. Exosomes: Their role in pathogenesis, diagnosis and treatment of diseases. Cancers. 2020; 13(1): 84. doi: 10.3390/cancers13010084
17. Ke Y, Wang XJ. TGFβ Signaling in Photoaging and UV-Induced Skin Cancer. J Invest Dermatol. 2021; 141(4): 1104-10.
18. Tienda-Vázquez MA, Hanel JM, Márquez-Arteaga EM, Salgado-Álvarez AP, Scheckhuber CQ, Alanis-Gómez JR, *et al*. Exosomes: A Promising Strategy for Repair, Regeneration and Treatment of Skin Disorders. Cells. 2023; 12(12): 1625. doi: 10.3390/cells12121625
19. Aisyah R, Jatmiko SW. Jalur Sinyal TGF-β Berperan Dalam Self Renewal, Diferensiasi, Dan Proliferasi Stem Cell. Saintika Med. 2019; 15(1): 50-59.
20. Ha DH, Kim H keun, Lee J, Kwon HH, Park GH, Yang SH, *et al*. Mesenchymal Stem/Stromal Cell-Derived Exosomes for Immunomodulatory Therapeutics and Skin Regeneration. Cells. 2020; 9(5): 1157. doi: 10.3390/cells9051157
21. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017; 2(1): 17023. doi: 10.1038/sigtrans.2017.23
22. Putra A, Pertiwi D, Milla MN, Indrayani UD, Jannah D, Sahariyani M, *et al*. Hypoxia-preconditioned MSCs have superior effect in ameliorating renal function on acute renal failure animal model. Maced J Med Sci. 2019; 7(3): 305-10.
23. Gentile P, Scioli MG, Bielli A, De Angelis B, De Sio C, De Fazio D, *et al*. Platelet-rich plasma and micrografts enriched with autologous human follicle mesenchymal stem cells improve hair re-growth in androgenetic alopecia. Biomolecular Pathway Analysis and Clinical Evaluation. Biomedicines. 2019; 7(2): 27. doi: 10.3390/biomedicines7020027.
24. MacLeod AS, Mansbridge JN. The innate immune system in acute and chronic wounds. Adv Wound Care. 2016; 5(2): 65-78.
25. de Jong OG, van Balkom BW, Gremmels H, Verhaar MC. Exosomes from hypoxic endothelial cells have increased collagen crosslinking activity through up-regulation of lysyl oxidase-like 2. J Cell Mol Med. 2016; 20(2): 342-50.