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Original Research Article

# Hypoxia-Induced Mesenchymal Stem Cell Exosomes Promote PDGF and IL-10 Expression During Burn Wound Healing

**Fanni Yuniar[1*], Eko Setiawan[1,2], Chodidjah Chodidjah[3]**

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

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**Abstract**

**Background**: Burn injuries remain a global health concern, with third-degree burns posing high morbidity and mortality risks. Effective wound healing requires both regeneration and inflammation control. Hypoxia-induced mesenchymal stem cell-derived exosomes (EH-MSCs) have emerged as a promising cell-free therapy due to their regenerative and immunomodulatory properties.

**Objective**: This study aimed to evaluate the effect of EH-MSCs on the expression of Platelet-Derived Growth Factor (PDGF) and Interleukin-10 (IL-10) in a Wistar rat model of third-degree burns.

**Methods**: An experimental study with a post-test only control group design was conducted at the Stem Cell and Cancer Research Laboratory, Sultan Agung Islamic University, Semarang, in April 2025. Thirty male Wistar rats (6–8 weeks, 200–250 g) were randomized into five groups: healthy control, burn + NaCl, burn + silver sulfadiazine, burn + EH-MSC 100 µg/mL, and burn + EH-MSC 200 µg/mL. Third-degree burns were induced using a 2 × 2 cm² pre-heated metal plate under ether anesthesia. EH-MSCs were isolated from rat umbilical cords using tangential flow filtration and validated with CD63 and CD9 markers. On day 5, PDGF and IL-10 expressions were measured via RT-PCR after orbital sinus blood sampling. Data were analyzed using Shapiro-Wilk and Levene's tests, followed by one-way ANOVA or non-parametric equivalents, with $p<0.05$ considered significant.

**Results:** PDGF and IL-10 expression increased in EH-MSC-treated groups, with the highest levels in the 200 µg/mL dose. IL-10 showed a significant difference among groups ($p = 0.030$), and post hoc tests confirmed higher expression in EH-MSC groups. PDGF also showed an upward trend, though overall one-way ANOVA was not significant ($p = 0.094$).

**Conclusion**: EH-MSCs significantly enhanced IL-10 expression and showed a tendency to increase PDGF expression, suggesting potential anti-inflammatory and early regenerative effects in third-degree burn repair.

**Keywords**: *Burn wound; Mesenchymal stem cells; Exosomes; PDGF, IL-10*
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## INTRODUCTION

Burn injuries remain a major global health concern, with the World Health Organization reporting approximately 26 5,000 deaths annually.[1] In Indonesia alone, burns account for about 195,000 deaths each year, ranking sixth among unintentional injuries.[2] Third-degree burns are particularly devastating, as they destroy the full thickness of the skin and may extend to deeper tissues, leading to long recovery periods, severe disability, and often requiring

*Corresponding author:
E-mail: pusatilmiah0@gmail.com
(Fanni Yuniar)

surgical interventions such as skin grafting.[3] Despite standard treatments, including antimicrobial dressings and surgical repair, outcomes remain suboptimal, with many patients experiencing chronic pain, delayed healing, and permanent scarring. These realities highlight the urgent need for more effective therapeutic approaches.

Recent advances in regenerative medicine have turned attention toward mesenchymal stem cells (MSCs) and their exosomes, which carry bioactive molecules that regulate tissue repair and immune responses. Hypoxia-preconditioned MSC-derived exosomes are particularly promising, as they demonstrate enhanced regenerative and anti-inflammatory properties due to distinct microRNA and protein cargo compared with normoxic conditions.[4,5] Platelet-Derived Growth Factor (PDGF) is a critical mediator of fibroblast proliferation, angiogenesis, and extracellular matrix deposition in wound healing,[6,7] while Interleukin-10 (IL-10) serves as a key anti-inflammatory cytokine essential for controlling excessive inflammation and promoting tissue remodeling.[8,9] Although several studies have reported the beneficial effects of MSCs, MSC secretomes, and MSC-derived exosomes in wound repair and burn healing,[10,11] evidence specifically addressing hypoxia-induced MSC-derived exosomes in third-degree burns remains limited. In particular, the direct effect of these exosomes on both PDGF and IL-10 expression in an in vivo third-degree burn model has not been clearly elucidated. This represents the main novelty of the present study.

Mechanistically, hypoxia preconditioning is thought to enhance the therapeutic activity of MSC-derived exosomes through HIF-1α-related alterations in exosomal cargo, including pro-regenerative microRNAs and proteins.[12] After uptake by target cells such as macrophages, fibroblasts, and endothelial cells, these exosomes may activate signaling pathways associated with anti-inflammatory polarization and tissue repair, including PI3K/Akt, STAT3, and other pro-survival pathways.[13] Such signaling can increase IL-10 production through immunomodulatory effects, while also promoting PDGF-associated regenerative responses that support fibroblast proliferation, angiogenesis, and extracellular matrix formation during wound healing.[7,14]

This study aims to evaluate the effect of exosomes derived from hypoxia-induced mesenchymal stem cells (EH-MSCs) on the expression of PDGF and IL-10 in Wistar rats with third-degree burns. This study provides novel evidence that EH-MSC-derived exosomes may enhance regenerative and anti-inflammatory responses in third-degree burn healing.

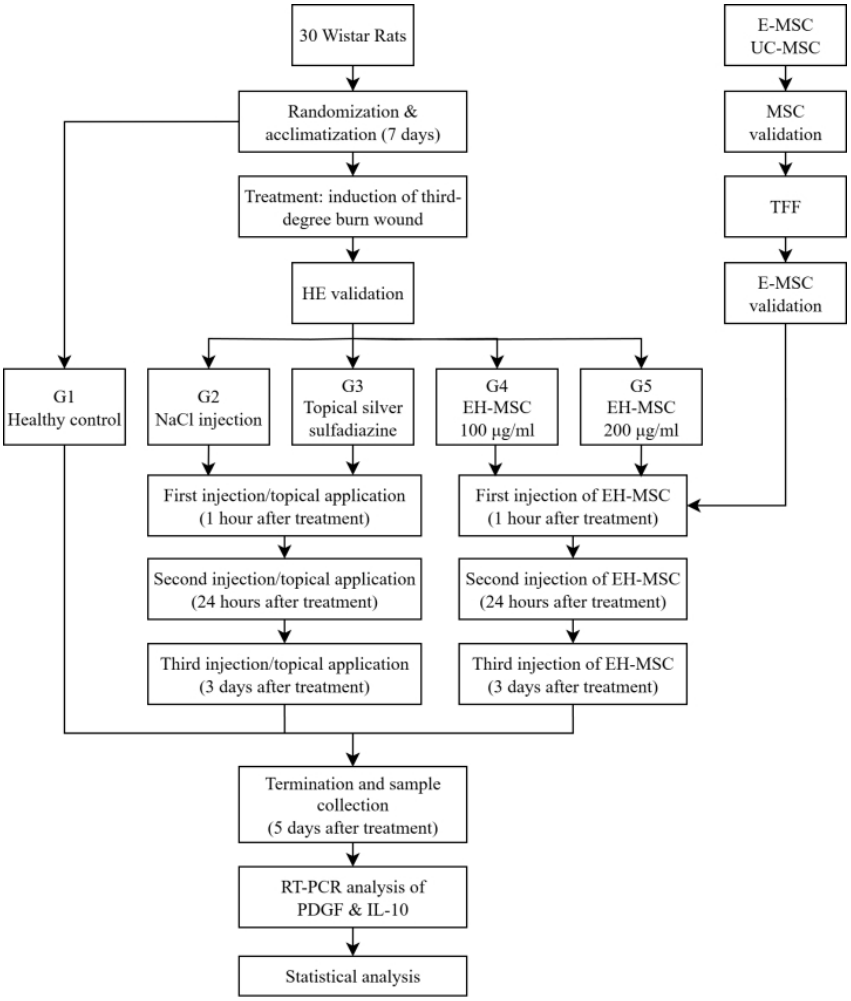


**Figure 1.** Experimental design flowchart of Wistar rats (n = 30) treated with E-MSC for third-degree burn wound healing

## MATERIALS AND METHODS

### Study design and experimental animals

This experimental in vivo study employed a post-test only control group design with a completely randomized allocation to evaluate the effect of EH-MSCs on the expression of PDGF and IL-10 in Wistar rats with third-degree burns (Figure 1). A total of 30 male Wistar rats aged 6–8 weeks and weighing 200–250 g were used. Sample size was determined using Federer's formula, with five rats assigned to each group and one additional rat included per group to anticipate potential dropouts. The animals were divided into five groups: healthy control without treatment, burn with NaCl injection, burn with topical silver sulfadiazine, burn with intradermal EH-MSCs at a dose of 100 µg/mL, and burn with intradermal EH-MSCs at a dose of 200 µg/mL. The rats were maintained in a well-ventilated laboratory at 20–28 °C with food and water provided ad libitum. Inclusion criteria were healthy, active animals without anatomical abnormalities, while exclusion criteria included prior use in other experiments or illness during the study.

All procedures were conducted at the Stem Cell and Cancer Research Laboratory, Sultan Agung Islamic University, Semarang, in April 2025. Ethical clearance was obtained from the Ethics Committee of the Faculty of Medicine, Sultan Agung Islamic University (No. 191/ IV/2025/Komisi Bioetik), and all efforts were made to minimize animal suffering through appropriate anesthesia and humane sacrifice methods.

### Isolation and characterization of mesenchymal stem cells

Mesenchymal stem cells were isolated from rat umbilical cords obtained under sterile conditions. After thorough washing with phosphate-buffered saline containing antibiotics, Wharton's jelly was separated and enzymatically digested using type I collagenase and dispase at 37 °C. The resulting cells were cultured in DMEM supplemented with 10–20% fetal bovine serum under hypoxic conditions (oxygen 1–5%) for 24 hours. Cells were subcultured to 70–80% confluency and characterized using flow cytometry with CD29 and CD90 positivity and minimal CD31 and CD45 expression.

### Exosome isolation and validation

Exosomes were isolated from conditioned media using tangential flow filtration through 100–500 kDa membranes, then validated by the presence of CD63 and CD9 markers and quantified to yield a concentration of 0.75 µg/mL.

### Third-degree burn induction and treatment administration

Third-degree burns were induced under ether anesthesia by shaving the dorsal fur and applying a 2 × 2 $cm^2$, 3 mm thick pre-heated metal plate to the exposed skin for 10–15 seconds. The burns were validated macroscopically by their dry, dark appearance with distinct borders and microscopically with Hematoxylin-Eosin staining, which confirmed coagulative necrosis and destruction of epidermal and dermal architecture. Following validation, the assigned treatments were administered: no treatment for the healthy control group, intradermal NaCl injection for the burn control, topical silver sulfadiazine for the standard therapy group, and intradermal EH-MSC injections for the treatment groups. All rats received a standard diet for five days, after which they were sacrificed under ether anesthesia.

### Measurement of PDGF and IL-10 expression

On day 5, approximately 0.2 mL of blood was collected from the orbital sinus under ketamine anesthesia at a dose of 4 mg/kgBW. Samples were centrifuged, and the supernatant was incubated with monoclonal antibodies for PDGF and IL-10. Expression levels were assessed using reverse transcription-polymerase chain reaction (RT-PCR). In addition, wound tissues were excised, fixed in 10% buffered formalin, embedded in paraffin, and sectioned at 4–5 µm thickness for Hematoxylin-Eosin staining to evaluate histological features.

### Statistical analysis

Data distribution was tested using the Shapiro-Wilk test, and homogeneity was assessed using Levene's test. If data were normal and homogeneous, one-way ANOVA was performed with LSD post hoc analysis; if normal but not homogeneous, ANOVA with Tamhane's test was applied; and if not normal, the Kruskal-Wallis test was used, followed by Mann-Whitney tests when significant differences were found. A p-value $<0.05$ was considered statistically significant.

## RESULTS

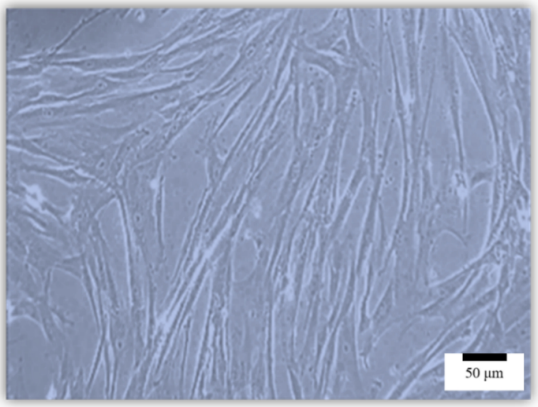


**Figure 2.** Morphology of MSCs at Passage 7 with 80% confluency under 40x magnification.

### Exosome validation

Validation of MSCs was successfully performed prior to treatment. Morphological analysis demonstrated fibroblast-like spindle cells adherent to the culture surface (Figure 2), and flow cytometry confirmed strong expression of MSC-specific markers CD29 and CD90, with minimal expression of CD31 and CD45, indicating a pure MSC population (Figure3). Further differentiation assays verified the

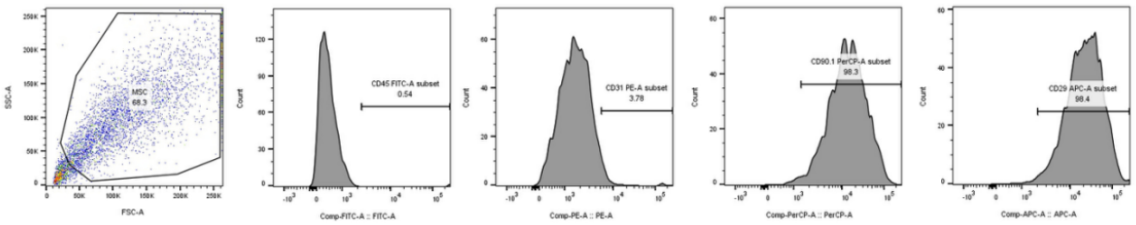

**Figure 3.** Flow cytometry analysis of the expression of specific MSC surface markers such as CD45, CD31, CD90, and CD29.

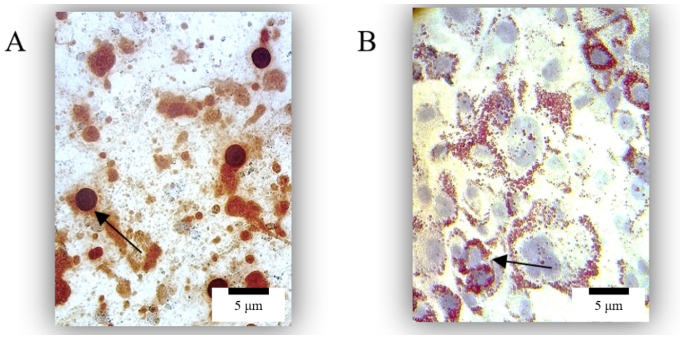


**Figure 4.** (A) Differentiation ability of MSCs into osteoblasts stained with Alizarin Red S and (B) adipocytes stained with Oil Red O (indicated by black arrows, 400x magnification).

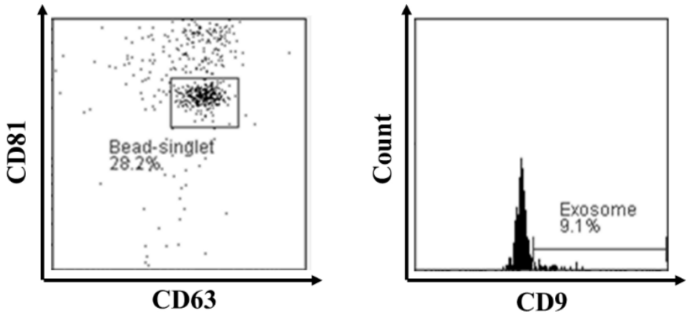


**Figure 5.** Results of Exosome Level Analysis using CD63 and CD9 markers.

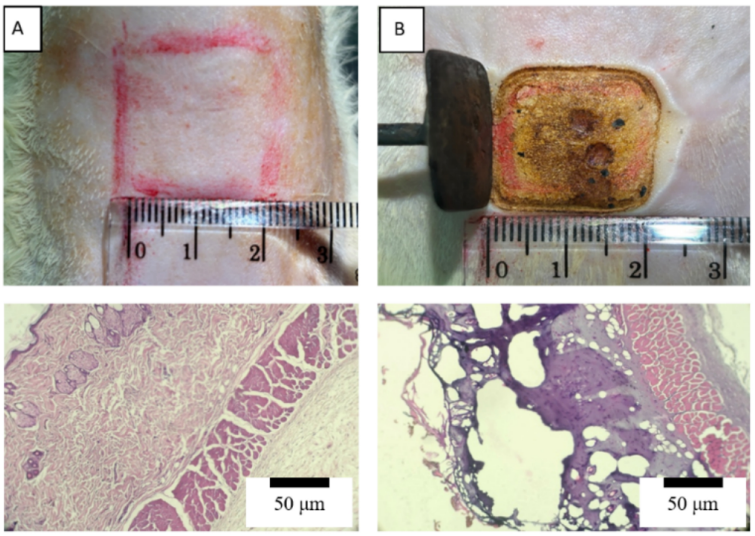


**Figure 6.** Macroscopic and microscopic features of third-degree burn induction. (A) Shaved skin area marked with a 2 × 2 cm square to ensure uniform wound size and location. (B) Third-degree burn induction using a heated metal block showing dark brown to black discoloration, indicating deep thermal damage and coagulative necrosis. Histological images (bottom) reveal intact skin structure in normal tissue (left), while the burned tissue (right) shows loss of epidermal and dermal architecture, collagen denaturation, and necrosis extending to subcutaneous layers.

adipogenic pathways (Figure 4). Hypoxic preconditioning and exosome isolation using Tangential Flow Filtration yielded EH-MSCs with validated exosome markers CD63 and CD9, and an average exosome concentration of 0.75 µg/mL (Figure 5).

**Third-degree burn validation**

The third-degree burn model was confirmed both macroscopically and histologically. Control rats showed normal epidermal and dermal architecture, while burn-induced rats displayed typical coagulative necrosis, vacuolization, and complete epidermal and dermal disruption, consistent with full-thickness burns (Figure 6). Following validation, rats were randomized into five groups for treatment allocation: healthy control, burn with NaCl injection, burn with silver sulfadiazine, burn with EH-MSC 100 µg/mL, and burn with EH-MSC 200 µg/mL.

Macroscopic and microscopic features of third-degree burn induction. (A) Shaved skin area marked with a 2 × 2 cm square to ensure uniform wound size and location. (B) Third-degree burn induction using a heated metal block showing dark brown to black discoloration, indicating deep thermal damage and coagulative necrosis. Histological images (bottom) reveal intact skin structure in normal tissue (left), while the burned tissue (right) shows loss of epidermal and dermal architecture, collagen denaturation, and necrosis extending to subcutaneous layers.

**PDGF expression**

Analysis of PDGF expression demonstrated a progressive increase across treatment groups, with mean values rising from $1.45 \pm 0.92$ in G1 to $2.91 \pm 1.28$ in G5, the highest being observed in the 200 µg/mL EH-MSC group (Table 1). The Shapiro-Wilk test confirmed normality across groups ($p = 0.220$–$0.787$), and Levene's test indicated homogeneity of variances ($p = 0.530$). However, one-way ANOVA revealed no statistically significant difference among the groups ($F = 2.299$, $p = 0.094$), indicating that although a clear biological trend was observed, the increases did not reach statistical significance (Figure 7). Therefore, the increase in PDGF expression should be interpreted as an upward trend rather than a statistically significant treatment effect. This pattern may indicate a potential biological effect, but the present study may have been underpowered to detect significant differences in PDGF expression.

**IL-10 expression**

Similarly, IL-10 expression increased in the EH-MSC-treated groups, with mean values rising from $0.98 \pm 0.43$ in G1 to $2.64 \pm 1.42$ in G5, the highest recorded in the 200 µg/mL dose (Table 1). The Shapiro-Wilk test confirmed normality across groups ($p = 0.063$–$0.773$), and Levene's test indicated homogeneity of variances ($p = 0.130$). One-way ANOVA indicated a statistically significant difference among the groups ($F = 3.344$, $p = 0.030$), prompting LSD post hoc analysis. The post hoc test revealed that IL-10 expression was significantly higher in G4 and G5 compared to G1 ($p = 0.020$ and $p = 0.002$, respectively), suggesting that EH-MSC treatment, particularly at 200 µg/mL, significantly enhanced the anti-inflammatory cytokine expression (Table 2, Figure 8).

**DISCUSSION**

The findings demonstrated an upward trend in both PDGF and IL-10 expression in treatment groups, particularly with the 200 µg/mL dose, compared with control groups. IL-10 expression differed significantly among groups based on one-way ANOVA ($p = 0.030$). LSD post hoc analysis revealed that IL-10 levels were significantly higher in EH-MSC-treated groups G4 and G5 compared to the healthy control group G1 ($p = 0.020$ and $p = 0.002$, respectively). This indicates that EH-MSCs, especially at higher doses, can effectively enhance anti-inflammatory cytokine expression. In contrast, PDGF expression increased in the EH-MSC groups but did not reach overall statistical significance ($p = 0.094$). However, post hoc analysis showed a significant difference between G1 and G5 ($p = 0.014$), indicating a potential biological effect that should be confirmed in studies with larger sample sizes.

Although this study did not directly evaluate intracellular signaling pathways, previous mechanistic studies suggest that hypoxia modifies exosomal cargo through HIF-related responses, resulting in enrichment of bioactive microRNAs, circular RNAs, and proteins that affect macrophages, endothelial cells, and fibroblasts.[15] Hypoxia can alter both the quantity and composition of exosomal cargo, thereby enhancing angiogenesis, cell survival, and immune regulation.[4]

One possible mechanism is the promotion of reparative macrophage polarization and pro-healing signaling in recipient cells. MSC-derived exosomes have been shown to promote M2 macrophage polarization during cutaneous wound healing, partly through transfer of exosomal microRNAs such as miR-223.[16] This effect may be amplified when the exosomes are derived from hypoxia-preconditioned MSCs.

The increase in PDGF expression is consistent with its role as a potent mediator of fibroblast proliferation, angiogenesis, and extracellular matrix deposition, which are essential for tissue regeneration following severe burns. Recent evidence has shown that PDGF is closely linked with fibroblast migration and collagen synthesis, processes that contribute to granulation tissue formation and wound closure.[17,18] Moreover, studies using exosomes have indicated that the delivery of PDGF-related signaling can accelerate angiogenesis and improve the quality of wound repair.[19,20] Thus, increased PDGF expression after EH-MSC administration may indicate stimulation of the proliferative phase, particularly fibroblast activation and neovascular support. This interpretation is consistent with prior wound-healing studies showing that hypoxic MSC-conditioned products can modulate PDGF dynamics during tissue repair.[21] The upward trend in PDGF expression in the present study therefore supports the hypothesis that EH-MSCs contribute to wound repair.

Likewise, the significant increase in IL-10 expression highlights the strong anti-inflammatory effects of EH-MSCs. IL-10 is a key cytokine that

suppress excessive inflammation by downregulating pro-inflammatory mediators such as TNF-α and IL-6, thereby facilitating the transition to the proliferative phase of wound healing.[8,14] Hypoxia preconditioning has been shown to enhance the immunomodulatory activity of MSC-derived exosomes by altering their microRNA and protein content.[4] In line with this, Cui et al. demonstrated that hypoxia-induced MSC exosomes improved functional outcomes in vivo by regulating inflammatory responses.[5] In this study, the higher IL-10 expression in the 200 µg/mL group suggests that EH-MSCs may similarly exert enhanced

**Table 1.** Descriptive statistics of PDGF and IL-10 expression in Wistar rats with third-degree burns after different treatments.

| Group | PDGF | | IL-10 | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| G1 (Healthy) | 1.454 | 0.918 | 0.982 | 0.433 |
| G2 (NaCl) | 1.610 | 0.611 | 1.734 | 0.378 |
| G3 (SSD) | 1.726 | 0.595 | 1.758 | 0.385 |
| G4 (EH-MSC 100 µg/mL) | 2.070 | 0.674 | 2.188 | 0.582 |
| G5 (EH-MSC 200 µg/mL) | 2.908 | 1.276 | 2.642 | 1.420 |

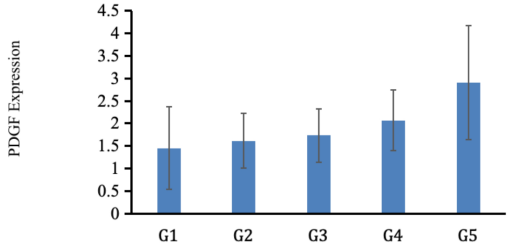


**Figure 7.** PDGF expression across treatment groups.

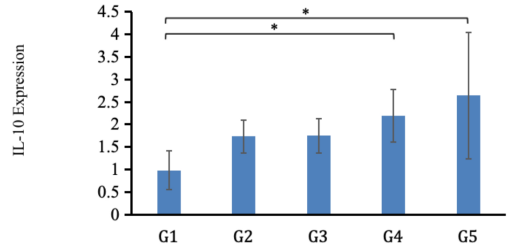


**Figure 8.** IL-10 expression across treatment groups. Asterisks (*) indicate statistically significant differences between groups based on LSD post hoc analysis ($p < 0.05$).

**Table 2.** LSD post hoc test results of IL-10 expression in Wistar rats with third-degree burns after different treatments.

| Group | Group Comparison | p-value |
|---|---|---|
| G1 (Healthy) | G2 (NaCl) | 0.130 |
| | G3 (SSD) | 0.119 |
| | G4 (EH-MSC 100 µg/mL) | 0.020 |
| | G5 (EH-MSC 200 µg/mL) | 0.002 |
| G2 (NaCl) | G3 (SSD) | 0.960 |
| | G4 (EH-MSC 100 µg/mL) | 0.352 |
| | G5 (EH-MSC 200 µg/mL) | 0.071 |
| G3 (SSD) | G4 (EH-MSC 100 µg/mL) | 0.377 |
| | G5 (EH-MSC 200 µg/mL) | 0.078 |
| G4 (EH-MSC 100 µg/mL) | G5 (EH-MSC 200 µg/mL) | 0.352 |

immunomodulatory effects, potentially reducing the risk of prolonged or dysregulated inflammation that often complicates burn healing.

Importantly, PDGF and IL-10 should not be interpreted as isolated markers, but as complementary mediators acting in overlapping phases of wound healing. IL-10 helps suppress excessive inflammation and supports the transition to the proliferative phase. In addition, IL-10 has been shown to enhance vascular responses and wound repair through STAT3-dependent mechanisms, including increased VEGF expression and endothelial progenitor cell recruitment.[22] PDGF, in turn, promotes fibroblast activity, matrix deposition, and angiogenic maturation, which are required for stable granulation tissue and wound closure.[7] Therefore, the simultaneous increase in IL-10 and PDGF in the EH-MSC groups may reflect a synergistic therapeutic effect: IL-10 promotes inflammation resolution, while PDGF supports tissue reconstruction and vascularized granulation. Nevertheless, this mechanistic interpretation remains indirect because exosomal cargo profiling and pathway-specific analyses were not performed in the present study.

These results are in agreement with several recent investigations. Liu et al. reported that human umbilical cord MSC transplantation accelerated burn wound healing by promoting angiogenesis and reducing inflammation.[23] More recently, Casado-Díaz et al. and Zhou et al. confirmed the potential of MSC-derived extracellular vesicles to improve skin wound healing through the delivery of growth factors and immunomodulatory signals.[20,24] Haraszti et al. further highlighted that exosomes obtained from hypoxia-preconditioned MSCs displayed higher yields and superior biological activity than those derived from normoxic cultures, which supports the methodological choice in this study.[25] These findings strengthen the interpretation that hypoxia-induced MSC exosomes may represent an advantageous approach for enhancing burn healing outcomes.

Despite these encouraging outcomes, some limitations remain. First the moderate sample size, although calculated using Federer's formula, may have limited the ability to detect subtler effects, particularly in PDGF expression. Second, the five-day observation window likely captured only the inflammatory and early proliferative phases burn repair rather than the full wound-healing process.[26,27] Therefore, the present findings should be interpreted as evidence of changes in early inflammatory and regenerative markers, rather than as a comprehensive evaluation of wound healing outcomes. Third, although exosomes were isolated, validated using CD63 and CD9 markers, and administered intradermally, this study did not directly track exosome distribution or cellular uptake within the wound tissue. Fourth, the use of a single intradermal dose may have reduced the therapeutic potential compared to repeated or systemic delivery, as suggested in other regenerative studies.[28,29]

Overall, this study contributes novel evidence by specifically examining the influence of EH-MSCs on PDGF and IL-10 expression in a third-degree burn model. The results support the concept that hypoxia-preconditioned MSC exosomes promote regenerative and anti-inflammatory pathways, advancing the field of cell-free therapy for burn management. Future studies should employ larger sample sizes, extended observation periods combined with macroscopic and histological assessments, incorporate exosome-tracing approaches, such as fluorescently labeled exosomes or tissue-based exosome markers, to confirm local biodistribution and uptake at the injury site, and dose-response analyses to more comprehensively evaluate the healing process. Investigating additional markers such as VEGF, TGF-β, and TNF-α, as well as profiling the microRNA cargo of EH-MSCs, may provide further mechanistic insights.[30,31] Such research will be essential to confirm the therapeutic efficacy of EH-MSCs and guide their translation into clinical practice

## CONCLUSION

This study demonstrated that EH-MSCs increased IL-10 expression in third-degree burn wounds, with the highest levels observed in the 200 µg/mL treatment group. IL-10 expression showed statistically significant differences between groups ($p$ = 0.030), with post hoc analysis confirming that EH-MSC treatment significantly elevated IL-10 levels compared to controls. PDGF expression also showed an upward trend in the EH-MSC groups, particularly at the higher dose, but the overall difference was not statistically significant ($p$ = 0.094). Therefore, the PDGF findings should be interpreted as a potential early regenerative signal rather than conclusive evidence of a treatment effect. Overall, these results suggest that EH-MSCs may modulate early anti-inflammatory responses and may have potential regenerative effects in burn repair. Further studies are recommended to explore long-term effects, optimal dosing, and molecular mechanisms to support clinical translation.

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## REFERENCES

1. World Health Organization. Burns. World Health Organization (WHO). 2023 [cited 2025 Aug 5]. Available from: https://www.who.int/news-room/fact-sheets/detail/burns
2. Wardhana A, Basuki A, Prameswara ADH, Rizkita DN, Andarie AA, Canintika AF. The epidemiology of burns in Indonesia's national referral burn center from 2013 to 2015. *Burn Open*. 2017 Oct;1(2):67–73. DOI: 10.1016/j.burnso.2017.08.002.
3. Lestari T, Syukur S, Revilla G, Sukma Rita R, Rustini R. The Burn Wound Healing Process: A Review. *Int J Progress Sci Technol*. 2023 Aug 18;40(1):77. DOI: 10.52155/ijpsat.v40.1.5565.
4. Jiang H, Zhao H, Zhang M, He Y, Li X, Xu Y, et al. Hypoxia Induced Changes of Exosome Cargo and Subsequent Biological Effects. *Front Immunol*. 2022 Apr 4;13. DOI: 10.3389/fimmu.2022.824188.

5. Cui G, Wu J, Mou F, Xie W, Wang F, Wang Q, et al. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. *FASEB J*. 2018 Feb 4;32(2):654–68. DOI: 10.1096/fj.201700600R.
6. Pierce GF, Mustoe TA, Altrock BW, Deuel TF, Thomason A. Role of platelet-derived growth factor in wound healing. *J Cell Biochem*. 1991 Apr 19;45(4):319–26. DOI: 10.1002/jcb.240450403.
7. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. *Wound Repair Regen*. 2008 Sep 3;16(5):585–601. DOI: 10.1111/j.1524-475X.2008.00410.x.
8. Sun ZL, Feng Y, Zou ML, Zhao BH, Liu SY, Du Y, et al. Emerging Role of IL-10 in Hypertrophic Scars. *Front Med*. 2020 Aug 27;7. DOI: 10.3389/fmed.2020.00438.
9. Iyer SS, Cheng G. Role of Interleukin 10 Transcriptional Regulation in Inflammation and Autoimmune Disease. *Crit Rev Immunol*. 2012;32(1):23–63.DOI: 10.1615/CritRevImmunol.v32.i1.30.
10. Dirja BT, Wardoyo EH, Putra A, Amalina ND. Enhanced Third Degree Burn Wound Healing by Hypoxic Mesenchymal Stem Cells' Secretome: IL-10 Upregulation and TNF-α/PGE2 Suppression. *Trends Sci*. 2024 Sep 30;21(10):8288. DOI: 10.48048/tis.2024.8288.
11. Hariani NP, Putra A, Subchan P, Setiawan E. Mesenchymal Stem Cell-Derived Exosomes Enhance FGF-1 and SDF-1 Expression in Rats with Second Degree Burns. *Mol Cell Biomed Sci*. 2025 Jul 1;9(2):115. DOI: 10.21705/mcbs.v9i2.635.
12. Pulido-Escribano V, Torrecillas-Baena B, Camacho-Cardenosa M, Dorado G, Gálvez-Moreno MÁ, Casado-Díaz A. Role of hypoxia preconditioning in therapeutic potential of mesenchymal stem-cell-derived extracellular vesicles. *World J Stem Cells*. 2022 Jul;14(7):453–72.DOI: 10.4252/wjsc.v14.i7.453.
13. Yang Y, Lee EH, Yang Z. Hypoxia-Conditioned Mesenchymal Stem Cells in Tissue Regeneration Application. *Tissue Eng Part B Rev*. 2022 Oct;28(5):966–77. DOI: 10.1089/ten.TEB.2021.0145.
14. Verma R, Balakrishnan L, Sharma K, Khan AA, Advani J, Gowda H, et al. A network map of Interleukin-10 signaling pathway. *J Cell Commun Signal*. 2016 Mar;10(1):61–7. DOI: 10.1007/s12079-015-0302-x.
15. 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 May 26;14(5):318–29. DOI: 10.4252/wjsc.v14.i5.318.
16. 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 Int*. 2019 Sep 9;2019:1–16. DOI: 10.1155/2019/7132708.
17. Kazlauskas A. PDGFs and their receptors. *Gene*. 2017 May;614:1–7. DOI: 10.1016/j.gene.2017.03.003.
18. Folestad E, Kunath A, Wågsäter D. PDGF-C and PDGF-D signaling in vascular diseases and animal models. *Mol Aspects Med*. 2018 Aug;62:1–11.DOI: 10.1016/j.mam.2018.01.005.
19. Lu K, Wu C, Bao J. Molecular modeling, expression and wound-repair activity in vivo of platelet-derived growth factor from Periplaneta americana. *Process Biochem*. 2021 Nov;110:151–62. DOI: 10.1016/j.procbio.2021.08.009.
20. Zhou C, Zhang B, Yang Y, Jiang Q, Li T, Gong J, et al. Stem cell-derived exosomes: emerging therapeutic opportunities for wound healing. *Stem Cell Res Ther*. 2023 Apr 26;14(1):107. DOI:10.1186/s13287-023-03345-0.
21. Muhar AM, Mukharim F, Hermansyah D, Putra A, Hidayah N, Amalina ND, et al. Hypoxic mesenchymal stem cell-conditioned medium accelerates wound healing by regulating IL-10 and TGF-β levels in a full-thickness-wound rat model. *Indones J Biotechnol*. 2022 Dec 30;27(4):187. DOI: 10.22146/ijbiotech.63914.
22. Short WD, Steen E, Kaul A, Wang X, Olutoye OO, Vangapandu H V., et al. IL-10 promotes endothelial progenitor cell infiltration and wound healing via STAT3. *FASEB J*. 2022 Jul 7;36(7). DOI: 10.1096/fj.201901024RR.
23. Liu L, Yu Y, Hou Y, Chai J, Duan H, Chu W, et al. Human Umbilical Cord Mesenchymal Stem Cells Transplantation Promotes Cutaneous Wound Healing of Severe Burned Rats. Covas DT, editor. *PLoS One*. 2014 Feb 20;9(2):e88348.DOI:10.1371/journal.pone.0088348.
24. Casado-Díaz A, Quesada-Gómez JM, Dorado G. Extracellular Vesicles Derived From Mesenchymal Stem Cells (MSC) in Regenerative Medicine: Applications in Skin Wound Healing. *Front Bioeng Biotechnol*. 2020 Mar 3;8. DOI: 10.3389/fbioe.2020.00146.
25. Haraszti RA, Miller R, Stoppato M, Sere YY, Coles A, Didiot MC, et al. Exosomes Produced from 3D Cultures of MSCs by Tangential Flow Filtration Show Higher Yield and Improved Activity. *Mol Ther*. 2018 Dec;26(12):2838–47. DOI: 10.1016/j.ymthe.2018.09.015.
26. Wallace HA, Basehore BM, Zito PM. Wound Healing Phases [Internet]. StatPearls. 2025 [cited 2026 Mar 20]. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6656798

27. Żwierełło W, Piorun K, Skórka-Majewicz M, Maruszewska A, Antoniewski J, Gutowska I. Burns: Classification, Pathophysiology, and Treatment: A Review. *Int J Mol Sci*. 2023 Feb 13;24(4):3749. DOI: 10.3390/ijms24043749.
28. Yang G, Waheed S, Wang C, Shekh M, Li Z, Wu J. Exosomes and Their Bioengineering Strategies in the Cutaneous Wound Healing and Related Complications: Current Knowledge and Future Perspectives. *Int J Biol Sci*. 2023;19(5):1430–54. DOI: 10.7150/ijbs.80430.
29. Novello S, Pellen-Mussi P, Jeanne S. Mesenchymal stem cell-derived small extracellular vesicles as cell-free therapy: Perspectives in periodontal regeneration. *J Periodontal Res*. 2021 Jun 28;56(3):433–42. DOI: 10.1111/jre.12866.
30. Liao Z, Zheng R, Shao G. Mechanisms and application strategies of miRNA-146a regulating inflammation and fibrosis at molecular and cellular levels (Review). *Int J Mol Med*. 2022 Dec 5;51(1):7. DOI: 10.3892/ijmm.2022.5210.
31. Winkler I, Engler JB, Vieira V, Bauer S, Liu YH, Di Liberto G, et al. MicroRNA-92a–CPEB3 axis protects neurons against inflammatory neurodegeneration. *Sci Adv*. 2023 Nov 24;9(47). DOI: 10.1126/sciadv.adi6855.