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MSC-derived exosomes ppregulate KGF and PDGF expression in a rat model of second-degree burn injury

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Abstract: Second-degree burn injuries necessitate efficient treatment approaches to expedite wound healing and reinstate skin integrity. Exosomes generated from mesenchymal stem cells (E-MSCs) are a promising cell-free therapeutic approach owing to their capacity to control inflammation and facilitate tissue regeneration. This research utilized a post-test-only control group experimental design with 28 male Wistar rats, randomly allocated into four groups: healthy control (G1), burn damage treated with NaCl (G2), and burn injury treated with E-MSCs at doses of 100 µL (G3) and 200 µL (G4). On the seventh day following therapy, the expression levels of keratinocyte growth factor (KGF) and platelet-derived growth factor (PDGF) were measured using RT-PCR. The expression of KGF was markedly elevated in G3 (0.65 ± 0.03) and G4 (0.92 ± 0.08) in comparison to G2 (0.32 ± 0.09; $p < 0.001$). Likewise, PDGF expression was significantly elevated in G3 (1.08 ± 0.24) and G4 (1.49 ± 0.19) compared to G2 (0.66 ± 0.08; $p < 0.001$). The results indicate a dose-dependent influence of E-MSC administration on the upregulation of KGF and PDGF, which are essential for epithelialization and angiogenesis in the wound healing process. In conclusion, E-MSCs demonstrate considerable promise as a cell-free treatment strategy for improving the healing of second-degree burns. Additional research is necessary to confirm these results and evaluate their practical relevance in clinical environments.

Keywords: burn healing; exosomes; keratinocyte growth factor; mesenchymal stem cells; platelet-derived growth factors

INTRODUCTION

Burn injuries, particularly second-degree burns, are characterized by damage to the skin's structural and functional integrity, as well as the loss of progenitor cells essential for regeneration and recovery[1]. Conventional treatments, such as autologous skin grafts, including split-thickness and full-thickness grafts, often face limitations, particularly in cases involving extensive burns where donor skin availability is a challenge[2,3]. This has prompted growing interest in regenerative approaches that accelerate re-epithelialization and minimize scar formation[4].

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Mesenchymal stem cells (MSCs) have gained attention for their ability to modulate inflammation, promote angiogenesis, and stimulate tissue repair[5]. However, direct MSC transplantation faces challenges including tumorigenicity, immunological concerns, and regulatory hurdles[6]. MSC-conditioned medium (MSC-CM), which contains soluble proteins, lipids, cytokines, and extracellular vesicles, has been shown to enhance fibroblast proliferation, keratinocyte migration, and angiogenesis[7,8].

Among the components of MSC-CM, mesenchymal stem cell-derived exosomes (E-MSCs) emerging as a promising candidate due to their regenerative capabilities[9,10]. E-MSCs are small extracellular vesicles containing bioactive molecules that can activate signaling pathways such as MAPK, PI3K/Akt, and JAK-STAT that promote tissue repair by enhancing the production of growth factors critical for healing, such as keratinocyte growth factor (KGF) and platelet-derived growth factor (PDGF)[10–12]. Other studies have shown that production of KGF and PDGF induced by E-MSC plays critical roles in keratinocyte and fibroblast activation, leading to faster wound closure and re-epithelialization[13,14]. While studies on MSC-conditioned media (MSC-CM) suggest its effectiveness in wound healing, this medium comprises a variety of components, including proteins, exosomes, and other bioactive molecules. The specific contribution of isolated E-MSCs to gene expression related to wound healing remains unclear[15].

While MSC-CM has been widely reported to improve wound healing[7,8], studies isolating purified E-MSCs to directly examine their effect on key regenerative genes are still limited. To our knowledge, this study is among the first to report dose-dependent upregulation of KGF and PDGF expression in an in vivo burn model[9,16]. KGF is a potent mitogen for epithelial cells that signals through FGFR2b to stimulate keratinocyte proliferation and migration[17], while PDGF is crucial for fibroblast activation, extracellular matrix deposition, and angiogenesis[18,19]. Most previous studies have focused on MSC-conditioned medium, which contains a mixture of soluble proteins and vesicles, making it difficult to isolate the direct effect of exosomes on wound-healing mediators. Isolating E-MSCs for study provides an opportunity to dissect their exact mechanisms of action, particularly their role in modulating gene expression[9,20].

This study aims to evaluate the effects of purified MSC-derived exosomes on the expression of KGF and PDGF genes in a rat model of second-degree burn injury. By focusing on purified E-MSCs, this study aims to provide detailed insights into their regenerative potential and therapeutic mechanisms. These findings are expected to contribute to the broader understanding of E-MSC applications in regenerative medicine, with particular relevance to improving outcomes for patients with burn injuries in resource-limited settings.

MATERIAL AND METHOD

Study Design

This study employed a true experimental post-test control group design to evaluate the effects of exosomes derived from E-MSC on the expression of KGF and PDGF in Wistar rats (*Rattus norvegicus*) with second-degree burn injuries (Figure 1).

Ethical Clearance

The study was approved by the Ethics Committee of the Faculty of Medicine, Sultan Agung Islamic University, under reference number No. 460/XI/2024/Komisi Bioetik.

Isolation of MSC

MSC were isolated from the umbilical cord of Wistar rats. The umbilical cord was collected immediately after birth and stored in a transport medium containing 2% Fetal Bovine Serum (FBS) at 4°C. The cord was washed several times with Phosphate-Buffered Saline (PBS) containing antibiotics to remove blood and contaminants. The Wharton's Jelly was separated from the outer membrane and

enzymatically digested using collagenase type I (0.1%-0.2%) and dispase (0.1%) at 37°C for 30-60 minutes. The cells were then cultured in DMEM medium supplemented with 10-20% FBS and incubated at 37°C with 5% CO2. MSC surface markers (CD73, CD90, and CD105) were verified using flow cytometry.

Isolation of Exosomes from MSC (E-MSC)

Exosomes were isolated from MSC using the Tangential Flow Filtration (TFF) method. MSC were cultured until 70-80% confluency, and the medium was replaced with serum-free medium to avoid contamination. The conditioned medium was collected after 48-72 hours and centrifuged at 300 g for 10 minutes to remove cells, followed by 2000 g for 20 minutes to remove debris. The supernatant was filtered through a 0.22 µm membrane, and exosomes were concentrated using a TFF system with a 200-500 kDa filter. The exosomes were characterized using flow cytometry for CD9, CD63, and CD81 markers.

Although exosome characterization was performed using flow cytometry for CD9, CD63, and CD81 markers, complementary techniques such as nanoparticle tracking analysis (NTA) or transmission electron microscopy (TEM) were not conducted. This limitation is acknowledged and should be considered when interpreting the findings.

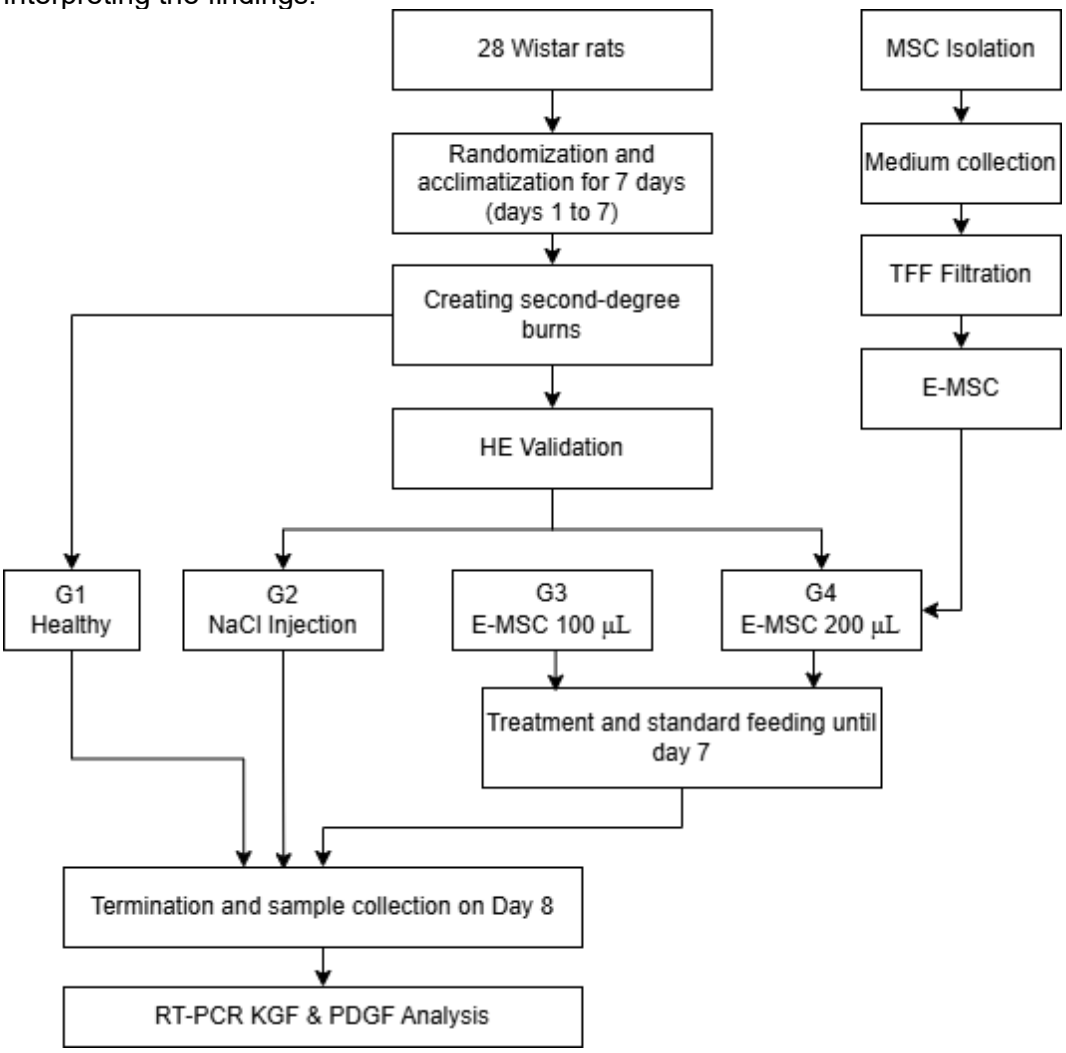

Figure 1. Experimental design of this study, involving 4 different groups.

Animal Model

Twenty-eight healthy male Wistar rats, aged 2-3 months and weighing 250-300 grams, were used in this study. The rats were housed in polypropylene cages (50 cm x 30 cm x 20 cm, DWK Life Sciences, Germany) under controlled environmental conditions (temperature: 28–32°C, humidity: 40–70%, and 12-hour

light-dark cycles) and provided with standard laboratory chow and water ad libitum. The rats were acclimatized for seven days before the experiment and randomly divided into four groups (n = 7 per group):

a) Group 1 (G1): Healthy rats without burn injury or treatment.
b) Group 2 (G2): Rats with second-degree burn injury treated with 100 µL of NaCl injection.
c) Group 3 (G3): Rats with second-degree burn injury treated with 100 µL of E-MSC injection.
d) Group 4 (G4): Rats with second-degree burn injury treated with 200 µL of E-MSC injection.

The 100 µL and 200 µL doses were adapted from Kusuma et al. (2023), who found that 200 µL of MSC-derived secretome most effectively increased TGF-β expression and reduced IL-6 in a rat wound model[21].

Induction of Burn Injury

Second-degree burn injuries were induced on the dorsal region of the rats. The area was shaved and disinfected with 1% polyvinylpyrrolidone iodine. A heated aluminum rod (6 mm diameter) was applied to the skin for 5 seconds to create the burn.

Treatment Administration

After burn induction, the rats were treated according to their respective groups. Group 2 received 100 µL of NaCl, Group 3 received 100 µL of E-MSC, and Group 4 received 200 µL of E-MSC, all administered subcutaneously. The rats were monitored for seven days post-treatment.

Sample Collection and RT-PCR Analysis

On day 7, the rats were euthanized, and skin tissue samples were collected from the burn site. The samples were homogenized in Trizol reagent (Invitrogen™, Thermo Fisher Scientific, USA), and RNA was extracted using chloroform and isopropanol. The RNA concentration was quantified using a Nanodrop spectrophotometer (Thermo Fisher Scientific, USA). Reverse transcription was performed using a cDNA synthesis kit (RevertAid™, Thermo Fisher Scientific, USA), and RT-PCR was conducted using SYBR Green Master Mix (SensiFAST™, Bioline, UK) with specific primers for KGF and PDGF.

Data Analysis

Data were analyzed using SPSS version 26.0. The Shapiro-Wilk test was used to assess normality, and Levene's test was used to evaluate homogeneity. One-way ANOVA followed by post hoc LSD tests was used to compare the expression levels of KGF and PDGF between groups. A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

MSCs were successfully isolated from rat umbilical cords and cultured under sterile conditions. These cells exhibited spindle-like morphology and demonstrated their capacity for differentiation into adipocytes and osteocytes when subjected to adipogenic and osteogenic induction, confirmed through Oil Red O and Alizarin Red staining, respectively (Figure 2). Flow cytometry analysis validated the MSC identity by detecting high expression of CD90 (98.5%) and CD29 (95.3%), with minimal expression of CD45 (1.6%) and CD31 (0%) (Figure 3).

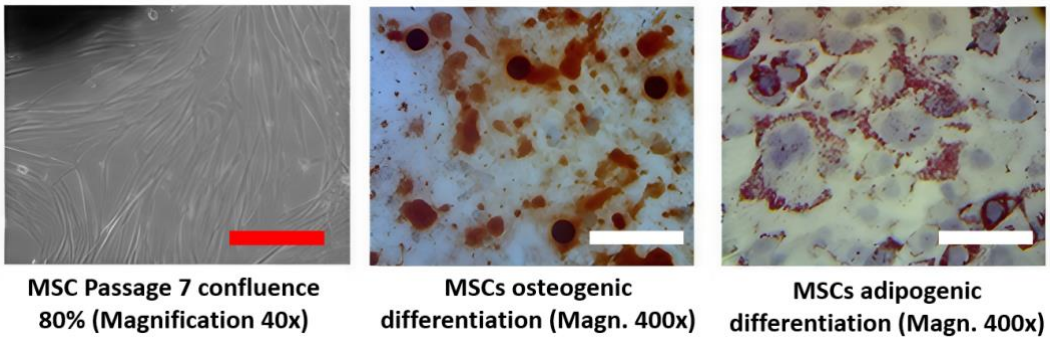

Figure 2. Results of E-MSC Isolation from Rat Umbilical Cord.
(Left) Isolated cells are spindle-shaped at 40x magnification. (Middle) Lipid droplets appear red around the cells after Oil Red O staining in the MSC population at 400x magnification. (Right) Calcium deposition appears red after Alizarin Red staining. Red bar: 100 µm. White bar: 10 µm

Exosomes derived from MSCs were isolated using tangential flow filtration (TFF). Flow cytometry analysis identified markers indicative of exosomes, including CD63, CD81, and CD9, with positive detection rates of 28.2%, 28.2%, and 9.1%, respectively (Figure 4). These findings confirmed the successful isolation of functional MSC-derived exosomes.

Second-degree burns were successfully induced using a heated aluminum rod applied for 5 seconds to the dorsal skin of Wistar rats (Figure 5). Histological analysis using Hematoxylin and Eosin (H&E) staining revealed significant damage to the epidermis and dermis, consistent with second-degree burns. This validation ensured that the animal model accurately represented the targeted condition for the study.

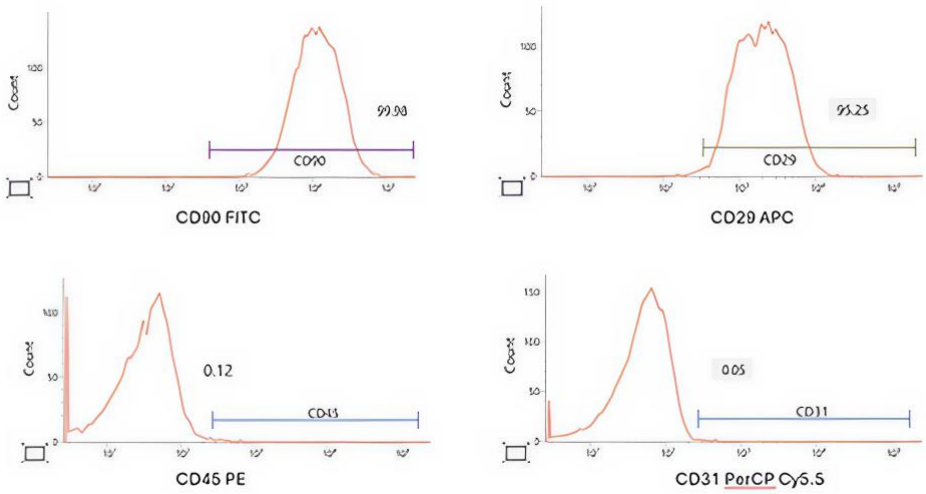

Figure 3. Flow cytometry analysis of MSC markers CD90, CD29, CD45, and CD31

The comparison of the KGF and PDGF genes across the group are presented as follows (Figure 6 and Table 1). The expression of KGF was significantly higher in groups treated with MSC-derived exosomes. Group G4 (200 µL exosome dose) exhibited the highest expression level of KGF (0.92 ± 0.08), followed by group G3 (100 µL exosome dose) with a value of 0.65 ± 0.03, and the control group G2 (NaCl injection) with the lowest level at 0.32 ± 0.09. Statistical analysis using one-way ANOVA confirmed significant differences between the groups ($p < 0.05$). Post hoc analysis further validated that the differences between G2 and G3, and G3 and G4, were statistically significant.

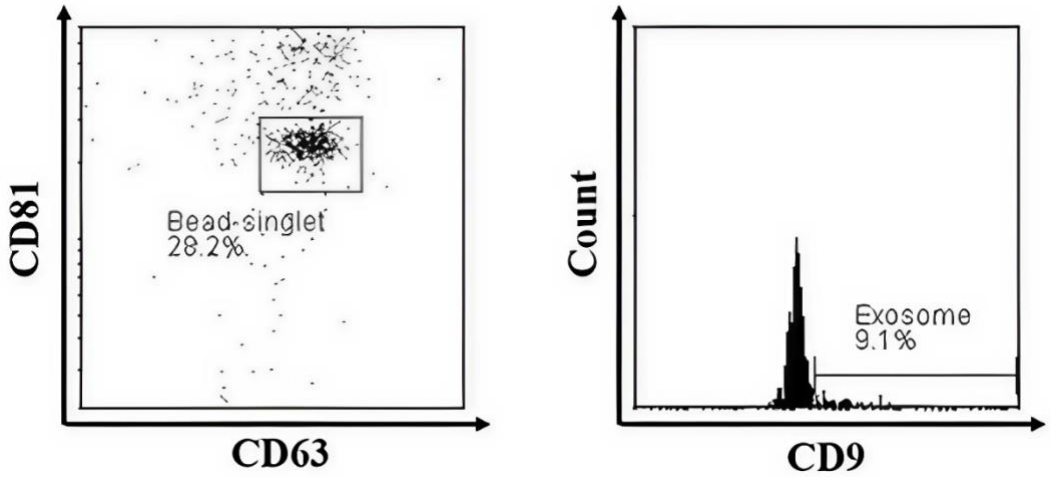

Figure 4. Validation of exosomes for the expression of markers CD81, CD63, and CD9.

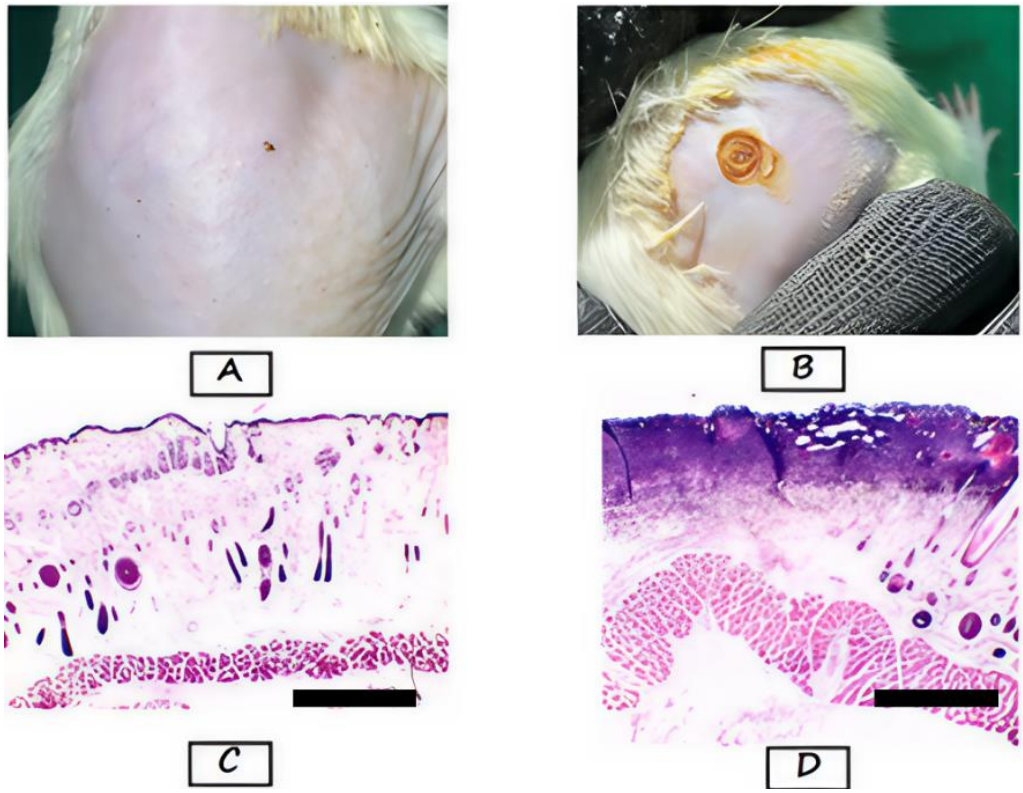

Figure 5. Validation of second-degree burn model.
(A) Healthy rat group, (B) Burn group rats, (C) Histopathology of healthy rats shows an intact structure of the epidermis and dermis layers with no damage or necrosis, (D) Histopathology of second-degree burn model rats shows loss of the epidermal layer, damage to the dermis, and necrosis in the epidermal part. Black bar: 10 µm.

Similarly, the PDGF expression levels followed a dose-dependent increase. Group G4 (200 µL exosome dose) had the highest PDGF expression (1.49 ± 0.19), followed by G3 (1.08 ± 0.24) and G2 (0.66 ± 0.08). One-way ANOVA indicated significant differences between the groups ($p < 0.05$), and post hoc analysis confirmed meaningful distinctions between each pair of groups.

This study adds to the growing evidence supporting cell-free regenerative therapies and is, to our knowledge, among the first to demonstrate that purified MSC-derived exosomes significantly increase the expression of KGF and PDGF in a dose-dependent manner in an in vivo model of second-degree burn injury. These results align with existing literature on E-MSCs, underscoring their regenerative potential and therapeutic efficacy in wound healing[8,16].

Table 1. Comparative expression profiles of KGF and PDGF across experimental groups.

Expression	G2	G3	G4	p-value
KGF				
Value	0.32±0.09	0.65±0.03	0.92±0.08	
Statistical tests (p)				
Shapiro wilk	0.069	0.822	0.662	
Lavene test				0.051
Oneway ANOVA				0.000
PDGF				
Value	0.66±0.08	1.08±0.24	1.49±0.19	
Statistical tests (p)				
Shapiro wilk	0.572	0.768	0.684	
Lavene test				0.054
Oneway ANOVA				0.000

Note:
* Shapiro wilk = Normal (p>0.05)
* Leuvene test = Homogen (p>0.05)
* Oneway ANOVA = Significant difference (p < 0.05)

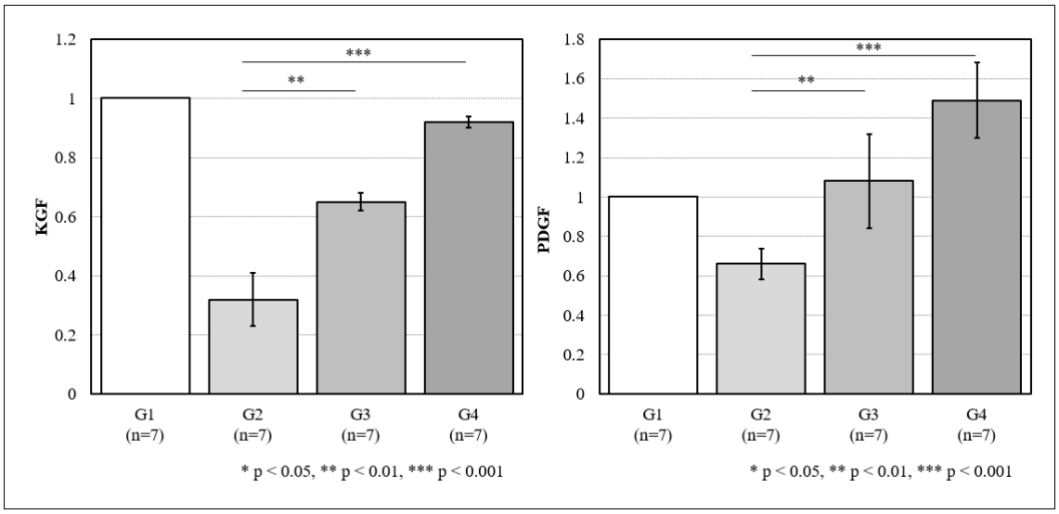

Figure 6. Comparative expression profiles of KGF (left) and PDGF (right) across experimental groups.

The observed upregulation of KGF and PDGF suggests that MSC-exosomes may activate signaling cascades involved in epithelialization and angiogenesis[17]. KGF acts primarily through FGFR2b to stimulate keratinocyte proliferation and migration via MAPK and PI3K/Akt pathways, while PDGF activates fibroblast proliferation and extracellular matrix deposition through PI3K/Akt and Ras-MAPK signaling[14,17]. The robust increase seen in the 200 µL group (G4) indicates that a higher exosome dose may more effectively trigger these downstream pathways. Although pathway activation was not directly measured, our data showing significant upregulation of KGF and PDGF suggest that PI3K/Akt and MAPK/ERK pathways were likely engaged, consistent with studies reporting that these pathways mediate keratinocyte migration and fibroblast proliferation in response to exosomal cargo[10,22,23]. JAK-STAT activation may also be implicated, as PDGF receptor engagement has been shown to trigger STAT phosphorylation and promote fibroblast proliferation[24,25].

The anti-inflammatory properties of E-MSCs likely contributed to a favorable microenvironment for KGF expression. By suppressing pro-inflammatory cytokines such as TNF-α and IL-1 and encouraging the shift of macrophages to an anti-inflammatory M2 phenotype, the exosomes facilitated cellular proliferation and wound closure. Furthermore, the presence of growth factors such as VEGF and TGF-β within the exosomes could synergize with KGF, amplifying their collective impact on tissue repair[15].

PDGF plays a pivotal role in the wound-healing process by promoting fibroblast proliferation, extracellular matrix deposition, and angiogenesis. PDGF achieves these effects by activating pathways such as PI3K/Akt and Ras-MAPK upon binding to its receptors (PDGFR-α and PDGFR-β)[13,26]. This study's results demonstrate a significant dose-dependent increase in PDGF expression in exosome-treated groups, with the 200 µL group showing the highest expression. These results suggest that E-MSCs deliver sufficient bioactive molecules to activate these pathways, thereby enhancing fibroblast activity and new blood vessel formation.

The contribution of VEGF, a component of E-MSCs, is notable in this context. VEGF enhances angiogenesis and boosts blood supply to the wound site, supporting PDGF's role in tissue repair. Additionally, the exosomes may activate the MAPK and JAK-STAT pathways, further enhancing PDGF gene transcription and subsequent protein production, as previously reported[25,27].

The combined enhancement of KGF and PDGF expression underscores the multifaceted therapeutic potential of E-MSCs. These vesicles serve as carriers of a complex array of bioactive molecules, including miRNAs (e.g., miRNA-21 and miRNA-146a), proteins, and lipids, which collectively contribute to wound healing[11,28,29]. E-MSCs not only directly stimulate gene expression but also create a regenerative microenvironment by modulating inflammation, reducing oxidative stress, and enhancing cellular communication[30,31].

This study’s findings are consistent with prior research that highlights E-MSCs as a cell-free alternative for regenerative medicine. For instance, Gangadaran et al. (2023) demonstrated that MSC-derived secretomes, including exosomes, accelerate wound healing by promoting angiogenesis and reducing fibrosis[16,32]. Similarly, Raziyeva et al. (2021) emphasized the role of E-MSCs in enhancing fibroblast and keratinocyte activity, critical for effective wound repair[33].

Beyond confirming these benefits, the present study provides new evidence that purified MSC-derived exosomes upregulate KGF and PDGF expression in a dose-dependent manner in a rat model of second-degree burns. The highest expression observed in the 200 µL group (G4) underscores a clear dose–response relationship, suggesting that exosome therapy can be optimized to enhance epithelialization and angiogenesis. These results help isolate the effect of exosomes from the broader MSC-conditioned medium and support the development of standardized, cell-free treatment protocols.

From a translational perspective, these findings support the exploration of MSC-exosome therapy as a standardized, cell-free option for burn care. Future studies should focus on dose scaling based on body weight or surface area to guide human-equivalent dosing, optimization of delivery route (local injection versus topical hydrogel), and comprehensive safety assessment to exclude adverse immune responses[34,35]. Such studies will be critical before moving to controlled clinical trials.

Several limitations should be acknowledged. First, only mRNA expression levels of KGF and PDGF were assessed using RT-PCR. Protein-level confirmation by Western blot or ELISA would have strengthened the findings and should be included in future research. Second, the study did not evaluate long-term outcomes such as wound closure kinetics, scar formation, or functional recovery, which are essential to assess clinical relevance. Third, we did not compare exosome therapy with conventional treatments such as split-thickness skin grafting or topical growth

factor application, which would provide valuable clinical context. Future studies should include such comparative arms to establish relative efficacy.

CONCLUSION

This study demonstrates that MSC-derived exosomes significantly enhance the expression of KGF and PDGF genes in a dose-dependent manner, highlighting their dual role in stimulating epithelialization and angiogenesis in a rat model of second-degree burn injury. By isolating the effect of purified exosomes, this work clarifies their specific contribution to wound-healing processes and strengthens the rationale for using exosome-based, cell-free therapy as an alternative or adjunct to conventional grafting techniques. The findings suggest that optimizing exosome dose and timing could improve wound closure and tissue regeneration while minimizing the risks associated with cell transplantation. Future research should focus on translating these results to clinical settings by validating efficacy in human subjects, investigating the involved molecular pathways, and evaluating long-term outcomes such as scar quality and functional recovery. These efforts will be critical for developing standardized, clinically applicable protocols for exosome-based regenerative therapy.

AUTHORS' CONTRIBUTIONS

Dewi Atika Putri: Conceptualization, Methodology, Software, Data curation, Writing- Original draft preparation, Visualization **Agung Putra**: Supervision, Validation, Writing- Reviewing and Editing **Titiek Sumarawati**: Supervision, Validation, Writing- Reviewing and Editing **Eko Setiawan**: Supervision, Validation, Writing- Reviewing and Editing.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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