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Hypoxia-Induced Mesenchymal Stem Cell Exosomes Modulate Protein Kinase A and VEGFR Expression in Ultraviolet B-Induced Hyperpigmentation in Mice

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Background: Hyperpigmentation is often exacerbated by ultraviolet-B (UVB) exposure through oxidative stress and activation of pathways like mitogen-activated protein kinase (MAPK) and vascular endothelial growth factor receptor (VEGFR). Current treatments carry risks and necessitate safer alternatives. This study investigated the therapeutic potential of hypoxia-induced mesenchymal stem cell (MSC) exosomes in reducing protein kinase-A (PKA) and VEGFR expression in UVB-induced hyperpigmentation.

Materials and methods: A post-test-only control group design was used with 30 male C57BL/6 mice divided into five groups: Healthy group, 0,9% NaCl-treated group, retinol-treated group, and two treatment groups (200 µL Exosomes-treated group and 300 µL Exosomes-treated group. UVB-induced hyperpigmentation was established with 180 mJ/cm² exposures over two weeks. Treatment was administered via subcutaneous injections for seven days. PKA and VEGFR mRNA levels were analyzed using qRT-PCR.

Results: PKA expression was significantly lower in the 200 µL Exosomes-treated group (0.34±0.05) and 300 µL Exosomes-treated group (0.21±0.04) groups compared with the 0,9% NaCl-treated group (1.12±0.08) (p<0.001). VEGFR expression similarly decreased in 200 µL Exosomes-treated group (0.32±0.05) and 300 µL Exosomes-treated group (0.18±0.04) versus the 0,9% NaCl-treated group (1.48±0.09) (p<0.001). Both exosome doses achieved reductions comparable to baseline levels observed in the Healthy group.

Conclusion: Hypoxia-induced MSC exosomes reduced PKA and VEGFR expression in UVB-induced hyperpigmentation, with the 300 µL dose showing greater efficacy. These findings suggested exosome therapy as a promising alternative for hyperpigmentation treatment.

Keywords: *hyperpigmentation, MSC, PKA, VEGFR, melanin*

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Introduction

Hyperpigmentation is a dermatological condition marked by an overproduction of melanin, resulting in darker patches on the skin compared to surrounding areas. While current treatment options, such as hydroquinone, retinol, oral therapies, chemical peeling, and laser therapy, can be effective, they may also present various side effects. For example, chemical peels can lead to inflammation and scarring, oral medications may irritate, burning sensations, and erythema, and laser treatments can sometimes result in post-inflammatory hyperpigmentation. Hydroquinone, although effective, has faced restrictions from the Food and Drug Administration (FDA) due to potential carcinogenic risks, raising significant health concerns.[1]

The development of hyperpigmentation is influenced by several factors, including sun exposure, genetics, and certain medications, with ultraviolet B (UVB) radiation being a major contributor.[2] UVB exposure results in oxidative stress through the production of reactive oxygen species (ROS), which activate various signaling pathways in skin cells.[3] Key pathways implicated in hyperpigmentation include mitogen-activated protein kinases (MAPK), nuclear factor kappa B (NF-kB), and P53.[4]

A significant mechanism pertinent to this study involves the activation of the MAPK/ extracellular signal-regulated kinases (ERK) pathway by UVB-induced ROS, which subsequently enhances protein kinase A (PKA) expression. This process regulates melanocyte proliferation, tyrosinase activity, and melanin production.[5] Additionally, UVB can activate vascular endothelial growth factor receptor (VEGFR) through the PKA pathway, leading to the phosphorylation of transcriptional regulators that promote VEGFR gene expression and protein synthesis.[6] Enhanced VEGFR activation plays a crucial role in melanogenesis, the process by which melanocytes produce melanin.[7,8] Therefore, exploring the effects of hypoxia-induced mesenchymal stem cell (MSC) exosomes on PKA and VEGFR activity is essential.

Previous study has shown that exosomal activity can modulate MAPK and VEGFR pathways.[9] Exosomes are extracellular nanovesicles (50-150 nm in size) that influence the microenvironment, gene expression, and cellular differentiation, contributing positively to skin health.[10] They have been effectively utilized in cosmetic applications to reduce wrinkles, enhance skin texture, improve hydration and elasticity, while also alleviating inflammation and UV-induced damage.[11]

Thus, this study was conducted to evaluate the efficacy of hypoxia-induced MSC-derived exosomes in mitigating hyperpigmentation through the modulation of PKA and VEGFR pathways. By using a controlled experimental design with UVB-induced hyperpigmentation in a murine model, we investigate the impact of varying exosome doses on key biomarkers associated with melanogenesis. This approach highlights the potential of exosome therapy as a safer and more targeted alternative to conventional hyperpigmentation treatments.

Materials and methods

Study Subjects

The This experimental study utilized a randomized post-test-only control group design to evaluate the effects of hypoxia MSC-derived exosomes on PKA and VEGFR expression in UVB-induced hyperpigmentation in mice. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, Universitas Islam Sultan Agung (No. 478/XI/2024/Komisi Bioetik).

Animal Model and Treatment Protocol

Thirty male C57BL/6 mice (aged 3 months, weighing 22 grams) were used as the experimental model. The mice were housed in polypropylene cages under controlled conditions (temperature: 24°C, humidity: 60%, and a 12-hour light-dark cycles) and were provided standard laboratory chow and water ad libitum.

The mice were randomly divided into five groups, with six mice in each group. The Healthy group received no treatment, while the negative control group (0.9% NaCl-treated group) was exposed to UVB radiation and given subcutaneous injections of 300ml of 0.9% NaCl. The positive control group (Retinol-treated group) also underwent UVB exposure but received topical retinol (0.1% in 200 µL olive oil). Treatment group 1 (200 µL Exosomes-treated group) was exposed to UVB radiation and treated with subcutaneous injections of 200 µL exosomes, while treatment group 2 (300 µL Exosomes-treated group) was exposed to UVB radiation alongside subcutaneous injections of 300 µL exosomes injection.

UVB-induced hyperpigmentation was induced using a broadband UVB lamp (peak emission: 302 nm) at a dose of 180 mJ/cm². Mice were exposed three times per week for two weeks. Starting on day 7, treatment groups received

daily subcutaneous injections of exosomes (200 µL or 300 µL) for seven days. Positive control mice were treated daily with 0.1% retinol in olive oil, while the negative control group received daily injections of NaCl.

MSCs Isolation, Hypoxic Conditioning, and Exosome Isolation

Umbilical cords from neonatal mice were collected in sterile conditions using 0.9% NaCl as a transport medium. In a biosafety cabinet, the umbilical cords were washed with phosphate-buffered saline (PBS) (Merck KGaA, Darmstadt, Germany; Cat. No. D8537) to remove blood and contaminants. Blood vessels were removed, and the tissues were minced into small pieces using sterile scissors. The fragments were evenly distributed in 25T flasks and incubated for 3 minutes to allow adherence. Dulbecco's modified eagle's medium (DMEM) (Gibco™, Waltham, MA, US; Cat. No. 11965092) containing 10% fetal bovine serum (FBS) (Gibco™; Cat. No. 26140079), 1% penicillin-streptomycin (Sigma-Aldrich, MA, US; Cat. No. P4333), and fungizone (Gibco™; Cat. No. 15290018) was added gently. Cultures were maintained at 37°C in 5% CO_2 with medium replacement performed every 3 days until cells reached 80% confluence.

For hypoxic conditioning, MSCs were conditioned under hypoxic conditions by placing culture flasks in a hypoxic chamber maintained at 5% oxygen, using nitrogen gas. Hypoxia was maintained for 24 hours at 37°C. The conditioned media, containing exosomes secreted by MSCs, was harvested for exosome production. The culture media used for conditioning consisted of DMEM supplemented with 10% FBS, 1% pen-strep, and fungizone.

Exosomes were isolated using the tangential flow filtration (TFF) method. The conditioned media from hypoxic MSCs were collected in a sterile bottle and filtered using an uPulse TFF system (Repligen, Waltham, MA, US; Cat. No. M100-PS10-01) equipped with membranes of 100 kDa and 500 kDa cutoffs to remove large particles. The exosome-enriched fraction was then validated using flow cytometry to confirm the presence of exosome surface markers CD81, CD63, and CD9 (BioLegend, San Diego, CA, US; Cat. Nos. 349502, 353018, and 312102, respectively). Validated exosome-enriched fractions were stored in 2.5 mL tubes at a temperature of 4 °C until further use.

MSCs Characterization by Flow Cytometry

MSCs were detached using Accutase (Innovative Cell Technologies, San Diego, CA, US; Cat. No. AT104), washed with PBS, and resuspended at 1×10^7cells/mL. Cells were stained with fluorophore-conjugated antibodies for CD90 (Anti-CD90 (FITC); BioLegend; Cat. No. 328108), CD29 (Anti-CD29 (PE); BioLegend; Cat. No. 303006), CD45 (Anti-CD45 (APC); BioLegend; Cat. No. 368510), and CD31 (Anti-CD31 (PE-Cy7); BioLegend; Cat. No. 303118) markers. Following 30 minutes of incubation in the dark at room temperature, samples were washed with PBS and analyzed using a flow cytometer (Becton Dickinson, Franklin Lakes, NJ, US; Cat. No. 338960).

Tissue Harvesting and Sample Preparation

On day 28, all mice were euthanized using a cocktail of ketamine (80 mg/kg), xylazine (10 mg/kg), and acepromazine (2 mg/kg). Skin samples were collected using sterile instruments. The collected skin tissues were stored in RNAlater and processed for total RNA isolation using Trizol reagent (Invitrogen™, Waltham, MA, US; Cat. No. 15596026). RNA purity and concentration were assessed using a spectrophotometer (NanoDrop™ 2000, Wilmington, DE, US; Cat. No. ND-2000). For histological analysis, skin samples were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 4 µm thickness. These sections were then stained with hematoxylin-eosin (H&E) using Harris hematoxylin and eosin Y solution (Sigma-Aldrich; Cat. No. HHS16) and Masson's Fontana stain (Masson Fontana Stain Kit, Warrington, PA, US; Cat. No. KTRMP) to evaluate hyperpigmentation.

Quantitative Real-Time PCR (qRT-PCR)

The qRT-PCR analysis utilized specific primers to measure the mRNA expression levels of PKA, VEGFR, and GAPDH, with GAPDH serving as the internal control. The primer sequences used in this study were as follows: for PKA, the forward primer was 5'-ATGACAGACCTTCCTGAGCA-3′ and the reverse primer was 5'-CTCCTTGGGACTTGGCTTTG-3'; for VEGFR, the forward primer was 5′-GTTCAGAGCGGAGAAAGCATT-TG-3′andthereverse primer was 5′-CACATCTGCAAG-TACGTTCGTTT-3′; and for GAPDH (housekeeping gene), the forward primer was 5'-GAAGGTGAAGGTCGAGTC-3' and the reverse primer was 5'-GAAGATGGTGATGGGATTTC-3'. The cDNA synthesis was performed using the SuperScript™ IV First-Strand Synthesis System (Thermo Fisher Scientific, Waltham, US; Cat. No. 18091050), while the PCR reactions were conducted using a T100™ Thermal Cycler (Bio-Rad, Hercules, CA, US; Cat. No. 1861096) under standard

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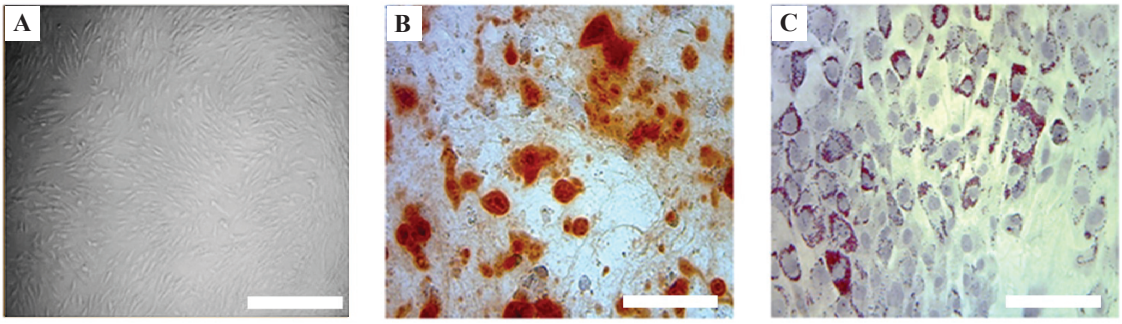

Figure 1. Differentiation and characteristics of MSCs. Adherent, fibroblast-like cells were observed after 14 days of culture. A: MSCs morphology with 90% confluency showed spindle-like cells (x200 magnification). B: MSCs differentiation test using adipogenic culture media (x200 magnification). C: The red staining represents the result of post-cultured calcium deposits with osteogenic culture media. White bar: 10µm.

cycling conditions. qRT-PCR was performed to measure the expression levels of PKA and VEGFR, using GAPDH as the internal control. The relative gene expression was normalized to GAPDH using the ΔΔCT method, where the threshold cycle (CT) values of target genes were first normalized to GAPDH (ΔCT) and then compared to the control group to determine fold changes (ΔΔCT). The analysis was conducted using the EcoStudy software.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 25.0; IBM Corp., Armonk, NY). Normality was assessed using the Shapiro-Wilk test, while homogeneity was evaluated using Levene's test. For normally distributed data, one-way ANOVA was used, followed by Bonferroni post-hoc analysis. Kruskal-Wallis tests were applied for non-parametric data. A *p*-value of <0.05 was considered statistically significant.

Results

Differentiation and Characteristics of MSCs

The cells exhibited strong adhesion to the bottom of the Petri dish and displayed a spindle-like morphology, characteristic of healthy, active MSCs. This study also evaluated the differentiation of MSCs into adult cell types. Exposure to osteocyte- or adipocyte-inducing media led to differentiation into osteocytes and adipocytes, which was confirmed by calcium and fat deposits stained red with Alizarin Red and Oil Red O (Figure 1).

Flow cytometric analysis confirmed MSC identity, 12 with cells showing positive expression for CD90 (99.8%) and CD29 (97.7%), and negative expression for CD45 (1.9%) and CD31 (3.7%) (Figure 2).

Hypoxia-Induced MSC Exosomes Increased Melanin Density

Mice exposed to UVB light exhibited higher melanin density compared with the non-exposed controls (Figure 3).

Hypoxia-Induced MSC Exosomes Reduced PKA Expression

On Day 28, the lowest PKA expression was observed in the 300 µL Exosomes-treated group (0.21±0.04), followed by the 200 µL Exosomes-treated group (0.34±0.05) and the retinol-treated group (0.49±0.06). The 0,9% NaCl-treated group (1.12±0.08) exhibited significantly higher levels, and the Healthy group (0.19±0.03) showed the lowest baseline expression. There were significant intergroup differences (p<0.001), with post hoc analysis confirming that 200 µL

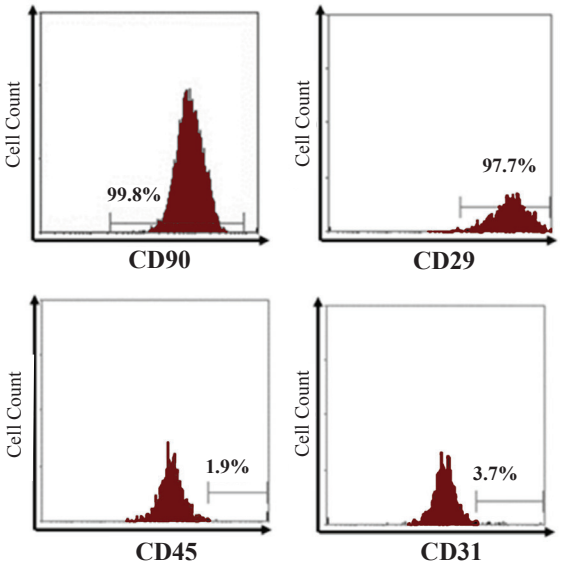

Figure 2. Flowcytometry analysis of CD90, CD29, CD45, and CD31 expression.

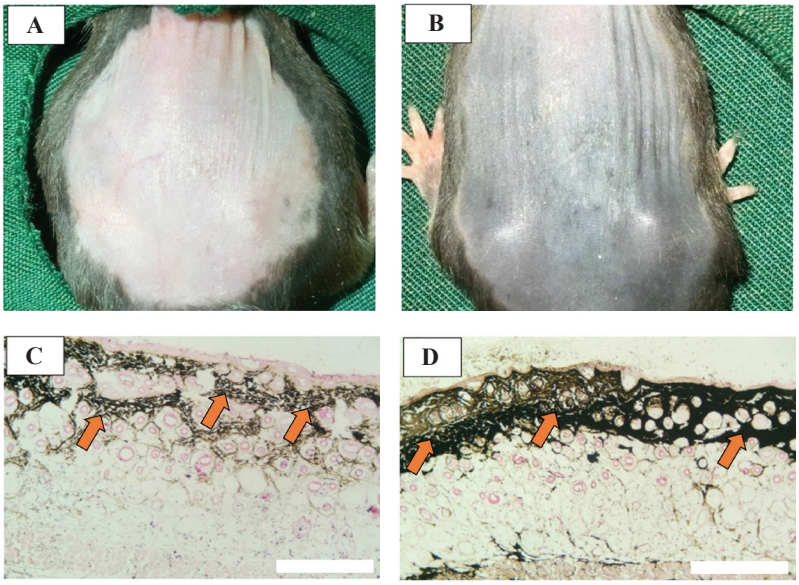

Figure 3. Hypoxia-induced MSC exosomes increased melanin density in UVB-induced hyperpigmentation. The degree of hyperpigmentation was evaluated after two weeks of UVB exposure followed by treatment administration. Masson's Fontana staining was utilized to validate hyperpigmentation. A: Mice in the control group exhibited a normal skin color. B: In contrast, UVB-irradiated mice displayed a distinctly darker skin tone. C: Healthy mice showed more prominent melanin, indicated by the black staining, compared to those exposed to UVB or those with hyperpigmentation. D: Mice with UVB-induced hyperpigmentation exhibited increased melanin density. White bar: 10µm.

Exosomes-treated group and 300 µL Exosomes-treated group had significantly lower (p<0.001) PKA expression compared to 0,9% NaCl-treated group (Figure 4).

Hypoxia-Induced MSC Exosomes Reduced VEGFR Expression

VEGFR expression was observed to be lower in 200 µL Exosomes-treated group (0.32±0.05) and 300 µL Exosomes-treated group (0.18±0.04), in comparison to the negative control group (1.48±0.09). The retinol-treated group (0.71± 0.07) exhibited intermediate levels, while the Healthy group (0.14±0.03) recorded the lowest baseline level. Statistical analysis supported these results (p<0.001) across the groups, as well as significant reductions in VEGFR expression in treatment group 1 and 2 when compared to 0,9% NaCl-treated group (p<0.001 for both) (Figure 5).

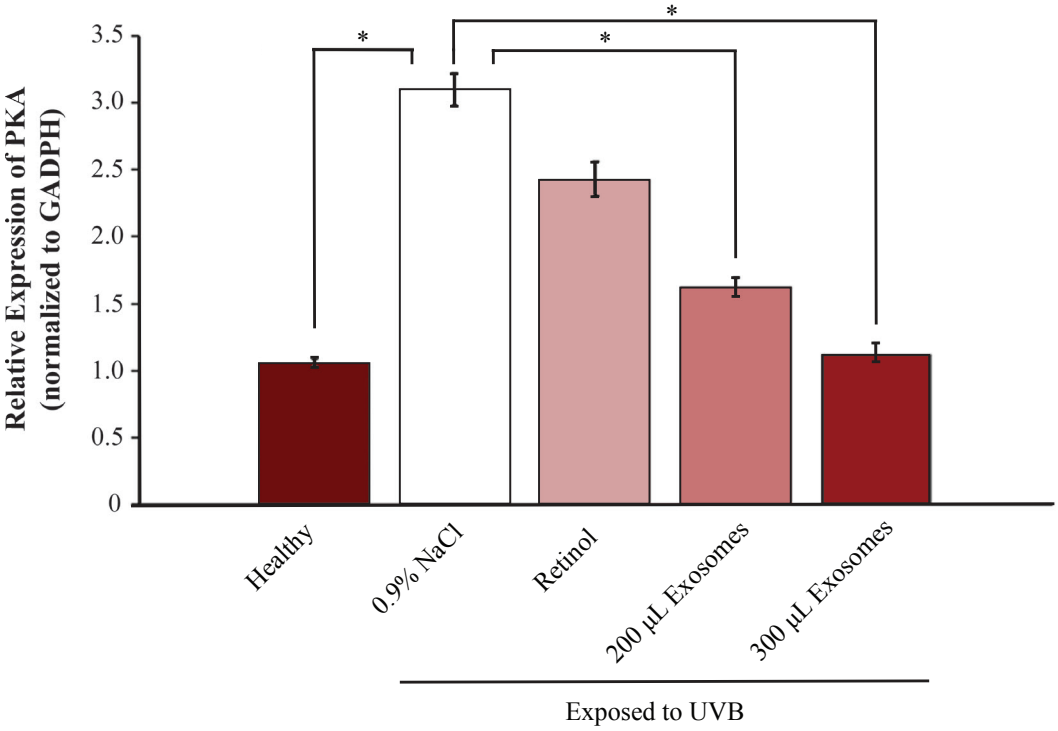

Figure 4. Hypoxia-induced MSC exosomes reduced PKA expression. PKA expression levels measured on day 7 in UVB-induced hyperpigmentation. Statistical significance was determined using one-way ANOVA followed by Bonferroni post-hoc analysis. Data are presented as mean±standard deviation, with asterisk (*) indicating statistical significance (p<0.05).

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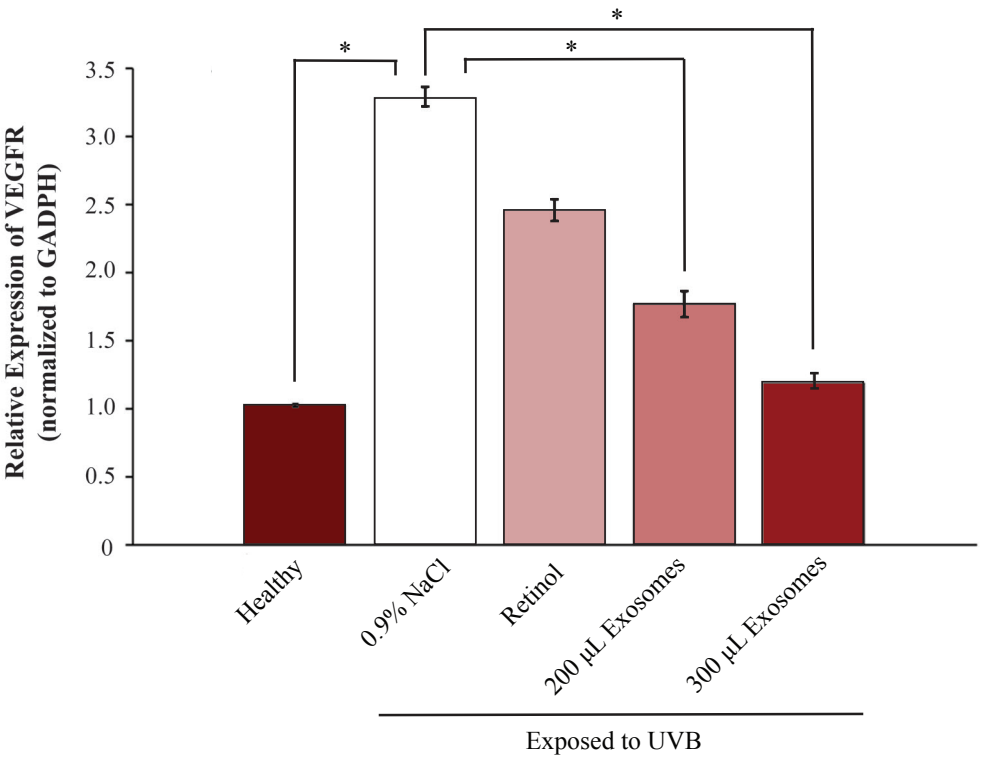

Figure 5. Hypoxia-Induced MSC Exosomes Reduced VEGFR Expression. VEGFR expression levels measured on day 7 in UVB-induced hyperpigmentation. Statistical significance was determined using one-way ANOVA followed by Bonferroni post-hoc analysis. Data are presented as mean±standard deviation, with asterisk (*) indicating statistical significance (p<0.05).

Discussion

Hyperpigmentation in this study was significantly reduced following the administration of exosome-MSC injections at both 200 µL and 300 µL doses, with the latter exhibiting slightly superior effects. This reduction corresponds with decreased PKA and VEGFR levels, supporting the role of exosome-MSCs in modulating key signaling pathways involved in melanogenesis. Previous studies have shown that MSC-derived exosomes possess anti-inflammatory and antioxidant properties that contribute to skin regeneration and pigmentation control.[13] The findings indicate that exosome-MSCs effectively mitigate hyperpigmentation by disrupting the MAPK-PKA interaction, which is crucial in melanogenesis. This disruption is achieved through the delivery of bioactive molecules, including miRNAs, that suppress A-kinase anchoring protein (AKAP) expression and downregulate melanogenesis-related genes such as tyrosinase. These results align with earlier studies demonstrating that exosomes regulate melanocyte activity by modulating molecular pathways like MAPK/ERK and inhibiting MITF expression.[14-16]

The study also confirmed that VEGF from keratinocytes and fibroblasts activates VEGFR on melanocytes, promoting melanogenesis via the MAPK pathway. The suppression of VEGFR activity by exosome-MSCs supports their role in inhibiting this process, leading to reduced melanin production. Similar research has shown that exosomal miRNAs, such as miR-146a and miR-330-5p, can suppress the MAPK and NF-κB pathways, thereby reducing oxidative stress and inflammatory responses that exacerbate pigmentation disorders.[16-18]

Compared to traditional treatments such as laser therapy, exosome-MSC therapy provides a non-invasive alternative with long-term benefits. The ability of exosomes to counteract oxidative stress and inflammatory signaling makes them a promising therapeutic option. Previous studies have emphasized the advantage of exosome-based treatments in promoting sustained skin regeneration by enhancing collagen and elastin synthesis.[17-20]

While the results demonstrate significant efficacy in reducing hyperpigmentation, the study's reliance on a mouse model presents limitations in translating findings to human skin, which exhibits greater complexity in immune response and metabolism. Additionally, although PKA mRNA expression was measured using qRT-PCR, direct confirmation of PKA protein levels and enzymatic activity was not conducted. This limitation suggests the need for future research utilizing Western blotting or enzyme activity assays to validate protein expression and function.[20,21]

Further investigations should focus on the application of exosome-MSC therapy in human subjects to assess

its clinical relevance. Exploring higher doses may help determine the maximum effective and tolerable dose, providing a clearer understanding of the therapy and safety profile. These findings contribute to the growing body of evidence supporting the use of exosome-based therapies in dermatological applications.

Conclusion

Exosome-MSC administration reduces PKA and VEGFR levels in hyperpigmented mice, indicating its potential as a therapeutic approach for pigmentation disorders. This suggests that exosome-MSCs play a crucial role in modulating key signaling pathways involved in melanogenesis. These findings support the need for further exploration of exosome-based treatments for hyperpigmentation and related skin conditions.

Authors' Contributions

SJA, MRAAS, and AP conceptualized and planned the research, performed data acquisition/collection, and calculated the experimental data and analysis. SJA also drafted the manuscript and designed the figures. ES assisted in interpreting the results. SJA, MRAAS, AP, and ES contributed to the critical revision of the manuscript.

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