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Effect of mesenchymal stem cells on reducing melanin levels in response to UV radiation in male C57BL/6 mice

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Academic editor

Hasan-Al-Faruque, PhD
University of Utah
USA

Article info

Received: 05 April 2025
Accepted: 25 October 2025
Published: 03 December 2025

Keywords

Mesenchymal stem cells, Melanin,
Mouse, ROS, UV radiation

ABSTRACT

Melanin is a pigment produced by melanocytes through polymerization and oxidation during melanogenesis. It is present in the skin, hair, and eyes as a natural bodily mechanism, although its levels can increase following damage. Ultraviolet (UV) radiation activates melanogenesis, leading to excess melanin production and elevated reactive oxygen species (ROS) levels, which can result in hyperpigmentation. Thus, this study aimed to explore the potential of mesenchymal stem cells (MSC) as an alternative method to prevent skin hypermelanosis caused by UV radiation in male C57BL/6 mice. The current study examined the effect of MSC therapy on melanin levels in mice exposed to UV radiation using histopathological analysis. Animals were divided into three groups such as normal, UV, and UV+MSC. The results showed that administering MSC reduced melanin levels in UV-exposed mice; however, this reduction was not statistically significant compared to the UV group at a dose of 0.1 cc. In addition, the decrease in melanin levels induced by MSC treatment in UV-exposed mice was confirmed through histopathological analysis. In conclusion, the study suggests the potential of MSC as an alternative strategy for preventing skin hypomelanosis in UV-exposed mice.

INTRODUCTION

Melanin pigments are high-molecular-weight biopolymers responsible for the pigmentation of the skin, hair, and eyes, playing a crucial protective role against ultraviolet (UV) radiation-induced damage [1]. Melanin pigments display dark colors ranging from brown to black. These pigments are synthesized from phenolic or indolic compounds and are often found in complex forms, usually bound to proteins or carbohydrates. In principle, their formation results from the autooxidation of phenolic compounds in the medium or through enzymatic processes involving tyrosinase (TRP-1 and TRP-2) and polyketide synthase as key enzymes in melanogenesis [1-3]. Hypomelanosis refers to a pathological reduction in melanin production or distribution in the skin, often resulting in lighter or patchy pigmentation. Under physiological conditions, melanin production maintains a balance between protection and pigmentation; however, excessive UV exposure can disrupt this balance, leading to hyperpigmentation or, conversely, hypomelanosis—characterized by reduced melanin production and uneven pigmentation [4,5]. Environmental, genetic, and hormonal factors may further exacerbate these conditions, particularly in regions with intense UV radiation exposure. Exposure to UV radiation from the sun is the primary factor in increased melanin production, particularly in countries near the equator [6-8].

Recent research has highlighted the promising role of MSC in modulating pigmentation processes through their paracrine activity and immunomodulatory properties. MSC



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secrete a variety of bioactive molecules that influence melanocyte function by regulating melanin biosynthesis at the molecular level. Studies suggest that MSC-derived factors can suppress melanogenesis by downregulating MITF (microphthalmia-associated transcription factor) and interfering with TYR, TRP-1, and TRP-2 expression through the activation of the ERK signaling pathway [9-11]. Furthermore, MSC possess low immunogenicity and exhibit anti-inflammatory effects by reducing pro-inflammatory cytokine levels, thereby creating a favorable microenvironment for tissue recovery and homeostasis. Several studies have shown that factors secreted from MSC can inhibit melanin synthesis in the skin. These factors can interact with TYR, TRP-1, and TRP-2, negatively regulating melanin synthesis and suppressing it by degrading MITF through the activation of the ERK pathway [6, 7]. Other studies have also indicated that MSC suppress immune reactions and reduce levels of inflammatory cytokines [12-15]. MSC are characterized by their multipotent differentiation potential, limited immunogenicity, and poor recognition by HLA-incompatible hosts. Based on these properties, MSC may serve as effective tools for tissue repair. Significantly, MSC have been shown to secrete several trophic factors, including paracrine molecules, which enhance the effects of nutrients on surrounding cells, improving proliferation and function during *in vitro* culture [8,9,16-18].

Given their multipotency, low antigenicity, and regenerative capacity, MSC have emerged as potential therapeutic agents for managing pigmentation disorders and repairing UV-induced skin damage. This study investigated the effect of MSC on melanin levels in response to UV radiation in male C57BL/6 mice. The study elucidated the mechanistic pathways through which MSC influence melanogenesis and evaluated their potential as a biological intervention for maintaining skin pigmentation balance following UV-induced stress. Therefore, this study aimed to demonstrate the potential of MSC as an alternative for preventing skin hypomelanosis caused by UV radiation exposure in male C57BL/6 mice.

MATERIALS AND METHODS

Ethical approval

This study has received Ethical Clearance from the Bioethics Commission for Medical / Health Research of the Faculty of Medicine, Sultan Agung Islamic University, Semarang, under number 473 / XI / 2024. The Bioethics Commission conducted research at the Stem Cell and Cancer Laboratory and Research, Semarang.

Experimental animals

Thirty male C57BL/6 mice (2–3 months old, 20–25 g) were obtained from PT Indoanilab, Bogor, Indonesia. Mice were acclimatized for one week under controlled conditions (22 ± 2 °C, 12-h light/dark cycle) with *ad libitum* access to food and water. Animals were randomly divided into three groups (n = 10/group) such as Normal group: No UV exposure, UV group: Exposed to UV radiation only, and UV + MSC group: Exposed to UVB radiation and treated with MSC.

Sample inclusion criteria included male C57BL/6 mice weighing 20-25 grams, in good health, aged 2-3 months, with exclusion criteria for sick or deceased mice during the study.

UVB exposure

UVB irradiation was performed using a broadband UVB lamp (Model CL-1000L, Analytik Jena, California, USA) with a peak emission at 302 nm. The dose delivered was 160 mJ/cm² daily for 14 consecutive days, targeting the shaved dorsal skin of each mouse to induce hypermelanosis [2-5].

The univariate analysis of baseline melanin levels in the experimental groups showed that the Normal group (N) had an average melanin level of 90.10, while the UV group exhibited a significant increase (336.10), indicating UV-induced hypermelanosis.

Preparation of mesenchymal stem cells

Human umbilical cord-derived MSC were obtained from the Stem Cell and Cancer Research Laboratory, Semarang, Indonesia. Cells were isolated via enzymatic digestion and characterized according to the International Society for Cellular Therapy (ISCT) criteria—positive for CD73, CD90, and CD105; negative for CD34 and CD45. MSC were administered intravenously through the tail vein at a dose of 0.1 cc suspended in phosphate-buffered saline (PBS; Gibco™, Thermo Fisher Scientific, Waltham, MA, USA) as described previously [7, 21,22].

The UV Device Specifications: UVB irradiation was performed using a handheld broadband UVB lamp (Model UVP CL-1000L, Analytik Jena, USA) with a peak emission at 302 nm, delivering 160 mJ/cm² for 14 consecutive days. MSC were administered intravenously via tail vein injection at a dose of 0.1 cc. Hematoxylin & Eosin (H&E) staining reagents were purchased from Sigma-Aldrich (St. Louis, USA).

Histological analysis

Skin samples were fixed in 10% neutral buffered formalin (Sigma-Aldrich, St. Louis, MO, USA) for 24 hours, dehydrated in graded ethanol (70%, 80%, 90%, and 100%; Merck KGaA, Darmstadt, Germany), cleared with xylene (Merck), and embedded in paraffin wax (Sigma-Aldrich). Sections of 4 µm thickness were cut using a rotary microtome and mounted on glass slides [13,22].

For Hematoxylin and Eosin (H&E) staining, slides were deparaffinized in xylene, rehydrated through descending grades of ethanol, and rinsed in distilled water. Hematoxylin solution (Sigma-Aldrich, USA) was applied for 8 minutes to stain cell nuclei blue, followed by washing under running tap water. Slides were then counterstained with Eosin Y solution (Sigma-Aldrich, USA) for 2 minutes, giving pink coloration to the cytoplasm, connective tissue, and melanin-containing areas. After dehydration and clearing, slides were mounted with DPX mounting medium and examined under a light microscope (Olympus BX43, Japan) at 40× magnification.

Measurement of melanin levels

Histological images were captured using a digital microscope camera (Olympus DP74, Japan) from five randomly selected high-power fields (HPFs) per sample. Quantitative melanin analysis was performed using histological sections. Images were captured from five random high-power fields (HPFs) per slide using a digital microscope camera (Olympus DP74, Japan). Melanin pigmentation was assessed based on intensity and distribution within the epidermis using ImageJ software (NIH, Bethesda, MD, USA). The mean optical density (OD) values of melanin-positive regions were calculated and

expressed as average melanin levels for each group. This approach provided both qualitative (visual grading) and quantitative (OD measurement) assessments of pigmentation. Melanin distribution and density were measured as mean optical density (OD) values in the epidermal region. Average melanin levels were expressed as mean $\pm$ SD per group.

Statistical Analysis

This study conducted a bivariate analysis to determine the effect of MSC in reducing hypermelanosis in Male C57BL/6 Mice induced by UVB light using SPSS version 22 software (IBM, USA). Before performing the bivariate analysis, a parametric test must first assess normality using the Kolmogorov-Smirnov/Sapiro-Wilk Test with a $p > 0.05$ value, indicating a normal data distribution. Additionally, it is necessary to test homogeneity in parametric tests using the Levene Test, which should also yield a $p > 0.05$ value, signifying homogeneous data variance. If both the data distribution is normal and the data variance is homogeneous, a parametric test, specifically the One-Way ANOVA Test, is conducted to evaluate the effectiveness of stem cell secretome against melanin in hypermelanosis mice by determining the significance of differences among all groups. Suppose the One-Way ANOVA Test results are significant. In that case, a further analysis (Post Hoc Test) is performed using Tukey's Honest Significant Difference (HSD) Test to identify which treatment effectively reduces hypermelanosis. Conversely, if the data distribution is not normal and the variance is not homogeneous, a non-parametric test, the Kruskal-Wallis Test, will be performed, followed by the Post Hoc Test using the Mann-Whitney Test. All statistical tests in this study utilized the Statistical Product and Service Solutions (SPSS) version 22 application, and the significance value is defined as a p -value < 0.05 for the analyzed variables.

RESULTS

Effect of MSC on the melanin level in UV-exposed mice

The intervention group (UV+MSC) had a lower mean melanin level (319.00) compared to the UV group (Table 1). Based on the results of the melanin normality test, the significance values (p -values) were obtained for the Normal group (0.094), the UV group (0.386), and the UV + MSC group (0.947). The data distribution in all groups is considered normal because it has a p -value > 0.05 . Further, the results of the variance homogeneity were obtained using the Levene statistical test, which yielded a p -value of 0.195 for the total melanin variable. Since the p -value is > 0.05 , it can be concluded that the data variance is homogeneous. The results of the normality and homogeneity tests indicate a normal and homogeneous distribution. Therefore, to determine the difference in melanin levels across all groups, a one-way ANOVA was performed. It revealed a significant difference in mean melanin levels among the groups ($p = 0.001$). Post hoc Tukey's HSD test demonstrated that UV exposure significantly increased melanin levels compared to the Normal group ($p < 0.05$). However, a reduction of melanin level in the UV+MSC group was found compared to the UV group, with no significance ($p > 0.05$), as shown in Figure 1.

Table 1. Melanin level in mice.

Group	Mean $\pm$ SD	Median	(Min – Max)	p-value
Normal	90.1 $\pm$ 79.7	99.0	0.00 – 197	0.094
UV	336.1 $\pm$ 165.1	388.5	0.00 – 552	0.386
UV+MSC	319.0 $\pm$ 168.8	345.0	0.00 – 584	0.947

n=30. Based on the results of the melanin normality test, the significance values (p-values) were obtained for each. Normal group: No UV exposure, UV group: Exposed to UV radiation only, and UV + MSC group: Exposed to UVB radiation and treated with MSC.

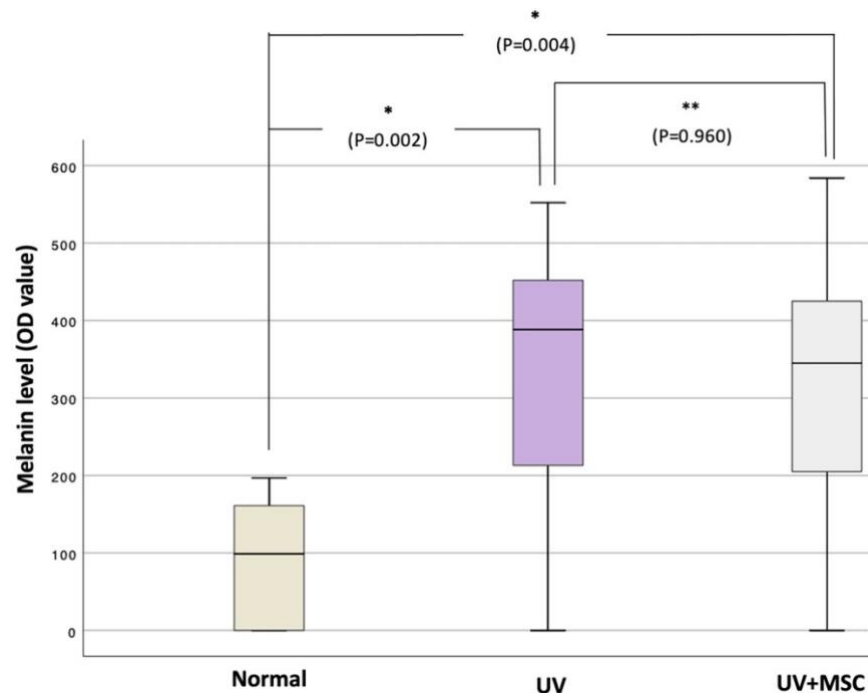


Figure 1. Post Hoc with Tukey's HSD test demonstrated that UV exposure significantly increased melanin levels compared to the comparison of melanin levels in the skin among groups in mice (n=30), the Normal group ($p < 0.05$). However, the reduction in the UV+MSC group compared to the UV group was not statistically significant ($p > 0.05$). Normal group: No UV exposure, UV group: Exposed to UV radiation only, and UV + MSC group: Exposed to UVB radiation and treated with MSC.

Effect of MSC on the histological features in UV-exposed mice

Macroscopic and microscopic observations were conducted using H&E staining to identify any differences in the color of skin samples in mice. Hematoxylin stains the cell nuclei blue, while Eosin colors the extracellular matrix, cytoplasm, and melanin tissue in various shades of pink. This technique enabled visualization of the structure, cell distribution, and morphological changes in the tissue samples across all three groups. The normal group showed normal epidermal architecture with minimal melanin deposition. In the UV group, thickened epidermis and increased melanin pigmentation within basal keratinocytes were detected. In the UV+MSC group, reduced melanin deposition was found as compared to the UV group, indicating partial reversal of UV-induced hypermelanosis (Figure 2).

The comparison of melanin levels between groups showed significant results with a p-value of <0.05 . This indicates that UV radiation for 14 days can significantly cause hypermelanosis. However, there was a decrease in the average amount of melanin in the UV + MSC group compared to the UV group, with a p-value of >0.05 . Normality ($p > 0.05$ for all groups) and homogeneity (Levene's $p = 0.195$) assumptions were met. Post-

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hoc Tukey's test confirmed significant differences between Normal and UV groups ($p < 0.05$), but not between UV and UV + MSC groups ($p > 0.05$), indicating that while MSC lowered melanin levels, the change was not statistically significant within the given dose and exposure period.

The statistical test comparing the groups showed significant differences, indicating that the decrease in average melanin caused by MSC was proven histopathologically.

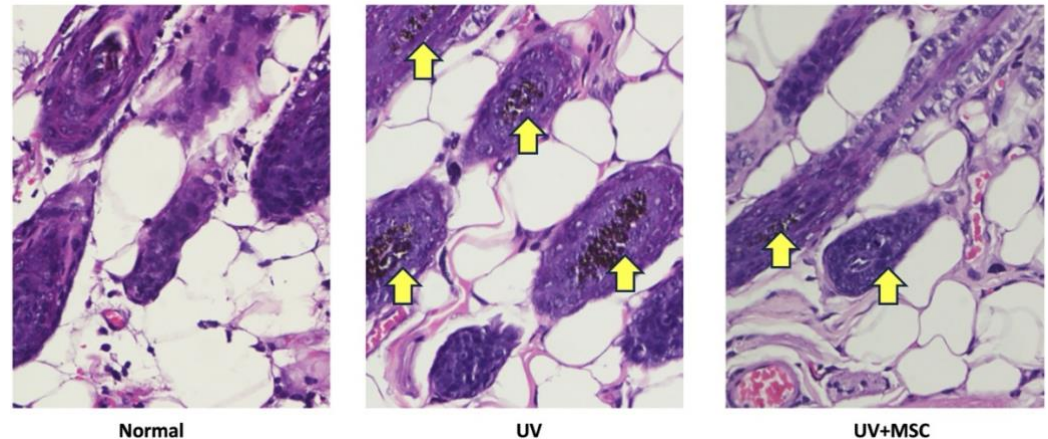


Figure 2. A photomicrograph of a section of mice skin from each group was conducted using Hematoxylin and Eosin (HE) staining to identify any differences in the color of the mice skin samples. Hematoxylin stains the cell nuclei blue, while Eosin colors the extracellular matrix, cytoplasm, and melanin tissue in various shades of pink. This technique enables visualization of the structure, cell distribution, and morphological changes in the tissue samples across all three groups. Normal group: Normal epidermal architecture with minimal melanin deposition. UV group: Thickened epidermis and increased melanin pigmentation within basal keratinocytes. UV + MSC group: Reduced melanin deposition compared to the UV group, indicating partial reversal of UV-induced hypermelanosis. It showed decreased melanin levels (hypermelanosis), with H&E-stained skin sections (40x) displaying melanin distribution (yellow arrow) showed that 0.1 cc MSC effectively suppresses melanin levels in the skin tissue of hyperpigmented male C57BL/6 mice exposed to UV radiation more than the UV+MSC group. Normal group: No UV exposure, UV group: Exposed to UV radiation only, and UV + MSC group: Exposed to UVB radiation and treated with MSC.

DISCUSSION

Exposure to UV radiation is one of the primary risk factors for photoaging of the skin, leading to hyperpigmentation and characterized by inflammatory conditions, melanin accumulation, and reduced collagen synthesis [17,18,22]. The direct effect of UV photon radiation on DNA results in the upregulation of the tyrosinase gene, a rate-limiting enzyme in melanin synthesis, as well as increased expression of cell surface receptors for various keratinocyte-derived melanogenic factors [16]. Hypermelanosis is defined by an increase in the amount of melanin present in melanocytes located in skin and hair follicles due to melanin's role in the pigmentation process. Previous research has shown that continuous exposure to UVB light stimulates melanogenesis, leading to excessive melanin production and ultimately resulting in hyperpigmentation, also known as hypermelanosis [13-15]. In this context, melanocytes function as sites for the production and distribution of melanin. This supports the view that UV light induction is a significant risk factor for hypermelanosis, as it causes DNA damage, characterized by increased expression of proteins involved in melanin formation, such as MITF. The administration of 0.1 cc MSC in hypermelanosis mice is expected to prevent melanogenesis and thereby reduce the occurrence of hypermelanosis. In this study, univariate and bivariate analyses were employed to evaluate the effect of secretome administration in reducing melanin induced by UVB light on the skin of mice.

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Based on the results of univariate analysis, it is evident that UV exposure in the UV group led to a significant increase in melanin production, as evidenced by the average amount of melanin rising to 336.10. These results align with the known effects of UV radiation, which can stimulate melanin production in the skin and hair as a response to damage [16-18]. In contrast, the UV+MSC group that received an intervention in the form of MSC injection showed a decrease in the amount of melanin to 319.00; however, this decrease was not statistically significant. These results suggest that secretome administration can reduce excess melanin in C57BL/6 mice induced by UV radiation. One factor that must be considered is the process of melanin regulation. Various factors, including genetic influences, environmental factors such as UV exposure, and cellular responses to oxidative damage, strongly influence melanin production [16-18]. Although MSC have potential as a therapy to regulate inflammation and oxidative stress, a more holistic therapeutic approach or a combination with other factors that directly target radiation-induced melanin production is necessary. Due to UV exposure, melanocytes in hair follicles adapt by increasing melanin production as a protective measure against DNA damage [19, 20].

Exposure to UV radiation remains a key driver of photoaging, inflammation, and hypermelanosis, consistent with prior research linking UVB exposure to oxidative DNA damage and upregulation of melanogenic pathways. In this study, MSC administration resulted in a reduction in melanin levels compared to the positive control group, but the reduction was not statistically significant.

A study reported that MSC-secreted factors inhibited melanogenesis by suppressing tyrosinase-related proteins via ERK pathway activation [21]. Similarly, human umbilical cord-derived MSC exerted protective antioxidant effects in UV-related tissue damage [21,22]. These are aligned with our observation that MSC can downregulate melanin production. In contrast, other studies have reported more significant reductions in melanin synthesis, possibly due to higher cell doses, longer follow-up periods, or the use of topical MSC-derived exosomes, which provide localized effects [17,18].

Therefore, while the current study indicates only modest effects, they remain consistent with the general body of evidence suggesting that MSC play a regulatory role in pigmentation. The key differences likely stem from variations in dose, route, and experimental models.

The limitation of this study is the dose limitation, where a single dose of 0.1 cc may have been insufficient to exert a strong systemic effect. Previous studies have shown that higher doses of MSC, or repeated administration, may be required to achieve more robust results. Additionally, the timing of administration is crucial, as MSC were administered during ongoing UV exposure. Therefore, future research is needed.

CONCLUSIONS

The administration of 0.1 cc MSC effectively suppresses melanin levels in the skin tissue of hyperpigmented male C57BL/6 mice exposed to UV radiation, resulting in lower melanin levels compared to both the mouse model that did not receive MSC and the normal group. Future studies should explore the effects of multiple doses of MSC to determine whether higher or repeated administrations provide a more significant reduction in melanin levels. Since melanin regulation is closely linked to oxidative stress pathways, further investigations should include the measurement of oxidative stress markers such as ROS levels, malondialdehyde, superoxide dismutase, and

glutathione peroxidase. These markers would provide deeper insights into the mechanism by which MSC influence melanogenesis under UV exposure. Additionally, evaluating different routes of administration (e.g., topical versus intravenous) and comparing various MSC sources (e.g., adipose-derived, bone marrow-derived, umbilical cord-derived) may help optimize therapeutic outcomes. More extended observation periods are also recommended to assess the durability of MSC effects on melanin regulation.

ACKNOWLEDGEMENTS

The authors thank Stem Cell Cancer Research and the Faculty of Medicine at Soegijapranata Catholic University in Semarang for their assistance during the experimental and research processes.

AUTHOR CONTRIBUTIONS

AKM: conceptualization, data analysis, writing. VC: data collection, data analysis. SI: conceptualization, writing. IAS: conceptualization, data analysis. All authors have read and approved the final manuscript.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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