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Hypoxia-preconditioned MSC-derived exosomes suppress IL-1β and caspase-1 expression in a UVB-induced skin damage model

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Abstract: Ultraviolet B (UVB) irradiation induces skin damage characterized by collagen degradation and enhanced inflammatory responses. Hypoxia-preconditioned exosomes derived from mesenchymal stem cells (MSCs) have emerged as a potential therapeutic strategy due to their anti-inflammatory and regenerative properties. This study aimed to evaluate the effects of hypoxia-preconditioned MSC-derived exosomes on IL-1β and caspase-1 gene expression in a UVB-induced skin damage model. An in vivo experimental study was conducted using 30 male Wistar rats divided into three groups: control, UVB-exposed, and UVB-exposed treated with hypoxia-preconditioned MSC-derived exosomes. UVB irradiation was administered for four weeks to induce collagen degradation, followed by weekly exosome injections in the treatment group. Gene expression levels of IL-1β and caspase-1 in skin tissue were quantified using qRT-PCR. UVB exposure significantly increased IL-1β and caspase-1 expression compared with the control group. Treatment with hypoxia-preconditioned MSC-derived exosomes significantly reduced the expression of both inflammatory markers compared with the untreated UVB group. These findings demonstrate that hypoxia-preconditioned MSC-derived exosomes attenuate inflammasome-associated inflammatory responses and may represent a promising therapeutic approach for mitigating UVB-induced skin damage.

Keywords: mesenchymal stem cell-derived exosomes; hypoxic preconditioning; IL-1β; caspase-1; UVB irradiation; NLRP3 inflammasome; skin inflammation.

INTRODUCTION

Recent research reports that MSCs Exosome Hypoxia contains various types of proteins and miRNAs that have an important role in the anti-inflammatory and anti-apoptosis processes. Some of the proteins contained in it include interleukin-10 (IL-10), *Transforming Growth Factor Beta* (TGF-β), and *Hepatocyte Growth Factor* (HGF), which have anti-inflammatory and pro-regenerative properties. Meanwhile, miRNAs such as miR-146a and miR-21 are known to have anti-inflammatory and anti-apoptosis effects by suppressing the expression of pro-inflammatory and pro-apoptotic genes.[1] Previous research reported that 100 µL of MSCs Exosome Hypoxia was able to increase collagen in mice exposed to UVB. This combination of protein and miRNA works synergistically in protecting cells from damage and promoting tissue recovery. However, research on the role of MSCs Exosome Hypoxia in suppressing the expression of IL-1β and Caspase 1 is still limited and needs to be done.[2,3,4]

Ultraviolet B (UVB) is known to trigger free radicals leading to inflammatory processes that can lead to degradation and decreased production of collagen, which is the main protein that supports the skin. Previous research has shown that

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pro-inflammatory proteins such as interleukin-1 beta (IL-1β) and caspase 1 play a role in reducing collagen.[5] But on the other hand, MSCs Exosome Hypoxia is known to contain proteins such as IL-10 and miRNA which are anti-inflammatory and proliferative. These exosomes contain signaling molecules and proteins that can modulate the inflammatory response as well as increase collagen production. The potential of therapy with exosomes of MSCs as anti-aging agents may have an effect on the decrease of IL-1β and caspase 1 in UVB-exposed skin, but this needs to be proven. Therefore, further studies are warranted to elucidate it is necessary to study the effect of administration of MSCs Exosome Hypoxia on IL-1β and caspase 1 to be conducted.[6,7,8]

Activation of caspase-1 leads to the release of *Nuclear Factor Kappa B* (NF-κB), which increases the production of pro-inflammatory cytokines such as *Tumor Necrosis Factor Alpha* (TNF-α). Increased TNF-α and NF-κB activity can accelerate the apoptosis process of fibroblast cells through pathways associated with apoptosis proteins. This accelerated apoptosis ultimately leads to a decrease in collagen, resulting in significant skin damage.[7]

While MSC exosomes have been studied for their regenerative properties, the enhanced effects of hypoxia-induced exosomes on inflammation and apoptosis pathways, particularly in UVB-induced collagen degradation, remain underexplored. This study aims to fill this gap by focusing on IL-1β and caspase-1 as critical biomarkers. This study is unique in utilizing hypoxia-preconditioned MSC exosomes to directly target key mediators of inflammation (IL-1β) and apoptosis (caspase-1) in a UVB-induced skin damage model, providing novel insights into their therapeutic potential. By focusing on IL-1β and caspase-1, which are critical in UVB-induced inflammation and collagen degradation, this research lays the groundwork for developing innovative treatments for photoaging and skin disorders.

MATERIAL AND METHOD

Ethical approval for this study was granted by the Faculty of Medicine, Sultan Agung Islamic University, Semarang (Approval No. 283/VII/2024/KomisiBioetik). A posttest-only control group design was employed to minimize variability and directly assess treatment effects on gene expression outcomes. Male Wistar rats were selected due to their genetic stability and established suitability for UVB-induced skin damage models. The doses of 200 µL and 300 µL of hypoxia-preconditioned MSC-derived exosomes were determined based on preliminary data indicating optimal anti-inflammatory and tissue-regenerative effects in preclinical settings.

Equipment and Materials

Cell culture procedures were performed using a class II biosafety cabinet (BSC), micropipettes, a CO_2 incubator, a dissecting kit, T25 culture flasks, a hypoxic chamber, and an oxygen meter.

UVB irradiation was delivered using a broadband UVB lamp with a peak emission at 302 nm.

Sample collection and tissue processing were conducted using hematocrit tubes, a 6 mm biopsy punch, a centrifuge, micropipettes with 1000 µL tips, razors, exposure cages, maintenance cages, and standard animal drinking systems.

Gene expression analysis was performed using a quantitative real-time PCR (qRT-PCR) system (Illumina platform). Microscopic and histological analyses were conducted using a light microscope, staining jars, glass slides, and coverslips. Data processing and statistical analyses were carried out using a standard laboratory computer workstation.

The materials used in this study included human umbilical cord tissue, 0.9% NaCl solution, phosphate-buffered saline (PBS), Dulbecco's Modified Eagle

Medium (DMEM), fetal bovine serum (FBS), fungizone, penicillin–streptomycin, 70% ethanol, ketamine, xylazine, and specific primers for IL-1β and caspase-1.

Msc Isolation Procedure from Umbilical Cord

All procedures were performed in a class II biosafety cabinet under sterile conditions using aseptic techniques. Human umbilical cords were collected in a sterile transport medium. The umbilical cord tissue was transferred to a Petri dish and thoroughly washed with phosphate-buffered saline (PBS) to remove residual blood. Blood vessels were carefully removed, and the remaining tissue was finely minced into small fragments.

The tissue fragments were evenly distributed onto T25 culture flasks and allowed to adhere to the flask surface for approximately 3 minutes. A complete culture medium consisting of Dulbecco's Modified Eagle Medium (DMEM) supplemented with fetal bovine serum (FBS), penicillin–streptomycin, and fungizone was slowly added to fully cover the tissue explants. The cultures were incubated at 37°C in a humidified atmosphere containing 5% CO_2.

Cell outgrowth from the explants was observed after approximately 14 days of culture. The culture medium was partially replaced every three days by removing half of the spent medium and replenishing it with fresh complete medium. Cells were maintained until reaching approximately 80% confluence, after which they were passaged for expansion. Cells from passage 1 were subsequently subcultured until passage 4. Conditioned medium was collected when cell confluence reached at least 70%.

Hypoxic Preconditioning and Exosome Isolation

Mesenchymal stem cells (MSCs) at approximately 80% confluence were supplemented with complete culture medium up to a total volume of 10 mL per flask. The culture flasks were then transferred to a hypoxic chamber. Nitrogen gas was introduced through the inlet valve to reduce oxygen levels, and an oxygen meter was used to monitor and maintain the chamber oxygen concentration at 5% O_2.

Hypoxic preconditioning was performed for 24 hours at 37°C to enhance exosome secretion and enrich bioactive components, including vascular endothelial growth factor (VEGF), interleukin-10 (IL-10), and regulatory microRNAs such as miR-21. These factors are associated with enhanced anti-inflammatory and regenerative properties.

After 24 hours, the conditioned medium was collected and subjected to tangential flow filtration (TFF) for exosome isolation. Exosomes were purified using a molecular weight cutoff membrane (10–500 kDa) to ensure selective enrichment of extracellular vesicles. The isolated vesicles were washed twice with phosphate-buffered saline (PBS) and resuspended in 300–500 µL of PBS or wash buffer containing fetal bovine serum (FBS), as appropriate.

Flow cytometry was performed for exosome characterization using designated control tubes for compensation and instrument setup. The purified hypoxia-preconditioned MSC-derived exosomes were subsequently used for in vivo administration.

IL-1β was selected as a primary inflammatory marker due to its central role in UVB-induced inflammatory signaling, while caspase-1 was chosen as an indicator of inflammasome activation and apoptosis, serving as key endpoints for treatment evaluation.

UVB Irradiation and Treatment Protocol

After a 7-day acclimatization period, the rats were anesthetized with a combination of ketamine (60 mg/kg body weight) and xylazine (20 mg/kg body weight). The dorsal hair was carefully shaved to ensure uniform UVB exposure.

The dorsal skin was exposed to broadband UVB irradiation (peak emission at 302 nm) at a minimum erythema dose (MED) of 160 mJ/cm² per session, administered 10 times over a 14-day period. Following UVB induction, treatment groups received a single subcutaneous injection of hypoxia-preconditioned MSC-derived exosomes at doses of 200 µL or 300 µL on day 15. Animals were subsequently observed for an additional 14 days, and tissue samples were collected on day 28 for further analysis.

Data Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean ± standard deviation (SD). Data normality was assessed using the Shapiro–Wilk test, and homogeneity of variance was evaluated using Levene's test. For normally distributed data with unequal variances, one-way analysis of variance (ANOVA) followed by Tamhane's T2 post hoc test was applied to compare differences among groups. For data that were not normally distributed, the Kruskal–Wallis test was used, followed by the Mann–Whitney U test for pairwise comparisons. A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

MSCs Validation

MSCs were then incubated in hypoxia conditions with an O2 concentration of 5% for 24 hours using *a hypoxia chamber* to stimulate higher secretome production, including exosomes. After the incubation period, the culture medium of MSCs containing secretomes is carefully collected. The medium is then filtered using *the Tangential Flow Filtration* (TFF) method, an effective purification technique for separating particles based on molecular size. The filtration process is carried out using *a specific molecular weight cut-off*, which allows the separation of molecules between 10 and 500 kDa in size. The end result of this filtration is a concentrate containing exosomes, which can be used for further analysis or potential therapeutic applications.[10–12]

Collagen Loss *Validation Results*

Validation that mice experience *collagen loss* due to UVB exposure was carried out through macroscopic observations, to ensure the validity of the animal model. In this study, Wistar mice were exposed to UVB light with an intensity of 160 mJ/cm² for 8 minutes per session, as many as 10 times in 14 days, at a distance of 20 cm. Macroscopic observations showed that UVB-exposed mice experienced a significant increase in the number and depth of wrinkles compared to unexposed mice, as shown in Figure 1. This indicates that UVB exposure successfully induces *collagen loss* in mice, making it a valid model for further studies of collagen breakdown mechanisms and therapeutic interventions.

In addition to being carried out macroscopicly, validation was also carried out microscopically using *Masson Trichrome* painting to see the density of collagen in mice exposed to UVB. Based on the results of painting, it was found that there was a decrease in collagen density after UVB exposure as seen in Figure 1.

Injection of Hypoxia Exosome MSCs was carried out once and tissue sampling was carried out on the 15th day after injection of Hypoxia Exosome MSCs. The tissue was then homogenized using RIPA buffer with the addition of protease inhibitors.[13] After the tissue formed the suspension, then centrifugation was carried out and supernatants were collected for analysis of TNF-α and GPx levels using the RT-PCR method.[14]

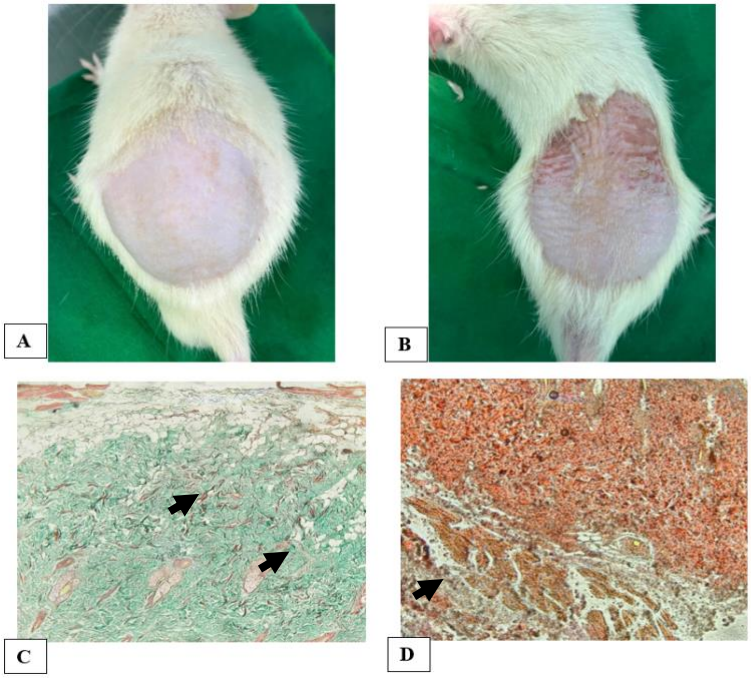


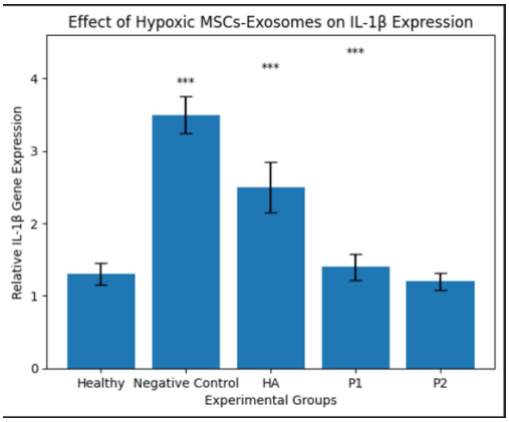
Figure 1. Collagen Loss *Validation*. Wrinkles were more pronounced in mice exposed to UVB (B) compared to those not exposed (A). Collagen shown in blue (black arrow) was less visible in the group exposed to UVB (D), compared to the group without UVB exposure (C)

Table 1. IL-1β and caspase-1 expression levels among experimental groups

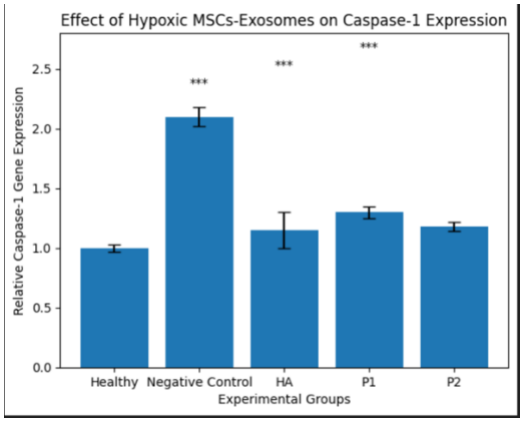
Variable	K1	K2	K3	K4	K5	ANOVA (p-value)
IL-1β (pg/mL)	1.33 ± 0.18[a]	3.50 ± 0.21[b]	2.50 ± 0.37[c]	1.40 ± 0.17[a]	1.17 ± 0.06[a]	< 0.001
Caspase-1 (pg/mL)	1.02 ± 0.01[a]	2.11 ± 0.07[b]	1.73 ± 0.16[c]	1.31 ± 0.04[a]	1.17 ± 0.07[a]	< 0.001

Based on normality and homogeneity analysis, it was found that the expression of IL-1β and Caspase 1 data was normal but not homogeneous, so a different test was carried out with *Anova* and *Post Hoc Tamhane* to determine the distribution of data per treatment group. The results of the analysis are shown in table 1. Caspase-1 expression data showed significant differences between groups. The K1 group has a value of 1.02 ± 0.01, as a basal expression. The K2 group showed a significant increase with a score of 2.11 ± 0.07, indicating an increase in inflammation and apoptosis due to UVB. The K3 group showed a decrease to 1.72 ± 0.16, but it was still higher than the control. The K4 group had a value of 1.30 ± 0.04, close to the control, showing a good protective effect. The K5 group showed the lowest score among the treatment groups, namely 1.17 ± 0.08, close to normal conditions.

The significant reduction in IL-1β levels in K4 (200 µL MSC-Exo) and K5 (300 µL MSC-Exo) groups compared to UVB-exposed controls (K2) highlights the exosomes' ability to modulate NF-κB activation and suppress pro-inflammatory cytokine production. The difference between K3 and K4 (P = 0.012) and K3 with K5 (P = 0.004) shows that MSCs Exosome Hypoxia is more effective than *Hyaluronic Acid*. Finally, an increase in the dose of Exosome Hypoxia MSCs from 200µL (K4) to 300uL (K5) showed a further significant reduction in IL-1β expression (P = 0.004), signaling that higher doses provided stronger anti-inflammatory benefits.



(a) IL-1β expression levels across experimental groups.



(b) Caspase-1 expression levels across experimental groups.

Figure 2. Effects of hypoxia-preconditioned MSC-derived exosomes on IL-1β and caspase-1 expression levels in UVB-induced skin damage.
Data are presented as mean ± SD. *p < 0.05; **p < 0.01; ***p < 0.001 compared with the UVB group.

A more significant decrease in caspase-1 in the K4 and K5 groups compared to K2 and K3 suggests that Hypoxia Exosome MSCs not only directly target inflammation but also modulate more upstream molecular pathways, such as inflammasomes and caspase-1. The dose-dependent decrease in caspase-1 expression, particularly in the K5 group, indicates that higher exosome concentrations effectively inhibit inflammasome activation, reducing apoptosis in UVB-damaged skin. This emphasis on caspase-1 reduces the production of IL-1β, thereby reducing UVB-induced inflammation. The decrease in IL-1β in K4 and K5 suggests that MSCs Exosome Hypoxia works effectively in inhibiting inflammatory pathways activated by UVB exposure, which not only helps reduce tissue damage but also supports the skin regeneration process.[15,16] The significant decrease in caspase-1 levels suggests that MSC-Exo modulates upstream inflammasome pathways, preventing the maturation of pro-inflammatory cytokines and reducing UVB-induced apoptosis.

The molecular mechanisms underlying the anti-inflammatory effects observed in this study may involve suppression of inflammasome activation pathways. UVB irradiation is known to induce reactive oxygen species production, leading to activation of the NLRP3 inflammasome and subsequent caspase-1–mediated maturation of IL-1β. The significant downregulation of both caspase-1 and IL-1β gene expression observed in the present study suggests attenuation of this inflammasome-driven inflammatory cascade.[17] Hypoxia-conditioned MSCs-exosomes have been reported to contain enriched anti-inflammatory cargo, including regulatory microRNAs such as miR-21, miR-146a, and miR-223, which are known to negatively regulate inflammasome signaling and NF-κB activation. These molecular components may inhibit caspase-1 activation either directly or through upstream suppression of NLRP3 inflammasome assembly, thereby reducing IL-1β production.[18] In addition, hypoxic preconditioning has been shown to enhance the immunomodulatory potential of MSC-derived exosomes by increasing the expression of cytoprotective and anti-inflammatory proteins. This enhanced bioactivity provides a plausible molecular basis for the coordinated suppression of inflammasome-related genes observed in this UVB-induced skin injury model.[19]

The exosomes produced by MSCs, especially when MSCs are Exosome Hypoxia, have higher content of growth factors, cytokines, and other bioactive molecules compared to MSCs cultured under normoxyan conditions.[20] These exosomes act as carriers of these molecules to target cells, which can then regulate various biological processes, including immune system modulation and

tissue repair. In the context of skin that experiences *collagen loss* due to UVB exposure, MSCs Exosome Hypoxia has the ability to suppress the activation of inflammasomes, protein complexes that respond to danger signals and cell damage.[21] These inflammasomes play a role in the activation of caspase-1, which in turn activates IL-1β from its inactive precursor form, pro-IL-1β.[22] The observed reduction in IL-1β expression is consistent with the known anti-inflammatory effects of hypoxia-induced MSC exosomes, which deliver miR-146a and IL-10 to suppress NF-κB activation and cytokine production.

Furthermore, MSCs Exosome Hypoxia also plays an important role in repairing skin tissue damaged by UVB.[23] They contain various growth factors such as VEGF (*Vascular Endothelial Growth Factor*), TGF-β (*Transforming Growth Factor-beta*), and HGF (*Hepatocyte Growth Factor*) which promote angiogenesis, cell regeneration, and extracellular matrix repair. These factors help repair collagen damage and support the skin's regeneration process, which is crucial for restoring the skin's structural integrity after UVB exposure.[24] Exosomes also contribute to reducing the inflammatory response exacerbated by tissue degradation by repairing collagen and extracellular matrix damage.[7,25]

The K2 group that received NaCl injections did not show significant therapeutic benefits because NaCl had no anti-inflammatory properties or the ability to repair cell damage. Therefore, IL-1β and caspase-1 expression remained high in this group, reflecting continued inflammation and tissue damage. The K3 group, which received *Hyaluronic Acid* injection, showed better results than K2, but was still less effective compared to K4 and K5.[26]

Hypoxia Exosome MSCs also play an important role in the effectiveness of therapy. In the K5 group, which received a higher dose (300 µL), the decrease in IL-1β and caspase-1 was more significant compared to K4 (200 µL), suggesting that higher doses of these exosomes may provide a greater number of bioactive molecules, which in turn enhances anti-inflammatory and reparative effects. This indicates the existence of a dose-response correlation, where increased doses of Hypoxia Exosome MSCs provide additional benefits in suppressing inflammatory pathways and repairing skin damage .[27]

TGF-β, on the other hand, not only has anti-inflammatory properties but also plays a role in the healing process and tissue regeneration. TGF-β can inhibit the proliferation of inflammatory cells and stimulate the production of extracellular matrix components that are essential for tissue repair.[28,29] Thus, TGF-β not only helps to lower inflammation but also promotes the repair of tissues damaged by inflammation, reinforcing the positive effect of MSCs Exosome Hypoxia in overcoming tissue damage caused by excessive inflammation. [30]

MSCs Exosome Hypoxia is also enriched with *growth factors* such as VEGF, HGF, and FGF. This *growth factor* plays an important role in repairing and regenerating damaged tissues.[31] VEGF promotes *angiogenesis*, which is important for supporting wound healing and increasing blood supply to damaged areas, while HGF and FGF play a role in the proliferation and differentiation of fibroblast cells that are important for collagen formation and tissue structure restoration. [32]

MSCs Exosome Hypoxia has bioactive content that plays an important role in regulating the inflammatory response and the apoptosis process. These contents include various types of microRNAs (miRNAs), anti-inflammatory cytokines, and *growth factors* that together contribute to lowering levels of interleukin-1β (IL-1β) and caspase-1, two major components involved in inflammation and inflammation-induced cell death 24. In contrast to *Hyaluronic Acid* which is known for its ability to retain skin moisture and slightly help in repairing tissues, it does not have a strong direct effect in inhibiting inflammatory pathways or lowering the expression of caspase-1 and IL-1β. *Hyaluronic Acid* acts more as a moisturizing and skin-protective agent than as an anti-inflammatory or reparative agent that targets deep molecular mechanisms [7].

This study has several limitations that should be acknowledged. First, the analysis was limited to gene expression of IL-1β and caspase-1 without confirmation at the protein level or assessment of inflammasome complex activation. Second, histological evaluation of skin tissue and direct measurement of collagen density were not performed, limiting structural correlation with molecular findings. Additionally, the biodistribution and bioavailability of administered MSCs-exosomes were not assessed, making it difficult to determine the extent of tissue uptake and local activity. The relatively small sample size per group may also limit the generalizability of the results. Future studies incorporating protein-level analysis, histopathological confirmation, and exosome tracking would strengthen the mechanistic understanding of hypoxic MSCs-exosome therapy in UVB-induced skin damage.

CONCLUSION

This study demonstrates that hypoxia-preconditioned MSC-derived exosomes exert significant anti-inflammatory and anti-apoptotic effects in a UVB-induced skin damage model. The marked downregulation of IL-1β and caspase-1 expression indicates attenuation of inflammasome-associated inflammatory signaling. These findings suggest that hypoxia-preconditioned MSC-derived exosomes may represent a promising therapeutic strategy for mitigating UVB-induced skin inflammation and supporting collagen preservation. Further studies are warranted to optimize dosing strategies and to clarify the underlying molecular mechanisms involved in their protective effects.

AUTHORS' CONTRIBUTIONS

Farah Diana Sari prepares samples, designs protocols, implements protocols, and writes manuscripts. Agung Putra and Sri Priyantini reviewed and supervised the script. All authors have read and agreed to the final manuscript.

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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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