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ORIGINAL ARTICLE

Hypoxia-conditioned mesenchymal stem cells (MSC) exosomes attenuate ultraviolet-B (UVB)-mediated malondialdehyde (MDA) and matrix metalloproteinase-1 (MMP)-1 upregulation in collagen loss models

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ABSTRACT

Aim To investigate the effects of exosome-derived human mesenchymal stem cells (EH-MSCs) on matrix metalloproteinase-1 (MMP)-1 and malondialdehyde (MDA) levels in ultraviolet-B (UVB)-irradiated Wistar rats.

Methods The study used a post-test-only control group design with randomized allocation. Thirty rats were exposed to UVB radiation (302 nm, 150 mJ/cm²) for 8 minutes, five times a week over two weeks. Five groups were established: a healthy control (G1), a negative control (G2), a positive control that received a 200 µL subcutaneous injection of hyaluronic acid (HA) (G3), a treatment group 1 that received a 200 µL subcutaneous injection of exosome-derived EH-MSCs (G4), and a treatment group 2 that received a 300 µL subcutaneous injection of EH-MSCs (G5). An ELISA was used to quantify the levels of MDA and MMP-1.

Results A significant reduction in the mean level of MDA in groups G4 (368.33 ± 59.67) and G5 (329.33 ± 82.06) was noted when compared to the negative control group G2 (686.58 ± 119.01) ($p<0.05$). Similarly, MMP-1 showed a significant decrease in mean levels for G4 (0.08 ± 0.04) and G5 (0.07 ± 0.04) compared to G2 (0.33 ± 0.06) ($p<0.05$).

Conclusion These findings suggest that EH-MSCs have potent antioxidant and anti-inflammatory properties, mitigating UVB-induced skin damage by reducing oxidative stress markers.

Keywords: extracellular matrix, hypoxia-induced factors, oxidative stress, photoaging, stem cell therapy

INTRODUCTION

Ultraviolet (UV) radiation exposure represents a significant environmental challenge to skin homeostasis, precipitating various pathophysiological changes manifesting as acute and chronic cutaneous damage (1). Prolonged UV exposure has been implicated in accelerated skin aging, immunosuppression, carcinogenesis, and structural deterioration of dermal matrix proteins, mainly collagen and elastin (2,3). The molecular cascade initiated by UV radiation primarily operates through the generation of reactive oxygen species (ROS), which serve as secondary mediators activating the mitogen-activated protein kinase (MAPK) signalling pathway (4). This activation leads to persistent cellular damage and triggers a complex inflammatory response characterized by upregulation of activating protein-1 (AP-1) and matrix metalloproteinases (MMPs) (5). Concurrent with these changes, UV radiation suppresses tissue inhibitors of matrix metalloproteinase (TIMP) expression, disrupting the homeostatic balance of collagen metabolism. The oxidative stress is further evidenced by elevated malondialdehyde (MDA), reliable tissue damage, and inflammation biomarkers. Of particular concern is UVB radiation, which penetrates deeper dermal layers, causing substantial damage to collagen-rich structures (6,7).

The global burden of UV-induced skin disorders rises annually, a trend correlating with progressive ozone layer depletion (8). Epidemiological data from Australia reveal concerning statistics, with UV-related skin conditions affecting 72% of males and 47% of females under 30 (3). These figures are even more striking in North American populations with Fitzpatrick skin types I-III, where prevalence rates of UV-induced skin damage reach 80-90% (7). Current therapeutic strategies often

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employ Hyaluronic Acid (HA) as a primary intervention for maintaining skin integrity and preventing collagen degradation (9). HA's multifaceted role encompasses the maintenance of skin hydration, structural support, protection against damage, and tissue repair (10,11). However, despite its widespread use in preventing UVB-induced collagen loss, HA's therapeutic efficacy is limited by its rapid physiological degradation, necessitating frequent reapplication. Moreover, HA's effects are predominantly confined to the superficial skin layers, failing to adequately address the underlying inflammation and free radical damage induced by UVB radiation (8,12).

At the molecular level, UVB exposure has been shown to enhance dermal fibroblast expression of MMP-1 by activating p53 and c-Jun transcription factors (13,14). The subsequent increase in MDA production, a byproduct of lipid peroxidation (9), is a critical indicator of oxidative stress and cellular damage (15,16). Recent investigations have highlighted the significance of various cytokines and growth factors, particularly interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), in modulating UVB-induced oxidative stress (17,18). These molecular mediators demonstrate promising effects in reducing MMP-1 levels and oxidative stress (19,20). Emerging research has identified that exosomes derived from hypoxia-preconditioned mesenchymal stem cells (H-MSCs) contain these beneficial cytokines and growth factors (21).

Furthermore, H-MSC exosomes (EH-MSCs) have been found to harbour specific microRNAs, including miR-21 (22,23), capable of regulating inflammatory pathways such as IL-6 and tumour necrosis factor (TNF)- α, which are typically overexpressed in chronic inflammation (24,25). While these findings indicate that MSC exosomes may have a therapeutic potential through the regulation of MMP-1 and MDA, the specific effects of MSC exosomes on these parameters in UVB-exposed skin have not been studied yet.

This research investigated the therapeutic potential of exosomes derived from EH-MSCs in modulating MMP-1 and MDA levels in UVB-exposed rat skin. This could provide valuable insights for more effective treatments of UV-induced skin damage.

MATERIALS AND METHODS

Materials and study design

This study was conducted from August to October 2024. The study used a post-test-only control group design with randomized allocation.

Thirty Wistar rats were acclimatized for 7 days and anesthetized with ketamine and xylazine. A 2×3 cm dorsal area was depilated for UVB exposure. The rats received UVB radiation (302 nm, 150 mJ/cm²) for 8 minutes five times a week over two weeks. Post-exposure, rats were divided into five groups: G1 (healthy control), G2 (negative control group were rats exposed to UVB radiation without receiving any treatment), G3 (positive control group were rats exposed to UVB radiation and received 200 µL subcutaneous injection of hyaluronic acid (HA)), G4 (treatment group 1 was exposed to UVB and received a 200 µL subcutaneous injection of exosome-derived EH-MSCs), and G5 (treatment group 2 was exposed to UVB and received a 300 µL subcutaneous injection of exosome-derived EH-MSCs). After confirming collagen loss by Masson-trichome staining, treatments began to assess therapeutic efficacy against UVB-induced skin damage.

This investigation received an approval from the Medical Faculty Ethics Committee at Sultan Agung Islamic University, Semarang (No 383/IX/2024/Komisi Bioetik).

Methods

Mesenchymal stem cells were isolated from pregnant rat umbilical cord tissue at gestation day 19, following modified established protocols (20). Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) with 10% foetal bovine serum (FBS) (Sigma-Aldrich) and 100 IU/mL penicillin/streptomycin (Sigma-Aldrich) under normoxic conditions until passage 5 (26,27).

MSC phenotype was characterized by flow cytometry using specific antibodies against CD73, CD90, CD105, and hematopoietic lineage markers. Immunolabeling was conducted at 4 °C for 30 minutes, and cellular analysis was performed using a BD Accuri C6 PLUS flow cytometer (BD Biosciences, San Jose, CA, USA).

The osteogenic and adipogenic differentiation potential of MSCs was evaluated by culturing them in specific induction media for 21 days. Osteogenic differentiation was confirmed through Alizarin Red staining to detect calcium deposition, while adipogenic differentiation was assessed using Oil Red O staining to identify lipid droplets (28–30).

MSC-derived exosomes were isolated using Tangential Flow Filtration (TFF) and validated by flow cytometry for CD81, CD63, and CD9 exosomal markers. Following identity confirmation, the validated MSC exosome preparations were aliquoted into 2.5 mL cryogenic storage tubes and maintained at 2-8 °C until further use (31,32).

A collagen loss model was established in rats using UVB exposure. Macroscopic validation involved visual examination for skin wrinkles, while histopathological validation used Masson's Trichrome staining to assess collagen density. The animal model was successfully established when a significant reduction in collagen density was observed compared to non-UVB-exposed controls.

MMP-3 and MDA concentrations were quantified using ELISA. Samples were incubated in a 96-well plate, followed by sequential additions of detection antibody, horseradish peroxidase (HRP) conjugate, and substrate. After stopping the reaction, absorbance was measured at 450 nm to determine protein concentrations.

Statistical analysis

All data (from at least three separate experiments) are presented as mean ± standard deviation (SD). Statistical analysis was performed using one-way ANOVA, and the least significant difference (LSD) comparison post hoc test p-value <0.05 indicated statistical significance.

RESULTS

MSCs were isolated and cultured from umbilical cord pregnant mice aged 21 days based on their plastic adherent capability under standard culture conditions. MSC cell morphology exhibited characteristic spindle-shaped, fibroblast-like cells with plastic adherent capability (Figure 1A). This study also exam-

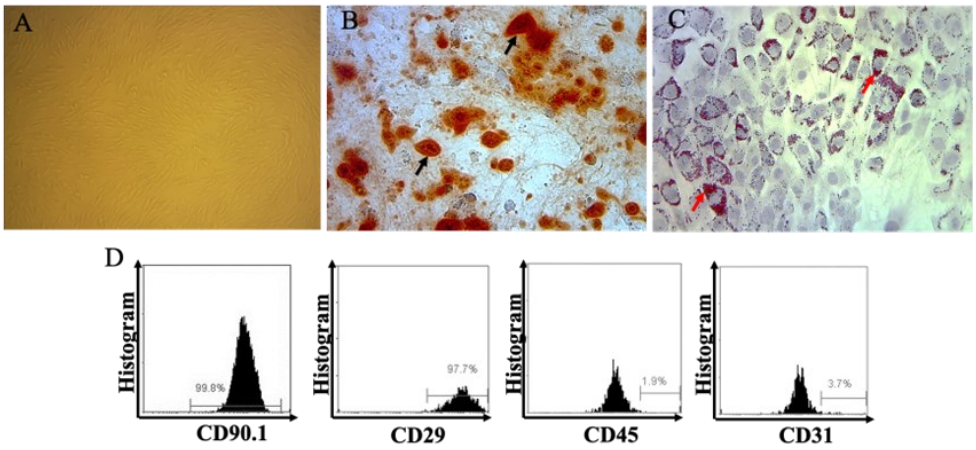

Figure 1. A) Characterization and differentiation of mesenchymal stem cells (MSCs) (magnification 10x; scale bar: 200 µm); B) The ability of MSCs to differentiate into bone-forming cells by Alizarin red staining is indicated by calcium deposition (black arrow); C) The red arrow indicates red staining in response to lipid deposition under Oil Red O staining (magnification 40x); D) Analysis of surface markers shows the expression of CD90, CD29, CD45 and CD31

ined the differentiation capacity at the end of the fifth passage expansion; the MSC-like osteogenic differentiation assay was conducted by administering the standard and osteogenic medium for 21 days. Calcium deposition was visualized in red appearance using the alizarin red dye staining (Figure 1B). The MSCs were also successfully differentiated into adipogenic lineages under oil red-O staining (Figure 1C). Moreover, the immunophenotypically of MSCs were analysed using flow cytometry. A high level of CD90 (99.80 ± 2.10%) and CD29 (97.70 ± 0.76%) and low level of CD45 (1.90 ± 0.05%) and CD31 (3.70 ± 0.34%) were found (Figure 1D).

Tangential flow filtration (TFF) was employed to filter the MSCs medium, which was believed to contain exosomes. Subsequently, flow cytometry was utilized to analyse the exosome content. The analysis revealed that the TFF method effectively isolated exosomes, with 9.1% of the total particles identified as exosomes (Figure 2A). The isolated exosomes exhibited an average mean fluorescence intensity (MFI) of 1056.35. Furthermore, the quantification of exosomes in the filtered medium yielded an average concentration of 960 ng/mL (Figure 2B).

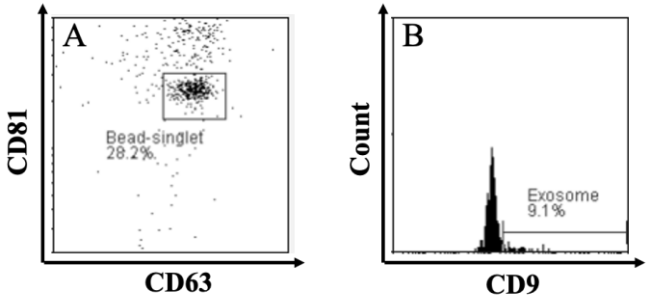

Figure 2. Exosome hypoxia mesenchymal stem cells (EH-MSCs) validation under flow cytometry analysis (A) Analysis of exosome surface markers shows the expression of CD81 and CD63 and (B) quantification of exosome by CD9 analysis

Following the UVB exposure protocol, significant changes were observed in the skin structure of the treated rats. The animals were subjected to UVB radiation at a minimal erythema dose of 150 mJ/cm² for 8 minutes per session, with treatments administered five times weekly over two weeks. This intense UVB exposure resulted in substantial collagen loss in the dermis of the treated rats. Masson's trichrome staining visually confirmed the extent of collagen degradation; in the skin samples from UVB-exposed rats, there was a striking absence of the characteristic blue staining typically seen in healthy skin samples (Figure 3B, 3D).

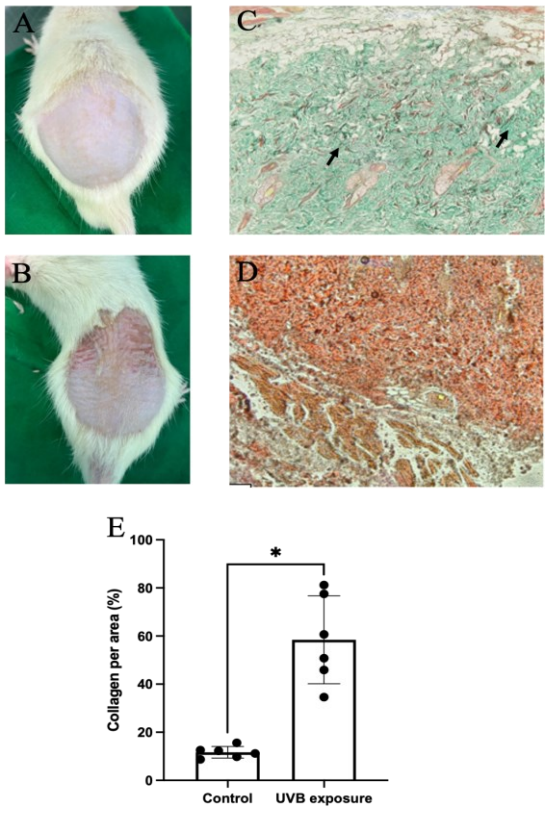

Figure 3. Masson's Trichrome Staining of rat skin samples. A) healthy skin; B) skin exposed to UVB radiation; C) a dense network of collagen fibres is visible as intense blue staining in the dermis (black arrow); D) there is a significant reduction or absence of blue staining, indicating severe collagen loss in the dermal layer; E) quantification of percentage collagen per area (n=5±SD; scale bar=100 µm)

The lack of blue coloration indicates severe collagen depletion in the dermal layer, providing clear evidence of UVB-

induced collagen loss. While the healthy skin exhibited a dense network of blue-stained collagen fibres, the UVB-exposed skin showed a marked reduction or complete absence of this blue staining (Figure 3A, 3C). After UVB exposure, the collagen area density increased significantly by 58.73% (Figure 3E). This observation underscores the detrimental effect of UVB radiation on dermal collagen content and overall skin structure.

UVB exposure has been shown to induce the release of oxidative stress associated with collagen loss. In this study, we found that the EH-MSCs gel could decrease levels of the MDA in a dose-dependent manner. Our study showed that the EH-MSCs 200µL (G4) significantly reduced MDA levels (368.33 ± 59.67) up to 3 times lower than in the whole treatment group (control group). The EH-MSCs 300 µL (G5) decreased MDA levels (329.33 ± 82.06). The negative control group (G2) showed MDA level (686.58 ± 119.01) (Figure 4).

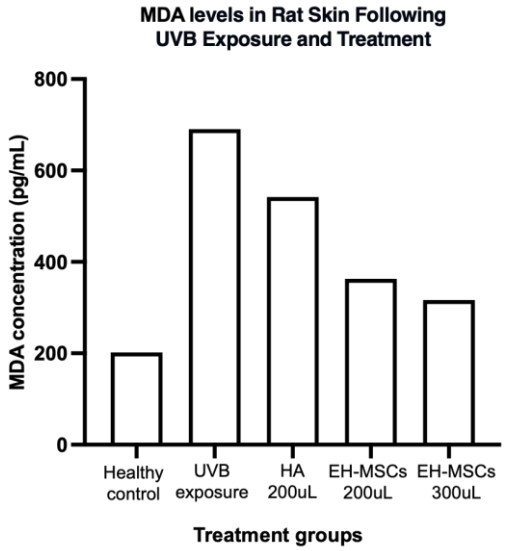

Figure 4. The effect of exosomes derived from hypoxic mesenchymal stem cells (EH-MSCs) significantly reduced malondialdehyde (MDA) levels related to collagen loss induced by UVB irradiation during EH-MSC treatment. N=6, data represent the mean ± SD. *p < 0.05 indicates a significant difference.

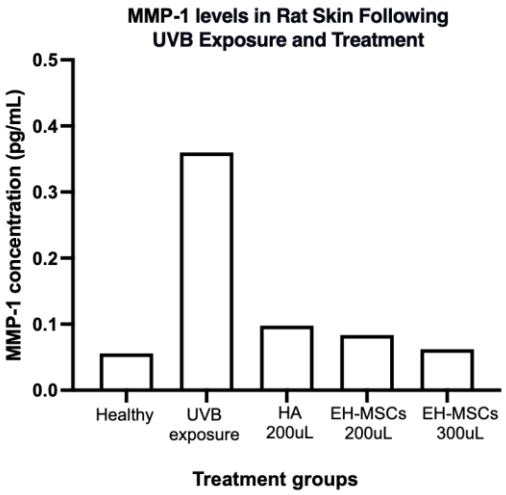

Figure 5. The effect of exosomes derived from hypoxic mesenchymal stem cells (EH-MSCs) significantly reduced matrix metalloproteinase-1 (MMP-1) levels related to collagen loss induced by UVB irradiation during EH-MSC treatment. N=6, data represent the mean ± SD. *p < 0.05 indicates a significant difference.

DISCUSSION

This study found that 300µl of EH-MSCs significantly reduced MDA level. EH-MSCs can induce various antioxidant enzymes and contain anti-inflammatory molecules that inhibit ROS, ultimately leading to decreased MDA (33,34). These findings align with a previous study that MSCs are resistant to oxidative and nitrosative stimuli *in vitro*, related to constitutively expressed antioxidant enzymes SOD1, SOD2, catalase (CAT), and high levels of glutathione peroxidase, thus reducing MDA level (35). Another study also reported that exosome hypoxia of MSCs produced contains several growth factors (TGF-β, PDGF, FGF, HGF), anti-inflammatory cytokines (IL-10), lipids, mRNA, miRNA, and mtRNA that activated Nrf2 expression leading to induced MDA level (36,37). Support by a previous study reported that through Nrf2 pathway activation, MSC-derived exosomes can enhance the expression and activity of antioxidant enzymes like SOD, effectively neutralizing and scavenging ROS, thus reducing oxidative stress and MDA. Neutralized MDA leads to a decrease in MMP-1, preventing collagen degradation (38).

Studies show that SOD interacts with type I and type IV collagen through matrix binding domains, protecting them from oxidative damage and inhibiting collagen-mediated injury. Similarly, UVB-induced MMP-1 expression levels were reduced in SOD-overexpressing transgenic mice compared to wild-type (WT) mice (39). Thus, SOD may play a crucial role in regulating skin aging. Our study also found that 300µl of EH-MSCs significantly reduced MMP-1 levels. EH-MSCs secrete extracellular vesicles containing anti-inflammatory and antioxidant molecules, such as IL-10, TGFβ, GPX, SOD1, SOD2, CAT, and sirtuins (SIRT1 and 3) (40,41). The anti-inflammatory molecules in EH-MSCs can inhibit the NF-κB transcription factor, which triggers ROS and MMP-1 overexpression (42). Previous studies also support this finding that administering MSC secretome containing IL-10 can inhibit MMP-1 in UVB-induced hyperpigmentation (43).

Overall, EH-MSCs may inhibit collagen loss by blocking the MMP-1 pathway and enhance antioxidant properties by increasing SOD levels. The findings support using EH-MSCs as a promising treatment for UVB-induced skin damage and aging.

AUTHORS CONTRIBUTIONS

Conceptualization, A.P., D.H., and E.S.; methodology, J.A.; validation, A.P., D.H., and E.S.; formal analysis, J.A.; data curation, J.A.; writing—original draft preparation, N.D.A. and T.S.; writing—review and editing, S.T. and D.H.; visualization, N.D.A. and T.S.; supervision, A.P., D.H., and E.S.; project administration, S.T. and D.H. All authors have read and agreed to the published version of the manuscript.

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TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

REFERENCES

1 Ansary TM, Hossain MR, Kamiya K, Komine M, Ohtsuki M. Inflammatory Molecules Associated with Ultraviolet Radiation-Mediated Skin Aging. Int J Mol Sci 2021; 22;(8):3974. doi: 10.3390/ijms22083974.

2 Oh CT, Lee D, Koo K, Lee J, Yoon HS, Choi YM, et al. Superoxide dismutase 1 inhibits alpha-melanocyte stimulating hormone and ultraviolet B-induced melanogenesis in murine skin. Ann Dermatol 2014;26;(6):681–7. doi: 10.5021/ad.2014.26.6.681.

3 Siebenga PS, van Amerongen G, Klaassen ES, de Kam ML, Rissmann R, Groeneveld GJ. The ultraviolet B inflammation model: Postinflammatory hyperpigmentation and validation of a reduced UVB exposure paradigm for inducing hyperalgesia in healthy subjects. Eur J Pain Lond Engl 2019;23;(5):874–83. doi: 10.1002/ejp.1353.

4 Subedi L, Lee TH, Wahedi HM, Baek S-H, Kim SY. Resveratrol-Enriched Rice Attenuates UVB-ROS-Induced Skin Aging via Downregulation of Inflammatory Cascades. Oxid Med Cell Longev 2017;2017:8379539. doi: 10.1155/2017/8379539.

5 Hwang IS, Kim JE, Choi SI, Lee HR, Lee YJ, Jang MJ, et al. UV radiation-induced skin aging in hairless mice is effectively prevented by oral intake of sea buckthorn (Hippophae rhamnoides L.) fruit blend for 6 weeks through MMP suppression and increase of SOD activity. Int J Mol Med 2012;30;(2):392–400. doi: 10.3892/ijmm.2012.1011.

6 Zhang J, Wang X, Vikash V, Ye Q, Wu D, Liu Y, et al. ROS and ROS-Mediated Cellular Signaling. Oxid Med Cell Longev 2016;2016:4350965. doi: 10.1155/2016/4350965.

7 Davalli P, Mitic T, Caporali A, Lauriola A, D'Arca D. ROS, Cell Senescence, and Novel Molecular Mechanisms in Aging and Age-Related Diseases. Oxid Med Cell Longev 2016;2016:3565127. doi: 10.1155/2016/3565127.

8 Corrêa MEAB, Dos Santos Haupenthal DP, Mendes C, Zaccaron RP, de Roch Casagrande L, Venturini LM, et al. Effects of Percutaneous Collagen Induction Therapy Associated with Hyaluronic Acid on Inflammatory Response, Oxidative Stress, and Collagen Production. Inflammation 2020;43;(6):2232–44. doi: 10.1007/s10753-020-01291-0.

9 Buhren BA, Schrumpf H, Hoff N-P, Bölke E, Hilton S, Gerber PA. Hyaluronidase: from clinical applications to molecular and cellular mechanisms. Eur J Med Res 2016; 21:5. doi: 10.1186/s40001-016-0201-5.

10 Jiang M, Yang S-Z, Zhang X-Y, Zhang L-Z, Gong J-S, Han T-T, et al. Protective effect of ferulic acid-hyaluronic acid copolymer against UVB irradiation in a human HaCaT cell line. Int J Biol Macromol 2024;279;(Pt 4): 135570. doi: 10.1016/j.ijbiomac.2024.135570.

11 Robati RM, Moeineddin F, Almasi-Nasrabadi M. The Risk of Skin Necrosis Following Hyaluronic Acid Filler Injection in Patients With a History of Cosmetic Rhinoplasty. Aesthet Surg J 2018;38;(8):883–8. doi: 10.1093/asj/sjy005.

12 Siquier-Dameto G, Boadas-Vaello P, Verdú E. Intradermal Treatment with a Hyaluronic Acid Complex Supplemented with Amino Acids and Antioxidant Vitamins Improves Cutaneous Hydration and Viscoelasticity in Healthy Subjects. Antioxid Basel Switz 2024;13;(7):770. doi: 10.3390/antiox13070770.

13 Lee Y-R, Noh E-M, Han J-H, Kim J-M, Hwang J-K, Hwang B-M, et al. Brazilin inhibits UVB-induced MMP-1/3 expressions and secretions by suppressing the NF-κB pathway in human dermal fibroblasts. Eur J Pharmacol 2012;674;(2–3):80–6. doi: 10.1016/j.ejphar.2011.10.016.

14 Ryu JY, Na EJ. MMP expression alteration and MMP-1 production control by syringic acid via AP-1 mechanism. Biomed Dermatol 2018;2;(1):15. doi: 10.1186/s41702-018-0023-x.

15 Hayami T, Kapila YL, Kapila S. MMP-1 (collagenase-1) and MMP-13 (collagenase-3) differentially regulate markers of osteoblastic differentiation in osteogenic cells. Matrix Biol J Int Soc Matrix Biol 2008;27;(8):682–92. doi: 10.1016/j.matbio.2008.07.005.

16 Zukhiroh Z, Putra A, Chodidjah C, Sumarawati T, Subchan P, Trisnadi S, et al. Effect of Secretome-Hypoxia Mesenchymal Stem Cells on Regulating SOD and MMP-1 mRNA Expressions in Skin Hyperpigmentation Rats. Open Access Maced J Med Sci 2022;10;(A):1–7. doi: 10.3889/oamjms.2022.10348.

17 Moon H-R, Jung JM, Kim SY, Song Y, Chang SE. TGF-β3 suppresses melanogenesis in human melanocytes cocultured with UV-irradiated neighboring cells and human skin. J Dermatol Sci 2020;99;(2):100–8. doi: 10.1016/j.jdermsci.2020.06.007.

18 Ke Y, Wang X-J. TGFβ Signaling in Photoaging and UV-Induced Skin Cancer. J Invest Dermatol 2021;141; (4S):1104–10. doi: 10.1016/j.jid.2020.11.007.

19 Mursiti S, Amalina ND, Marianti A. Inhibition of breast cancer cell development using Citrus maxima extract through increasing levels of Reactive Oxygen Species (ROS). J Phys Conf Ser 2021;1918;(5):052005. doi: 10.1088/1742-6596/1918/5/052005.

20 Suzery M, Cahyono B, Amalina ND. Citrus sinensis (L) Peels Extract Inhibits Metastasis of Breast Cancer Cells by Targeting the Downregulation Matrix Metalloproteinases-9. Open Access Maced J Med Sci 2021;9;(B):464–9. doi: 10.3889/oamjms.2021.6072.

21 Wu P, Zhang B, Shi H, Qian H, Xu W. MSC-exosome: A novel cell-free therapy for cutaneous regeneration. Cytotherapy 2018;20;(3):291–301. doi: 10.1016/j.jcyt.2017.11.002.

22 Li J, Huang Y, Sun H, Yang L. Mechanism of mesenchymal stem cells and exosomes in the treatment of age-related diseases. Front Immunol 2023;14:1181308. doi: 10.3389/fimmu.2023.1181308.

23 Liu W, Li L, Rong Y, Qian D, Chen J, Zhou Z, et al. Hypoxic mesenchymal stem cell-derived exosomes promote bone fracture healing by the transfer of miR-126. Acta Biomater 2020;103:196–212. doi: 10.1016/j.actbio.2019.12.020.

24 Hu P, Yang Q, Wang Q, Shi C, Wang D, Armato U, et al. Mesenchymal stromal cells-exosomes: a promising cell-free therapeutic tool for wound healing and cutaneous regeneration. Burns Trauma 2019;7:38. doi: 10.1186/s41038-019-0178-8.

25 Bian D, Wu Y, Song G, Azizi R, Zamani A. The application of mesenchymal stromal cells (MSCs) and their deriv-

ative exosome in skin wound healing: a comprehensive review. Stem Cell Res Ther 2022;13;(1):24. doi: 10.1186/s13287-021-02697-9.
26 Munir D, Pahlevi Nasution I, Restimulia L, Putra A, Amalina ND. The role of mesenchymal stem cells in allergic rhinitis and its relationship with IL-10, plasma cells and regulatory T cells. Med Glas Off Publ Med Assoc Zenica-Doboj Cant Bosnia Herzeg 2023;20;(2):175–80. doi: 10.17392/1541-23.
27 Daryanti E, Putra A, Sumarawati T, Amalina ND, Prasetio A, Sidiq HA. The Comparison of Normoxic and Hypoxic Mesenchymal Stem Cells in Regulating Platelet-derived Growth Factors and Collagen Serial Levels in Skin Excision Animal Models. Open Access Maced J Med Sci 2023;11;(A):181–7. doi: 10.3889/oamjms.2023.10966.
28 Restimulia L, Ilyas S, Munir D, Putra A, Madiadipoera T, Farhat F, et al. The CD4+CD25+FoxP3+ Regulatory T Cells Regulated by MSCs Suppress Plasma Cells in a Mouse Model of Allergic Rhinitis. Med Arch Sarajevo Bosnia Herzeg 2021;75;(4):256–61. doi: 10.5455/medarh.2021.75.256-261.
29 Masyithah Darlan D, Munir D, Putra A, Alif I, Amalina ND, Jusuf NK, et al. Revealing the decrease of indoleamine 2,3-dioxygenase as a major constituent for B cells survival post-mesenchymal stem cells co-cultured with peripheral blood mononuclear cell (PBMC) of systemic lupus erythematosus (SLE) patients. Med Glas Off Publ Med Assoc Zenica-Doboj Cant Bosnia Herzeg 2022;19;(1). doi: 10.17392/1414-21.
30 Utami A, Putra A, Wibowo JW, Amalina ND, Satria Irawan RC. Hypoxic secretome mesenchymal stem cells inhibiting interleukin-6 expression prevent oxidative stress in type 1 diabetes mellitus. Med Glas Off Publ Med Assoc Zenica-Doboj Cant Bosnia Herzeg 2023;20;(2). doi: 10.17392/1538-23.
31 Restimulia L, Ilyas S, Munir D, Putra A, Madiadipoera T, Farhat F, et al. Rats' umbilical-cord mesenchymal stem cells ameliorate mast cells and Hsp70 on ovalbumin-induced allergic rhinitis rats. Med Glas Off Publ Med Assoc Zenica-Doboj Cant Bosnia Herzeg 2022;19;(1). doi: 10.17392/1421-21.
32 Mayasari YI, Subchan P, Putra A, Chodijah C, Hussana A, Sumarawati T, et al. Secretome Hypoxia Mesenchymal Stem Cells Inhibited Ultraviolet Radiation by Inhibiting Interleukin-6 through Nuclear Factor-Kappa Beta Pathway in Hyperpigmentation Animal Models. Open Access Maced J Med Sci 2023;11;(A):188–94. doi: 10.3889/oamjms.2023.11222.
33 Jung KJ, Lee GW, Park CH, Lee TJ, Kim JY, Sung EG, et al. Mesenchymal Stem Cells Decrease Oxidative Stress in the Bowels of Interleukin-10 Knockout Mice. Gut Liver 2020;14;(1):100–7. doi: 10.5009/gnl18438.
34 Liu Z, Hu G-D, Luo X-B, Yin B, Shu B, Guan J-Z, et al. Potential of bone marrow mesenchymal stem cells in rejuvenation of the aged skin of rats. Biomed Rep 2017;6;(3):279–84. doi: 10.3892/br.2017.842.
35 Stavely R, Nurgali K. The emerging antioxidant paradigm of mesenchymal stem cell therapy. Stem Cells Transl Med 2020;9;(9):985–1006. doi: 10.1002/sctm.19-0446.
36 Yaghoubi A, Ghojazadeh M, Abolhasani S, Alikhah H, Khaki-Khatibi F. Correlation of Serum Levels of Vitronectin, Malondialdehyde and Hs- CRP With Disease Severity in Coronary Artery Disease. J Cardiovasc Thorac Res 2015;7;(3):113–7. doi: 10.15171/jcvtr.2015.24.
37 Astari L, Cahyono H, Widjajanto E. Correlation of Interleukin-10, Superoxide Dismutase (SOD), and Malondialdehyde (MDA) Levels with HbA1c in Pediatric Type 1 Diabetes Mellitus. J Trop Life Sci 2017;7;(3):286–92. doi: 10.11594/jtls.07.03.15.
38 Li J, Li Z, Wang S, Bi J, Huo R. Exosomes from human adipose-derived mesenchymal stem cells inhibit production of extracellular matrix in keloid fibroblasts via down-regulating transforming growth factor-β2 and Notch-1 expression. Bioengineered 2022;13;(4):8515–25. doi: 10.1080/21655979.2022.2051838.
39 Zhang Y, Pan Y, Liu Y, Li X, Tang L, Duan M, et al. Exosomes derived from human umbilical cord blood mesenchymal stem cells stimulate regenerative wound healing via transforming growth factor-β receptor inhibition. Stem Cell Res Ther 2021;12;(1):434. doi: 10.1186/s13287-021-02517-0.
40 Khamis T, Abdelalim AF, Saeed AA, Edress NM, Nafea A, Ebian HF, et al. Breast milk MSCs upregulated β-cells PDX1, Ngn3, and PCNA expression via remodeling ER stress /inflammatory /apoptotic signaling pathways in type 1 diabetic rats. Eur J Pharmacol 2021;905:174188. doi: 10.1016/j.ejphar.2021.174188.
41 Putra A, Ridwan FB, Putridewi AI, Kustiyah AR, Wirastuti K, Sadyah NAC, et al. The Role of TNF-α induced MSCs on Suppressive Inflammation by Increasing TGF-β and IL-10. Open Access Maced J Med Sci 2018;6;(10):1779–83. doi: 10.3889/oamjms.2018.404.
42 Park G-H, Kwon HH, Seok J, Yang SH, Lee J, Park BC, et al. Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: A 12-week prospective, randomized, split-face study. J Cosmet Dermatol 2023;22;(12):3418–26. doi: 10.1111/jocd.15872.
43 Dirja BT, Wardoyo EH, Putra A, Amalina ND. Enhanced Third Degree Burn Wound Healing by Hypoxic Mesenchymal Stem Cells' Secretome: IL-10 Upregulation and TNF-α/PGE2 Suppression. Trends Sci 2024;21;(10):8288. doi: 10.48048/tis.2024.8288.