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Hypoxia Mesenchymal Stem Cell-Derived Exosomes (EH-MSCs) enhance IGF-1 and suppress IL-1β in hair follicle regeneration

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Abstract: Alopecia is a condition characterized by hair loss, often caused by inflammation and disruption of growth factor pathways, such as interleukin-1 beta (IL-1β) and insulin-like growth factor-1 (IGF-1). This study evaluated the effects of Exosome Hypoxia Mesenchymal Stem Cells (EH-MSCs) on IL-1β and IGF-1 levels in fluconazole-induced alopecia-like Wistar rats. Using a randomized in vivo experimental design, rats were divided into five groups: a healthy control, a fluconazole-only group, a minoxidil-treated group, and two EH-MSC-treated groups with different doses (100 µg/kgBW and 200 µg/kgBW). IL-1β and IGF-1 levels were analyzed using ELISA. The results revealed that EH-MSCs significantly suppressed IL-1β levels, particularly at a dose of 200 µg/kgBW, achieving values comparable to the healthy control group. Similarly, IGF-1 levels were restored significantly, with the 200 µg/kgBW dose showing near-normal levels. These effects are attributed to the inhibition of NF-κB signaling by exosomal miR-146a and the upregulation of IGF-1 through miR-126-mediated PI3K/Akt activation. The findings highlight the dual role of EH-MSCs in reducing inflammation and promoting hair follicle regeneration. This study provides critical insights into the therapeutic potential of EH-MSCs as a cell-free alternative for treating alopecia and lays the groundwork for further research on their clinical applications.

Keywords: Alopecia, Exosomes, Hair Follicle Regeneration, IGF-1, IL-1β, Mesenchymal Stem Cells.

INTRODUCTION

Alopecia is a medical condition characterized by hair loss, which may occur gradually or suddenly, primarily affecting the scalp. It impacts both men and women across various ages, with causes ranging from genetic predispositions and nutritional deficiencies to autoimmune diseases and certain medications[1]. Alopecia Areata (AA), an autoimmune condition, leads to the immune system attacking hair follicles, causing localized hair loss. Other types include androgenetic alopecia (pattern baldness) and traction alopecia, often associated with persistent tension

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from certain hairstyles[2]. Alopecia can have profound psychological effects, especially in women, contributing to emotional stress, reduced self-esteem, and even depression[3,4]. Despite its significant impact, effective and safe treatments for alopecia remain limited. Current FDA-approved treatments, such as finasteride and minoxidil, are associated with side effects like sexual dysfunction and skin irritation, respectively, and do not address underlying immune or genetic factors[5,6].

Emerging research highlights the critical roles of pro-inflammatory cytokines and growth factors in alopecia pathogenesis. Elevated levels of interleukin-1 beta (IL-1β) are linked to excessive inflammation in hair follicles, leading to structural damage and exacerbating autoimmune conditions like AA[7–10]. Conversely, reduced levels of insulin-like growth factor-1 (IGF-1) impair the anagen phase, accelerating hair loss and hindering regeneration[11,12]. Studies suggest IGF-1 supports follicular cell survival and prevents apoptosis, while IL-1β promotes inflammatory responses detrimental to hair follicle health[9,13]. Consequently, targeting IL-1β and IGF-1 regulation represents a promising avenue for alopecia treatment.

Recent advancements in regenerative medicine emphasize the potential of mesenchymal stem cell-derived exosomes (MSC-Exos) as cell-free therapies[14]. MSC-Exos are extracellular vesicles containing bioactive molecules, such as proteins, cytokines, and microRNAs, capable of modulating inflammation and promoting tissue regeneration[15,16]. Specifically, exosomes derived from hypoxia-preconditioned mesenchymal stem cells (EH-MSCs) exhibit enhanced therapeutic efficacy due to their unique molecular profile[17]. EH-MSCs have demonstrated enhanced anti-inflammatory and regenerative capacity compared to normoxic MSC-Exos, owing to the upregulation of angiogenic and immunomodulatory miRNAs such as miR-146a and miR-126[17,18]. Preliminary studies demonstrate that MSC-Exos can regulate IL-1β and IGF-1 levels, reducing inflammation and fostering hair follicle regeneration[19].

While several studies have explored MSC-Exos or adipose-derived stem cell exosomes (ADSC-Exos) for hair regeneration, most have been limited to in vitro or early-stage in vivo analyses and often lack mechanistic depth. However, no prior in vivo study has evaluated the specific efficacy of EH-MSCs in an alopecia model, particularly regarding IL-1β suppression and IGF-1 restoration. This gap underscores the need for translational evidence demonstrating the therapeutic superiority of EH-MSCs as a next-generation cell-free therapy for alopecia, as highlighted by recent studies that emphasize the promise of stem cell–derived exosomes in hair regeneration but note the scarcity of mechanistic in vivo data[20–22].

Compared with normoxic MSC-Exos, EH-MSCs exhibit a distinct molecular profile enriched in angiogenic and immunomodulatory mediators such as miR-146a, miR-126, HIF-1α, and VEGF, which enhance their anti-inflammatory and regenerative effects[17,23]. These molecular adaptations confer superior ability to modulate NF-κB and PI3K/Akt pathways, making EH-MSCs particularly effective in restoring inflammatory and growth factor balance in hair follicle regeneration[24,25].

This study aims to address this gap by investigating the effects of EH-MSCs on IL-1β and IGF-1 levels in a fluconazole-induced alopecia-like rat model. By evaluating the ability of EH-MSCs to reduce inflammation and enhance growth factor expression, this research seeks to provide a scientific basis for their application in alopecia treatment. Ultimately, the findings aim to contribute to the development of safer and more effective therapeutic approaches for alopecia, thereby improving patient outcomes and quality of life.

To the best of our knowledge, this is the first study to investigate the therapeutic effects of exosomes derived from EH-MSCs in a fluconazole-induced alopecia-like rat model. While previous studies have explored MSC-derived exosomes in hair regeneration, none have examined their effects under hypoxic conditioning within this specific pathological model. Moreover, this study is among

the first to propose that the observed anti-inflammatory and regenerative outcomes may be mediated through the miR-146a/NF-κB and miR-126/PI3K-Akt signaling pathways. By integrating these mechanistic insights with an in vivo model that mimics inflammatory alopecia, our research introduces a novel perspective on the dual modulatory potential of EH-MSCs, offering a new foundation for the development of cell-free alopecia therapies.

MATERIAL AND METHOD

Study Design

The study employed an in vivo experimental design to evaluate the effects of Exosome Hypoxia Mesenchymal Stem Cells (EH-MSCs) on IL-1β and IGF-1 levels in fluconazole-induced alopecia in Wistar rats. The design included five treatment groups as stated in Figure 1: healthy controls without intervention (G1), fluconazole-induced rats treated with NaCl 0.9% (G2), fluconazole-induced rats treated with 5% minoxidil (G3), and fluconazole-induced rats treated with EH-MSCs at doses of 100 µg/kgBW (G4) and 200 µg/kgBW (G5). Each treatment group consisted of six rats, accounting for dropouts, and experiments were conducted in triplicate.

All animals were randomly assigned to treatment groups using a simple randomization approach. Histological and ELISA analyses were performed by investigators blinded to group identity to minimize bias.

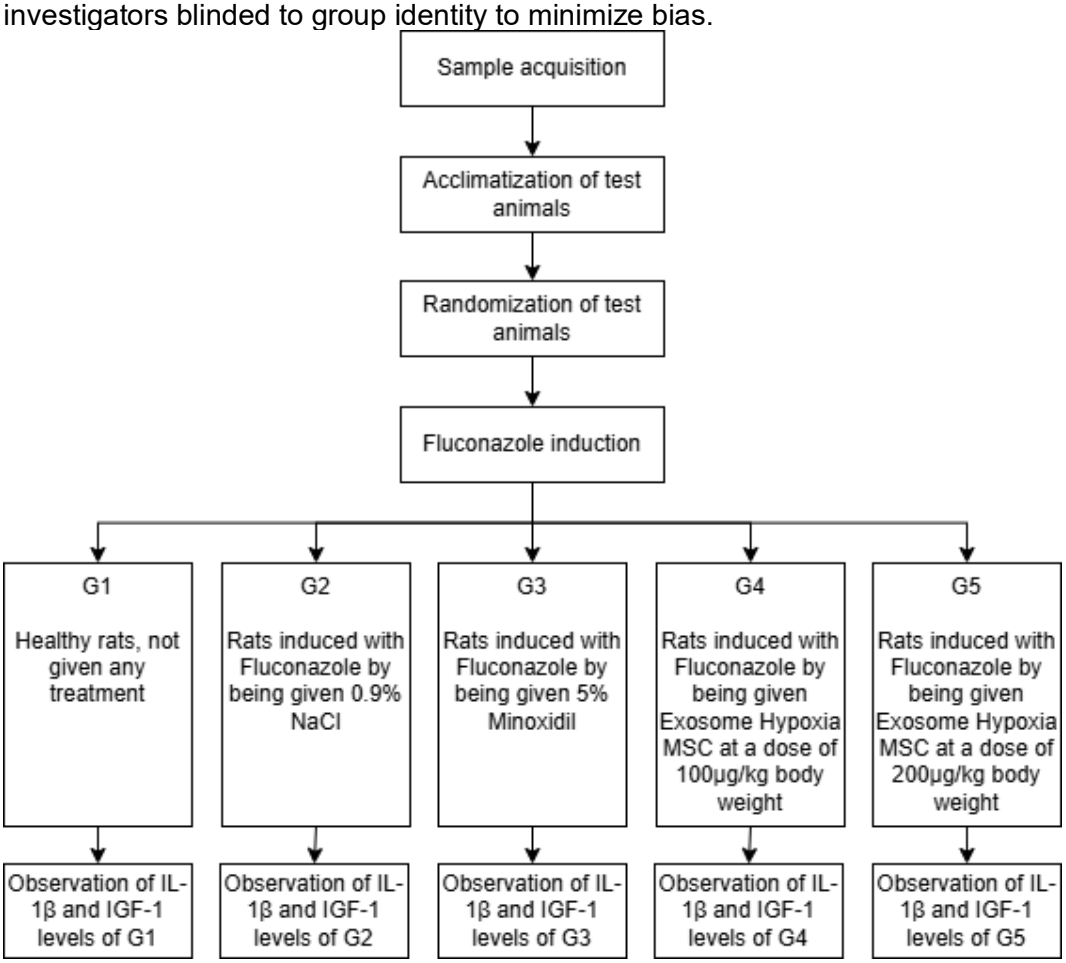

Figure 1. Experimental design of this study, involving 5 different groups.

Ethical clearance

The study was approved by the Ethics Committee of the Faculty of Medicine, Sultan Agung Islamic University, under reference number No.24/I/2025/Komisi Bioetik.

Study Location and Duration

The study was conducted at the SCCR Laboratory, Semarang, Indonesia, from October to November 2024.

Population and Samples

The study used male Wistar rats aged 6–8 weeks and weighing 200–250 grams, sourced from the SCCR Laboratory, Semarang, Indonesia. Rats were acclimatized in a controlled environment (20–28°C with adequate ventilation) for seven days, receiving food and water ad libitum. Inclusion criteria were healthy male rats with no anatomical abnormalities. Rats were excluded if they exhibited anatomical defects, prior experimental use, or illness during the study. A total of 30 rats were used to ensure sufficient statistical power.

Alopecia Induction and Treatment

The fluconazole-induced alopecia-like model was selected to reproduce drug-induced oxidative stress and inflammatory responses that mimic certain pathogenic mechanisms shared with autoimmune alopecia, such as excessive ROS generation and NF-κB activation[10,26]. Although it does not fully recapitulate autoimmune AA, this model offers a reproducible, controllable, and ethically feasible approach to evaluate inflammatory-mediated hair loss and the anti-inflammatory effects of candidate therapies. The translational limitation of this model is acknowledged; future research should extend validation to autoimmune-based alopecia models.

Fluconazole (35 mg/kgBW, 99%, Merck) was administered orally to groups G2–G5 for 14 days to induce alopecia. Hair loss was validated macroscopically by visual observation of hair thinning and patchy hair loss and microscopically using hematoxylin and eosin (HE) staining. Post-induction, the groups received subcutaneous injections: NaCl (99.5%, Merck) for negative control group (G2), minoxidil (5% topical solution, Rogaine) for positive control group (G3), EH-MSCs (100 µg/kgBW) for low-dose treatment group (G4), and EH-MSCs (200 µg/kgBW) for for high-dose treatment group (G5). The selected doses of 100 µg/kgBW and 200 µg/kgBW were based on prior in vivo reports demonstrating exosome safety and efficacy within this range for regenerative or anti-inflammatory effects[15,16]. Preliminary pilot data from our laboratory further confirmed that doses above 200 µg/kgBW did not produce additional benefits and were thus not pursued to minimize variability and ethical animal use.

EH-MSCs were administered subcutaneously on day 22. This time point was selected to align with the telogen phase of the rat hair cycle, during which follicular regeneration signals are most responsive to external stimulation[27]. Delivering EH-MSCs during telogen is intended to promote a transition back to anagen and enable effective evaluation of follicular recovery.

EH-MSCs Isolation and Validation

Mesenchymal stem cells were isolated from umbilical cords following standard protocols. After reaching 80% confluency, cells were exposed to hypoxic conditions (5% oxygen, nitrogen injection via hypoxia chamber). Exosome isolation was performed using the TFF system, and the resulting exosomes were validated by flow cytometry for CD81, CD63, and CD9 markers. All procedures were conducted in a sterile biosafety level 2 environment.

Sample Collection

Skin tissue samples were collected on day 29 under aseptic conditions. Samples (~5 mg) were snap-frozen in liquid nitrogen and stored at -80°C. Homogenization was performed in RIPA buffer supplemented with protease inhibitors at 4°C. Supernatants were obtained by centrifugation at 13,000 rpm for 20 minutes.

Biochemical Analysis

IL-1β and IGF-1 levels in tissue supernatants were quantified using ELISA kits. Each sample was analyzed in duplicate, with absorbance measured at 450

nm using a spectrophotometer (Shimadzu UV-1900). Calibration curves were generated for both analytes to ensure precision.

Data Analysis

Data normality and homogeneity were assessed using the Shapiro–Wilk and Levene's tests, respectively. When both assumptions were satisfied, one-way ANOVA followed by LSD post hoc tests was used to determine between-group differences. When the data were normally distributed but did not meet the homogeneity assumption, one-way ANOVA with Tamhane's post hoc test was applied. Statistical significance was set at $p < 0.05$. All analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS AND DISCUSSION

Results

The isolated MSCs exhibited fibroblast-like morphology and adhered to flask surfaces (Figure 2A), a hallmark of mesenchymal stem cells. Flow cytometry confirmed the presence of MSC-specific markers CD90 (99.5%) and CD29 (96.1%) and low expression of hematopoietic markers CD45 (1.3%) and CD31 (6.6%) (Figure 2B). Differentiation assays validated their multipotency as they differentiated into osteocytes and adipocytes (Figure 3). Hypoxic preconditioning and exosome isolation yielded a concentration of 0.74 µg/mL, verified using CD63 and CD9 markers (Figure 4).

Fluconazole-induced alopecia was validated both macroscopically and microscopically (Figure 5 and 6). Rats in the fluconazole-only group exhibited visibly reduced hair coverage compared to healthy controls, confirming successful alopecia-like induction. Microscopic analysis revealed a predominance of telogen-phase follicles in fluconazole-treated groups.

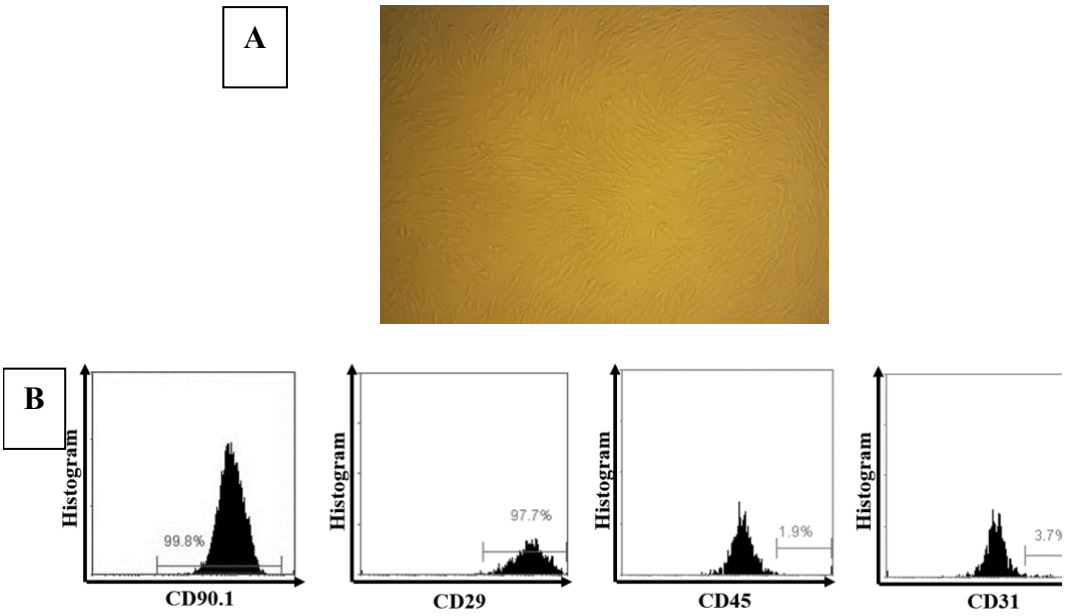

Figure 2. Characterization of MSCs.
Note: *(A) MSCs show fibroblast-like morphology at 100× magnification. (B) Flow cytometry confirms expression of MSC markers CD90 and CD29, with minimal CD45 and CD31 expression.*

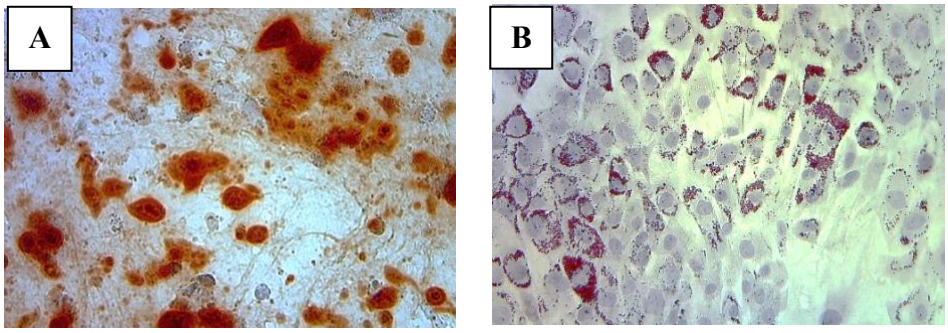

Figure 3. Multipotent differentiation capacity of MSCs.
Note: *(A) Osteogenic differentiation visualized by Alizarin Red staining. (B) Adipogenic differentiation identified by Oil Red O staining.*

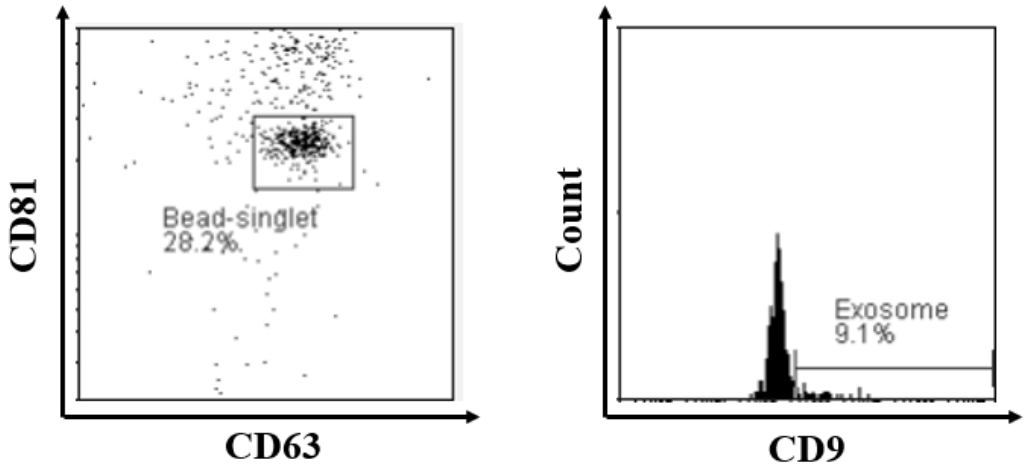

Figure 4. Validation of EH-MSC-derived exosomes.
Note: *Flow cytometry analysis confirms exosome marker expression (CD63 and CD9).*

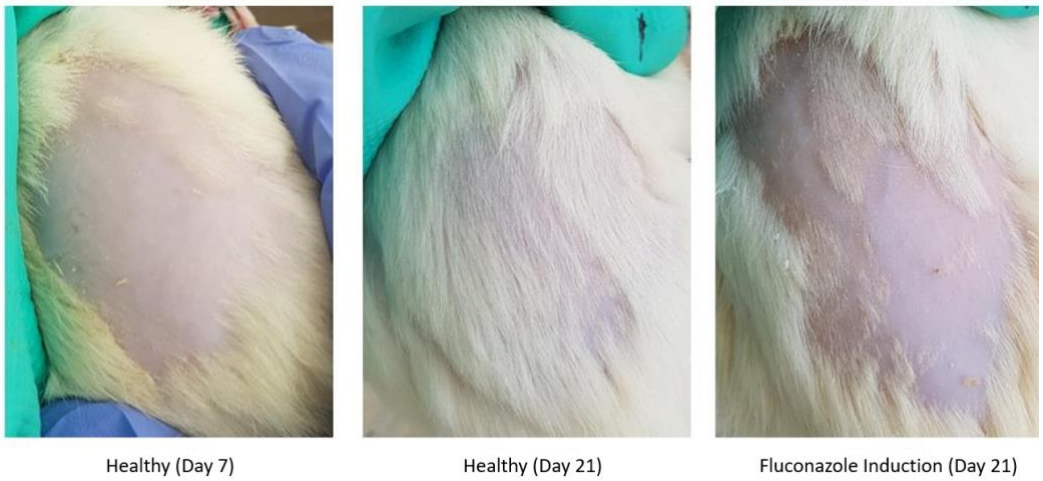

Figure 5. Macroscopic validation of alopecia induction.
Note: *Fluconazole-treated rats exhibit reduced hair coverage compared to healthy controls.*

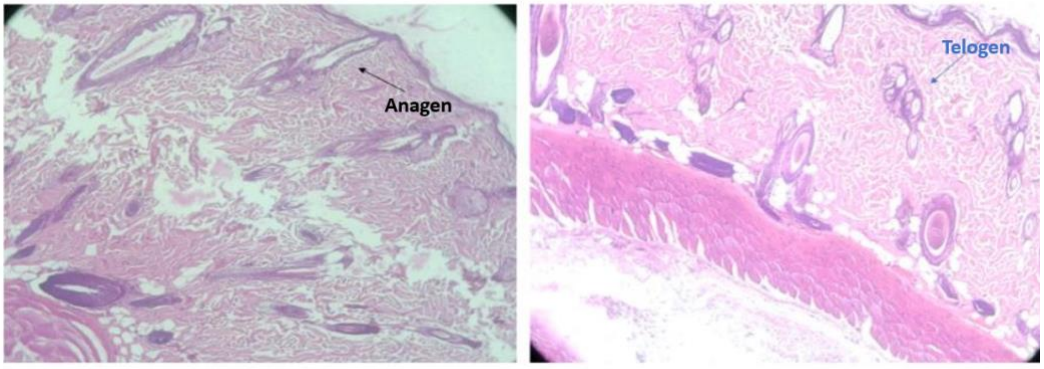

Figure 6. Microscopic observation of skin sections (HE staining).
Note: *Fluconazole-treated rats show telogen-dominant follicles, whereas EH-MSC-treated rats exhibit restoration toward anagen phase.*

Table 1. Mean expression and statistical tests of IL-1β and IGF-1 levels across groups.

Expression/ statistical test	Healthy (G1)	Negative control/ 0.9% NaCl (G2)	Positive control/ 5% Minoxidil (G3)	100 µg/kgBW EH-MSCs (G4)	200 µg/kgBW EH-MSCs (G5)	
IL-1β (pg/mL)	277.70 ± 10.13	1157.20 ± 109.72	799.10 ± 95.07	450.47 ± 32.91	271.90 ± 11.87	
Shapiro wilk (p)	0.165†	0.652†	0.714†	0.964†	0.635†	
Lavene test (p)						0.003
Oneway ANOVA (p)						<0.001*
Post hoc Tamhane's T2 (p)						
Healthy (G1)		<0.001*	<0.001*	<0.001*	0.992	
0.9% NaCl (G2)	<0.001*		0.001*	<0.001*	<0.001*	
5% Minoxidil (G3)	<0.001*	0.001*		0.001*	<0.001*	
100 µg/kgBW EH-MSCs (G4)	<0.001*	<0.001*	0.001*		<0.001*	
IGF-1 (pg/mL)	32.97 ± 6.91	17.19 ± 1.90	23.25 ± 1.25	27.91 ± 0.31	31.04 ± 1.58	
Shapiro wilk (p)	0.325†	0.100†	0.370†	0.550†	0.765†	
Lavene test (p)						<0.001
Oneway ANOVA (p)						<0.001*
Post hoc Tamhane's T2 (p)						
Healthy (G1)		0.019*	0.162	0.759	0.999	
0.9% NaCl (G2)	0.019*		0.001*	<0.001*	<0.001*	
5% Minoxidil (G3)	0.162	0.001*		0.002*	<0.001*	
100 µg/kgBW EH-MSCs (G4)	0.759	<0.001*	0.002*		*0.041	

Note:
† Normal (p>0.05)
‡ Homogenous (p>0.05)
* Significant difference (p < 0.05)

EH-MSC treatment significantly reduced IL-1β levels compared to the negative control group (G2) ($p < 0.05$), with the high-dose treatment group (G5) showing values not significantly different from the healthy control group (G1, $p = 0.992$) (Table 1, Figure 7A). The low-dose treatment group (G4) also differed

significantly from all other groups ($p < 0.05$). For IGF-1, both EH-MSC-treated groups (G4 and G5) showed significantly higher levels than the negative and positive control groups (G2 and G3) ($p < 0.05$) (Table 1, Figure 7B). Moreover, IGF-1 levels in the low- and high-dose groups did not differ significantly from the healthy control (G1 vs G4, $p = 0.759$; G1 vs G5, $p = 0.999$), indicating that EH-MSC administration restored IGF-1 expression to near-normal values.

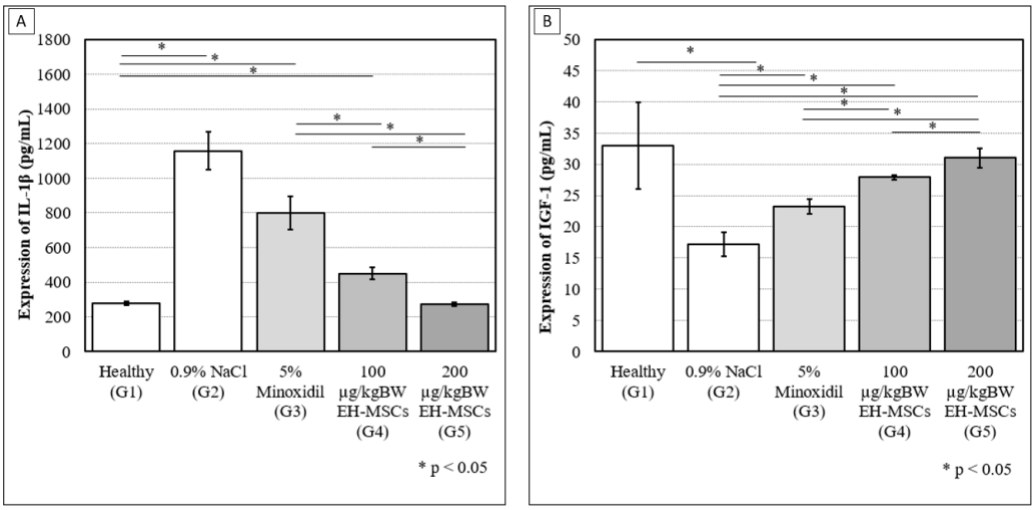

Figure 7. Expression of IL-1β and IGF-1 in different treatment groups.
Note: *(A) IL-1β expression was significantly decreased in the high-dose treatment group (G5) compared to negative control group (G2). (B) Conversely, IGF-1 expression was significantly increased in the high-dose treatment group (G5) compared to negative control group (G2). Bars represent mean ± SD; * indicates significant difference between groups (*p < 0.05).*

Discusssion

Rats in the fluconazole-only group exhibited significantly reduced hair density, while healthy controls showed normal regrowth. Microscopic analysis revealed a dominance of telogen-phase follicles in the fluconazole-treated groups, consistent with fluconazole-induced oxidative stress and inflammatory responses[26]. The reduction in hair density correlates with increased ROS levels and NF-κB activation[7,28]. This model successfully replicates key aspects of alopecia, providing a robust and reproducible platform for evaluating therapeutic interventions.

The findings confirm that EH-MSCs possess characteristics that enhance their therapeutic potential under hypoxic conditions. Dong et al. (2023) similarly demonstrated that hypoxic preconditioning enhances the regenerative potential of MSC-derived exosomes, underscoring their importance in inflammatory and regenerative therapies[17]. In the present study, the observed decrease in IL-1β and increase in IGF-1 suggest that EH-MSCs can both attenuate inflammation and promote follicular regeneration. These effects are consistent with, though not direct evidence of, the actions of miR-146a and miR-126, which have been previously reported to modulate NF-κB and PI3K/Akt pathways in similar experimental systems[18,29,30]. Therefore, the mechanistic explanations discussed here should be interpreted as inferences supported by prior literature, not as experimentally confirmed findings in this study.

The suppression of IL-1β aligns with the recognized anti-inflammatory potential of exosomal components capable of inhibiting NF-κB signaling, thereby reducing cytokine production and follicular injury[18,31]. Lower IL-1β concentrations may indirectly facilitate IGF-1 recovery by mitigating inflammatory stress on dermal papilla cells, which are critical for maintaining anagen phase homeostasis. This inverse relationship between inflammation and growth factor regulation suggests

that controlling cytokine imbalance could restore the regenerative microenvironment necessary for hair growth. Conversely, the increase in IGF-1 following EH-MSC treatment indicates enhanced anabolic signaling that supports follicular proliferation and differentiation. IGF-1 not only extends the anagen phase but also counteracts apoptosis, allowing effective regeneration. Conversely, the increase in IGF-1 following EH-MSC treatment indicates enhanced anabolic signaling that supports follicular proliferation and differentiation. IGF-1 not only extends the anagen phase but also counteracts apoptosis, allowing effective regeneration[13,23,27,30].

This study highlights the dual role of EH-MSCs in suppressing inflammation and promoting regeneration, offering a promising mechanism for therapeutic application. By concurrently addressing IL-1β and IGF-1 dysregulation, EH-MSCs provide a comprehensive approach to treating both the inflammatory and degenerative aspects of alopecia. While minoxidil primarily improves hair regrowth through vasodilation and enhanced follicular microcirculation[32], the findings of this study suggest that hypoxia-conditioned MSC-derived exosomes act upstream by modulating key inflammatory mediators such as IL-1β and promoting growth factor signals such as IGF-1. This broader mechanism is consistent with recent studies reporting the dual anti-inflammatory and regenerative effects of MSC-derived exosomes in hair follicle regeneration[14,33]. Compared to ADSC-Exos, which primarily activate Wnt/β-catenin signaling, hypoxia-conditioned EH-MSCs may provide broader anti-inflammatory and pro-angiogenic benefits[17,19]. The proposed mechanism underlying the dual anti-inflammatory and regenerative effects of EH-MSCs is summarized in Figure 8.

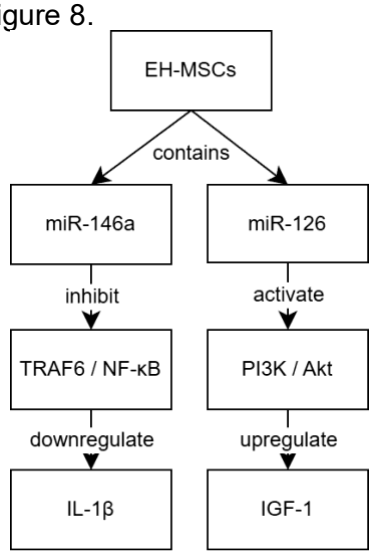

Figure 8. Proposed mechanism of EH-MSC-derived exosomes in hair follicle regeneration.

From a translational perspective, the application of EH-MSC-derived exosomes faces several challenges. Large-scale Good Manufacturing Practice (GMP) production requires standardized isolation and purification methods that preserve exosome bioactivity. In addition, exosome stability during storage and transport remains a major limitation, as prolonged freezing or repeated thawing may alter vesicle integrity and reduce therapeutic efficacy. Future research should explore optimized cryopreservation protocols and delivery systems (e.g., hydrogel or nanocarrier formulations) to enhance exosome stability and bioavailability. These considerations are crucial for clinical translation, especially for topical or injectable alopecia therapies.

This study has several limitations. First, it employed a fluconazole-induced model that mimics drug-related inflammatory alopecia rather than autoimmune alopecia areata, which may limit generalizability. Second, the specific miRNA cargo (such as miR-146a and miR-126) was not directly profiled; thus, mechanistic

interpretations are based on inference rather than direct evidence. Third, only two EH-MSC doses were tested, limiting dose–response assessment. Fourth, quantitative histological analysis (e.g., follicle count or anagen/telogen ratios) was not performed, restricting tissue-level interpretation. Fifth, long-term follow-up was not included, so sustained regenerative effects remain uncertain.

To address these limitations, future studies should perform miRNA sequencing or qPCR validation to confirm signaling pathway involvement, coupled with Western blot analysis to verify downstream protein targets such as TRAF6, IRAK1, DLK1, and p-Akt. Longer-term studies using autoimmune or androgenic alopecia models, as well as quantitative morphometric analyses, will further clarify the therapeutic durability and mechanism of EH-MSC exosomes.

CONCLUSION

This study is among the first to demonstrate that EH-MSCs effectively suppress IL-1β levels and increase IGF-1 expression in a fluconazole-induced alopecia-like rat model. These findings suggest that EH-MSCs reduce inflammation and promote hair follicle regeneration through the inhibition of NF-κB signaling and the activation of the PI3K/Akt pathway. The results also indicate that EH-MSCs, particularly at a dose of 200 µg/kgBW, have comparable therapeutic effects to healthy control conditions, offering a promising alternative to conventional treatments such as minoxidil.

Future research should explore the profiling of exosomal miRNAs and their specific roles in modulating inflammatory and regenerative pathways to strengthen the understanding of EH-MSC mechanisms. Additionally, testing EH-MSCs in more complex models, including autoimmune alopecia or clinical trials, will be essential to evaluate their broader therapeutic potential and establish optimal dosing protocols for clinical applications.

AUTHORS' CONTRIBUTIONS

Evan Christian Sumarno: Conceptualization, Methodology, Software, Data curation, Writing- Original draft preparation, Visualization **Sri Priyantini Mulyani**: Supervision, Validation, Writing- Reviewing and Editing **Chodijah**: Supervision, Validation, Writing- Reviewing and Editing **Eko Setiawan**: Supervision, Validation, Writing- Reviewing and Editing

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DATA AVAILABILITY STATEMENT

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

DISCLOSURE STATEMENT

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

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