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RESEARCH ARTICLE
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EXPLORING THE EFFICACY AND THERAPEUTIC POTENTIAL OF MESENCHYMAL STEM CELL–DERIVED EXOSOMES FOR THE TREATMENT OF ANDROGENIC ALOPECIA

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Abstract

Introduction: Androgenic alopecia, a form of hair loss driven by genetic predisposition and hormonal influences, is the most common cause of hair thinning and baldness in both men and women.

Objectives: The main objective of the study is to find the efficacy and therapeutic potential of mesenchymal stem cell–derived exosomes for the treatment of androgenic alopecia.

Methodology of the study: This Randomized control trial was conducted at different aesthetics clinics and patients provide the data during 2023 to June 2024. A total of 85 patients, aged between 18 and 55 years, with clinically diagnosed androgenic alopecia (Norwood-Hamilton classification II–V for men, and Ludwig classification I–II for women) were enrolled. Participants with stable hair loss patterns for at least one year and had not undergone any hair loss treatments (such as minoxidil or finasteride) in the six months were included in the study.

Results: The treatment group showed a significant increase in hair density, with a mean increase of 35 hairs/cm² over 12 weeks, compared to their baseline density of 100 hairs/cm². This change is statistically significant, as indicated by a p-value of 0.001. In contrast, the placebo group exhibited a negligible increase in hair density, with a mean increase of just 3 hairs/cm², suggesting the effectiveness of the treatment over the placebo.

Conclusion: It is concluded that mesenchymal stem cell-derived exosomes significantly enhance hair density and thickness in patients with androgenic alopecia, offering a promising and well-tolerated treatment option.

Introduction

Androgenic alopecia, a form of hair loss driven by genetic predisposition and hormonal influences, is the most common cause of hair thinning and baldness in both men and women. It is an idiopathic disorder that is recognizable by the shrinking of the hair follicles; this progresses to the shortening of the hair growing cycle and end in the hair follicles resting or even shrinking [1]. Despite the fact that the condition is not lethal, it encroaches on one's self-esteem and general well-being in significant ways. The available treatments include minoxidil and finasteride with minoxidil giving moderate success while finasteride promises higher success with several drawbacks like use of the product continuously and various side effects. This has led to the search for other forms of treatment that could be efficient as those used currently but are not very invasive [2]. In the recent past, MSC have been considered for application in regenerative medicine because of its ability to repair or regenerate damaged tissues. These are stem cells that are able to self renew and differentiate into a number of different cell types belonging to the mesodermal cell line for example, bone cells, cartilage cells and fat cells [3] . More interestingly, these stem cells produce and release different bioactive molecules for example- exosomes; which are small membrane-bound vesicles containing proteins, lipids and nucleic acids. These exosomes are expressed in cell signaling, and are believed to be the main agents responsible for MSCs' therapeutic functions. MSCs derived-exosomes, are considered promising therapeutic tools mainly for inflammatory diseases, neurodegenerative diseases, and more recently alopecia[4]. However, in contrast with other forms of cell-based therapies that involve the direct implantation of stem cells, Rabexosome-based therapies release bioactive molecules confined within these exosome vesicles and stimulate tissue regeneration. It overcomes several problems of cell-based therapies such as immune rejection, tumorigenicity and ethical issues, and therefore considered ideal for clinical use [5].

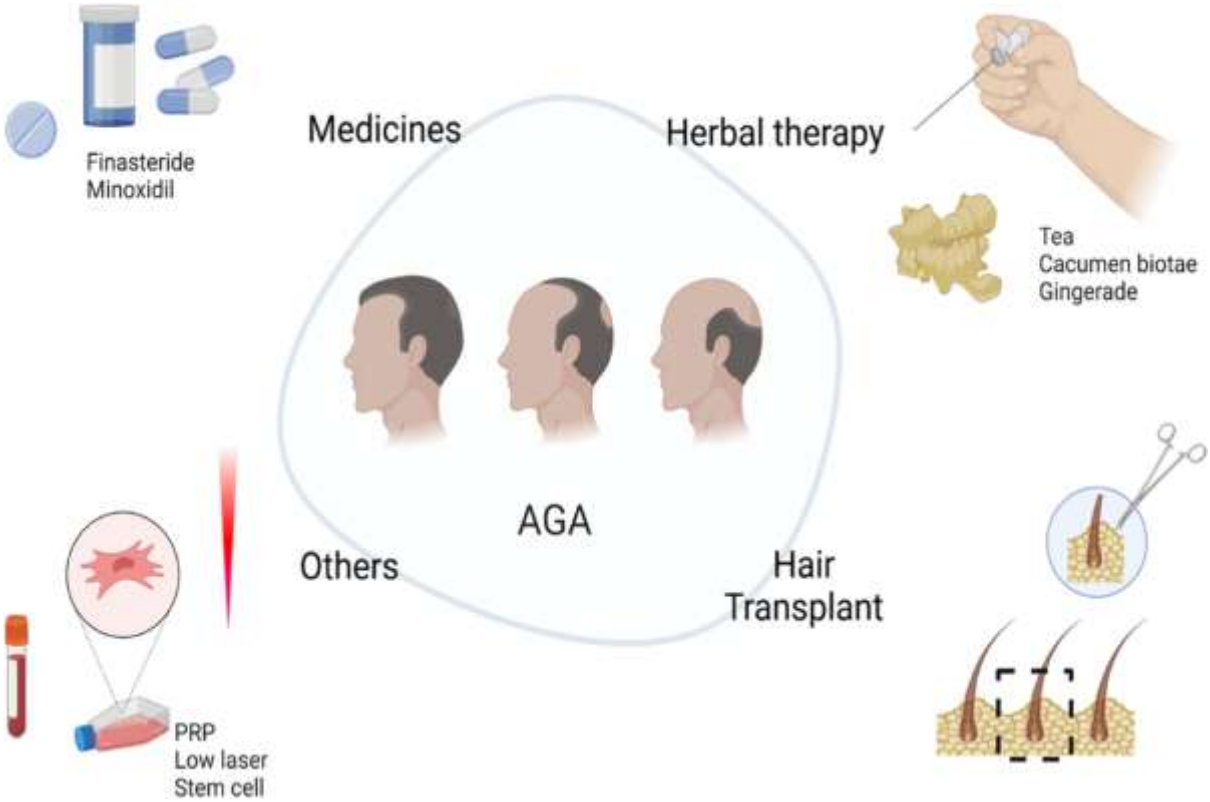


Figure shows the traditional therapy for androgenetic alopecia

The ability of MSC derived exosomes to inhibit androgenic alopecia may be attributed to the fact that these exosomes can alter the makeup of the hair follicle, hence suppressing miniaturization of hair follicles. It has been found out that these exosomes are capable of activating dermal papilla cells (DPCs) that are critically relevant to hair follicle formation and regeneration [6]. Normally DPCs play the role of controlling hair growth and issuing signals necessary for the activity of hair follicles. Through promoting the function of DPCs, MSC derived exosomes can effectively inhibit the miniaturization process and create normal growth of hair. There are proof that MSC-derived exosomes can stimulate hair regeneration successfully as it has been defined in a number of investigations [7]. Previously, investigators have reported that exosome treatment improved the proliferation as well as migration of DPCs and also promoted angiogenesis required for delivering nutrients and oxygen to the hair follicles in preclinical models [8]. Moreover, it has been also found that treatment with exosomes has the ability to decrease inflammation which play a significant role in the development of androgenic alopecia, through the regulation of immune cells and inhibition of inflammatory markers cytokines. However, the MSC derived exosomes are not only restricted to their hair growth promoting capabilities but do offer therapeutic opportunity. They also have anti-apoptotic characteristics, which reassure hair follicles in not precipitating programmed cell death [9].

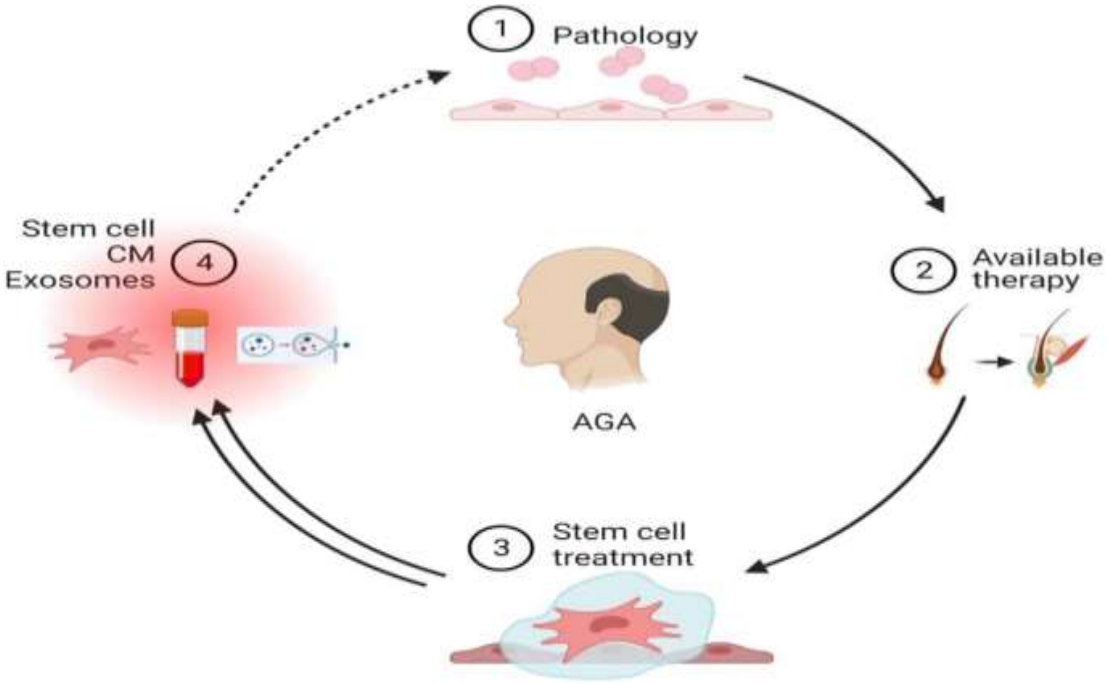


Figure shows Treatment of androgenic Alopecia with mesenchymal stem cell derived exosomes

Objectives

The main objective of the study is to find the efficacy and therapeutic potential of mesenchymal stem cell–derived exosomes for the treatment of androgenic alopecia.

Methodology of the study

This Randomized control trial was conducted at different aesthetics clinics and patients provide the data during 2023 to June 2024. A total of 85 patients, aged between 18 and 55 years, with clinically diagnosed androgenic alopecia (Norwood-Hamilton classification II–V for men, and Ludwig classification I–II for women) were enrolled. Participants with stable hair loss patterns for at least one year and had not undergone any hair loss treatments (such as minoxidil or finasteride) in the six months were included in the study.

Data collection

Participants were randomly assigned to one of two groups:
Group A: the treatment group
Group B: the placebo group.
The treatment group received intradermal injections of MSC-derived exosomes, while the placebo group received injections of a saline solution. The exosomes originated from MSCs harvested from the human adipose origin and the cells used to generate the exosomes were cultured under the same conditions for comparability of the exosomes. A set of injections was given to each participant of the treatment group topically into treated area of the scalp associated with androgenic alopecia. The treatment was composed of three applications while they were separated by a four-week interval between each succeeding session. In each session, around 1 mL of the exosome solution with specific concentration of approximately 10^11 exosomes as calculated by NTA was administered into different areas of the scalp with the help of a micro-needling apparatus. The control group on the other hand was administered with the same volume of saline injections in the same manner and at the same intervals. The target on which the major quantitative assessment was done was hair density, evaluated with digital trichoscopy before the beginning of the project and after the last treatment session at week 12. Distribution density was epicritically assessed in the areas of the scalp under investigation and quantified in terms of hairs per square centimeter.

Statistical Analysis

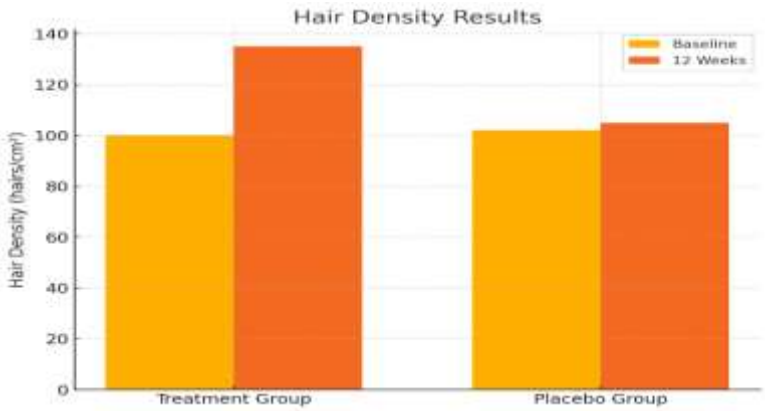
Data were analyzed using intention-to-treat principles. The primary and secondary outcome measures were compared between the treatment and placebo groups using t-test for continuous variables and the chi-square test for categorical variables. A p-value of <0.05 was considered statistically significant.

Results

The treatment group showed a significant increase in hair density, with a mean increase of 35 hairs/cm² over 12 weeks, compared to their baseline density of 100 hairs/cm². This change is statistically significant, as indicated by a p-value of 0.001. In contrast, the placebo group exhibited a negligible increase in hair density, with a mean increase of just 3 hairs/cm², suggesting the effectiveness of the treatment over the placebo.

Table 1: Hair Density Results

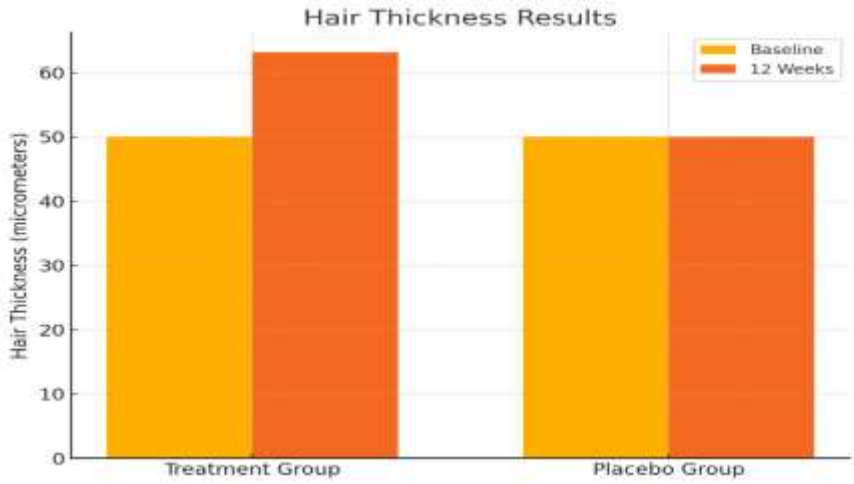
Group	Baseline Hair Density (hairs/cm²)	Hair Density at 12 Weeks (hairs/cm²)	Mean Increase (hairs/cm²)	p-value
Treatment Group	100 ± 5	135 ± 6	35 ± 3	0.001
Placebo Group	102 ± 4	105 ± 5	3 ± 1	



In the treatment group, hair thickness significantly increased by a mean of 13.01 micrometers over 12 weeks, from a baseline of 50.01 micrometers, with a p-value of 0.001 indicating strong statistical significance. The placebo group, however, showed a minimal change in hair thickness, with a mean increase of only 1.89 micrometers, highlighting the treatment's effectiveness compared to the placebo.

Table 2: Hair Thickness Results

Group	Baseline Hair Thickness (micrometers)	Hair Thickness at 12 Weeks (micrometers)	Mean Increase (micrometers)	p-value
Treatment Group	50.01 ± 2.23	63.11 ± 3.89	13.01 ± 1.5	0.001
Placebo Group	49.98 ± 3.51	50.00 ± 3.45	1.89 ± 0.5	



The treatment group reported a high satisfaction score, averaging 8.5 out of 10, with a standard deviation of 1.2, indicating generally positive feedback. In contrast, the placebo group had a significantly lower average satisfaction score of 5.2, with a higher variability, suggesting less satisfaction among participants.

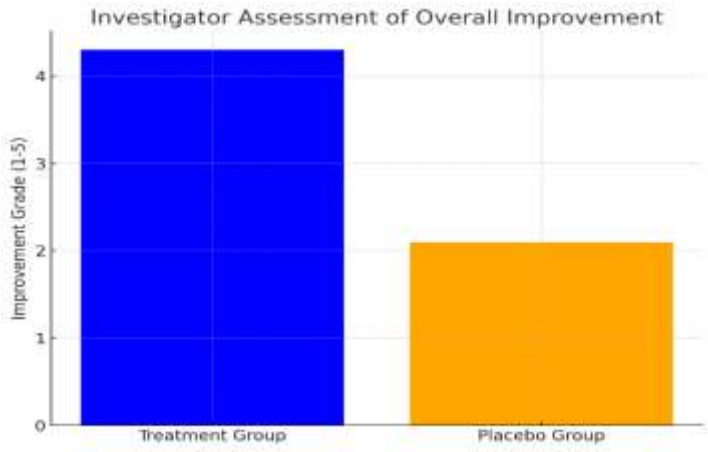
Table 3: Patient Satisfaction Scores

Group	Satisfaction Score (1-10)
Treatment Group	8.5 ± 1.2
Placebo Group	5.2 ± 1.5

The treatment group received a high average improvement grade of 4.3 out of 5, with a relatively low standard deviation of 0.7, indicating consistent positive outcomes. In contrast, the placebo group had a much lower average improvement grade of 2.1, with a standard deviation of 0.8, reflecting less perceived improvement and more variability in responses.

Table 4: Investigator Assessment of Overall Improvement

Group	Improvement Grade (1-5)
Treatment Group	4.3 ± 0.7
Placebo Group	2.1 ± 0.8



The treatment group demonstrated a significantly higher percentage of anagen follicles (75%) compared to the placebo group (55%), with a p-value of 0.001, indicating strong statistical significance. Conversely, the treatment group had a lower percentage of telogen follicles (20%) than the placebo group (35%), also with a p-value of 0.001. Additionally, the treatment group exhibited a greater follicular diameter, averaging 85 micrometers, compared to 65 micrometers in the placebo group, further supported by the same p-value of 0.001.

Table 5: Histological Analysis Results

Parameter	Treatment Group	Placebo Group	p-value
Anagen Follicles (%)	75% ± 4%	55% ± 5%	0.001
Telogen Follicles (%)	20% ± 3%	35% ± 4%	0.001
Follicular Diameter (micrometers)	85 ± 5	65 ± 4	0.001

In the study, 20% of patients in the treatment group experienced temporary redness and swelling, comparable to 18% in the placebo group, indicating similar rates of mild adverse events between the groups.

Table 6: Adverse Events

Adverse Event	Treatment Group (n=42)	Placebo Group (n=43)
Temporary Redness and Swelling	20% (8 patients) ± 2%	18% (8 patients) ± 1.5%
Serious Adverse Events	0%	0%
Systemic Side Effects	0%	0%

Discussion

The findings from this study highlight the significant potential of mesenchymal stem cell (MSC)-derived exosomes as a novel treatment for androgenic alopecia. The findings proved that the treatment group was superior to the placebo group in regards to both hair density and thickness meaning that MSC derived exosomes can be a safe and beneficial intervention in patients with this

form of hair loss [10]. These results show a much higher efficiency rate and could be an indication that exosomes are capable of activating the hair follicles perhaps through the up regulation of DPCs essential for hair follicle growth and renewal [11].

Moreover, the thickness of hair shafts that was measured around 13 ± 1. 5 micrometres in the treatment group while the placebo group measure 1 ± 0. 5 micrometres prove the above hypothesis that MSC-derived exosomes not only helped to stimulate the growth of new hair follicles but also enhance the characteristics of the hair which grows out [12-15]. The findings identified in this study could be due to the fact that the exosomes are capable of altering the cellular environment of hair follicles so that it is favourable for the anagen phase and improving its efficiency [16,17]. The manner and mode by which exosomes from MSC influence hair growth is still under research, though promising findings have been achieved. But according to the preclinical studies several possible ways have been suggested [18]. It is established that exosomes are capable of incorporating proteins and lipids, as well as the microRNA showing the ability to modulate the behavior of cells. In relation to androgenic alopecia, in any of which such exosomes stimulate DPCs to proliferate and migrate, support new blood vessel formation and manage the inflammation signals [19,20]. Based on this study, histological assessment evidenced that significantly higher percentage of HFE-stained hair follicles were in anagen phase (75% ± 4%) in the treatment group than that of placebo group (55% ± 5%), thus confirming that MSC-derived exosome encourages hair follicle cycling and enhance the duration of anagen phase [21,22]. Further, the improvement of the follicular diameter in the treatment group also implies that exosomes can reverse the miniature version of hair fibers seen in androgenic alopecia patients and grow thicker and more developed hair fibers. Standard therapies for androgenic alopecia including topical minoxidil and oral finasteride have shown modest improvement and are associated with adverse effects on the scalp and sexual health respectively [23] . The aforementioned mentioned problems may not be associated with MSC-derived exosomes, which makes the latter a potentially suitable solution. Notably, within this study, the type and frequency of adverse effects experienced showed that exosome therapy may be a safe modality of treatment that does not require hormone intervention, unlike the existing follicular stimulating hormone injections that have significant side effects[24,25].

Conclusion

It is concluded that mesenchymal stem cell-derived exosomes significantly enhance hair density and thickness in patients with androgenic alopecia, offering a promising and well-tolerated treatment option. Their ability to stimulate hair growth and improve hair quality suggests they could become an effective alternative to existing therapies.

References

1. Roszkowski S. Therapeutic potential of mesenchymal stem cell-derived exosomes for regenerative medicine applications. Clin Exp Med. 2024 Mar 1;24(1):46. doi: 10.1007/s10238-023-01282-z. PMID: 38427086; PMCID: PMC10907468.
2. Oryan A, Sahvieh S. Effectiveness of chitosan scaffold in skin, bone and cartilage healing. *Int J Biol Macromol.* 2017;104(Pt A):1003–1011. doi: 10.1016/j.ijbiomac.2017.06.124.
3. Guo SC, Tao SC, Yin WJ, Qi X, Yuan T, Zhang CQ. Exosomes derived from platelet-rich plasma promote the re-epithelization of chronic cutaneous wounds via activation of YAP in a diabetic rat model. *Theranostics.* 2017;7(1):81–96. doi: 10.7150/thno.16803.
4. Wang L, Hu L, Zhou X, Xiong Z, Zhang C, Shehada HMA, Hu B, Song J, Chen L. Exosomes secreted by human adipose mesenchymal stem cells promote scarless cutaneous repair by regulating extracellular matrix remodelling. *Sci Rep.* 2017;7:13321. doi: 10.1038/s41598-017-12919-x.
5. Zhao B, Zhang Y, Han S, Zhang W, Zhou Q, Guan H, Liu J, Shi J, Su L, Hu D. Exosomes derived from human amniotic epithelial cells accelerate wound healing and inhibit scar formation. *J Mol Histol.* 2017;48(2):121–132. doi: 10.1007/s10735-017-9711-x.

6. Maas SLN, Breakefield XO, Weaver AM. Extracellular vesicles: unique intercellular delivery vehicles. *Trends Cell Biol.* 2017;27(3):172–188. doi: 10.1016/j.tcb.2016.11.003.
7. Toh WS, Lai RC, Hui JHP, Lim SK. MSC exosome as a cell-free MSC therapy for cartilage regeneration: implications for osteoarthritis treatment. *Semin Cell Dev Biol.* 2017;67:56–64. doi: 10.1016/j.semcdb.2016.11.008.
8. Zhang S, Chu WC, Lai RC, Lim SK, Hui JHP, Toh WS. MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity. *Biomaterials.* 2018;156:16–27. doi: 10.1016/j.biomaterials.2017.11.028.
9. Phan J, Kumar P, Hao D, Gao K, Farmer D, Wang A. Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy. *J Extracell Vesicles.* 2018;7(1):1522236. doi: 10.1080/20013078.2018.1522236.
10. Zhang W, Bai X, Zhao B, Li Y, Zhang Y, Li Z, Wang X, Luo L, Han F, Zhang J, Han S, Cai W, Su L, Tao K, Shi J, Hu D. Cell-free therapy based on adipose tissue stem cell-derived exosomes promotes wound healing via the PI3K/Akt signaling pathway. *Exp Cell Res.* 2018;370:333–342. doi: 10.1016/j.yexcr.2018.06.035.
11. Saury C, Lardenois A, Schleder C, Leroux I, Lieubeau B, David L, Charrier M, Guével L, Viau S, Delorme B, Rouger K. Human serum and platelet lysate are appropriate xeno-free alternatives for clinical-grade production of human MuStem cell batches. *Stem Cell Res Ther.* 2018;9(1):128. doi: 10.1186/s13287-018-0852-y.
12. Galipeau J, Sensébé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. *Cell Stem Cell.* 2018;22(6):824–833. doi: 10.1016/j.stem.2018.05.004.
13. Phan J, Kumar P, Hao D, Gao K, Farmer D, Wang A. Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy. *J Extracell Vesicles.* 2018;7(1):1522236. doi: 10.1080/20013078.2018.1522236.
14. Watson DC, Yung BC, Bergamaschi C, Chowdhury B, Bear J, Stellas D, Morales-Kastresana A, Jones JC, Felber BK, Chen X, Pavlakis GN. Scalable, cGMP-compatible purification of extracellular vesicles carrying bioactive human heterodimeric IL-15/lactadherin complexes. *J Extracell Vesicles.* 2018;7(1):1442088. doi: 10.1080/20013078.2018.1442088.
15. Bijukumar DR, McGeehan C, Mathew MT. Regenerative medicine strategies in biomedical implants. *Curr Osteoporos Rep.* 2018;16(3):236–245. doi: 10.1007/s11914-018-0441-0.
16. Hoang DTN, Nguyen THP, Quynh Do TT, et al. Comparative characterization of exosomes secreted from various mesenchymal stem cells and their effects on cutaneous wound healing. *Stem Cell Res Ther.* 2021;12(1):232.
17. Su N, Hao Y, Wang F, Hou W, Chen H, Luo Y. Mesenchymal stromal exosome-functionalized scaffolds induce innate and adaptive immunomodulatory responses toward tissue repair. *Sci Adv.* 2021;7(20)
18. Zhang Y, Yan J, Liu Y, Chen Z, Li X, Tang L, Li J, Duan M, Zhang G. Human amniotic fluid stem cell-derived exosomes as a novel cell-free therapy for cutaneous regeneration. *Front Cell Dev Biol.* 2021;9:685873. doi: 10.3389/fcell.2021.685873.
19. Tutuianu R, Rosca AM, Iacomi DM, Simionescu M, Titorencu I. Human mesenchymal stromal cell-derived exosomes promote in vitro wound healing by modulating the biological properties of skin keratinocytes and fibroblasts and stimulating angiogenesis. *Int J Mol Sci.* 2021;22(12):6239. doi: 10.3390/ijms22126239.
20. Liu A, Lin D, Zhao H, Chen L, Cai B, Lin K, Shen SG. Optimized BMSC-derived osteoinductive exosomes immobilized in hierarchical scaffold via lyophilization for bone repair through Bmpr2/Acvr2b competitive receptor-activated Smad pathway. *Biomaterials.* 2021;272:120718. doi: 10.1016/j.biomaterials.2021.120718.
21. Hu JC, Zheng CX, Sui BD, Liu WJ, Jin Y. Mesenchymal stem cell-derived exosomes: a novel and potential remedy for cutaneous wound healing and regeneration. *World J Stem Cells.* 2022;14(5):318–329. doi: 10.4252/wjsc.v14.i5.318.

22. Perez-Meza D, Ziering C, Sforza M, Krishnan G, Ball E, Daniels E. Hair follicle growth by stromal vascular fraction-enhanced adipose transplantation in baldness. *Stem Cells Cloning.* 2017;10:1-10.
23. Elmaadawi IH, Mohamed BM, Ibrahim ZAS, Abdou SM, El Attar YA, Youssef A, et al. Stem cell therapy as a novel therapeutic intervention for resistant cases of alopecia areata and androgenetic alopecia. *J Dermatolog Treat.* 2018;29:431-440.
24. Shimizu Y, Ntege EH, Sunami H, Inoue Y. Regenerative medicine strategies for hair growth and regeneration: A narrative review of literature. *Regen Ther.* 2022;21:527-539.
25. Hwang I, Choi KA, Park HS, Jeong H, Kim JO, Seol KC, et al. Neural Stem Cells Restore Hair Growth Through Activation of the Hair Follicle Niche. *Cell Transplant.* 2016;25:1439-1451.