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A Comprehensive Literature Review: The Potential of Exosomes in Hair Growth and Transplantation

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ABSTRACT

Exosomes, small extracellular vesicles secreted by various cell types, have gained attention in regenerative medicine, particularly for hair growth and dermatological applications. Containing bioactive molecules like microRNAs, growth factors, and proteins, exosomes regulate cellular processes and promote hair follicle regeneration. Derived from mesenchymal stem cells, exosomes increase dermal papilla cell proliferation and modulate inflammation and oxidative stress in the scalp, fostering a better environment for hair growth. They also promote angiogenesis, ensuring blood supply to hair follicles. Exosomes are being studied for their potential to treat alopecia, scalp disorders, and wound healing, owing to their ability to modulate immune responses and tissue regeneration.

A search of PubMed and Cochrane revealed promising results, though more clinical studies are needed to assess their safety and effectiveness. Exosomes show potential for improving skin health and treating hair loss, and further research may lead to innovative therapies for various dermatological conditions.

Keywords: exosome, hair growth

INTRODUCTION

Exosomes are extracellular vesicles (~30-150nm) released by various cell types whose main role is intercellular communication. In dermatology, exosomes have garnered attention for their potential use in skin regeneration, wound healing, and various skin conditions.[1]

Exosomes have been shown to enhance wound healing, particularly in chronic or hard-to-heal wounds like diabetic ulcers or burns.[2] The literature indicates that exosomes derived from different cell types, such as mesenchymal stem cells, are effective in regenerating skin and both reducing the development of and treating existing scars.[3] Furthermore, exosome-based treatments can improve age-related skin conditions, such as wrinkles, loss of elasticity, and pigmentation.[4]

Some clinical trials and experimental studies have already demonstrated using exosomes as a therapeutic option for several inflammatory skin diseases.[5,6] Additionally, studies have shown that exosomes are also effective in stimulating hair growth and improving clinical conditions in alopecia.[7,8]

Understanding how exosomes exert their effects on hair follicles and skin cells is crucial to determining their potential as therapeutic agents; therefore, this review aims to understand how exosomes exert their effects on the skin, hair follicles, and other relevant processes involved in hair growth. We performed a comprehensive literature search to identify relevant studies on the use of exosomes for dermatological purposes, with a specific focus on hair growth.

BIOGENESIS AND COMPOSITION OF EXOSOMES

Numerous cell types secrete exosomes for a variety of processes. In addition to intercellular communication, exosomes have been found to contain a diverse array of biomolecules, including proteins, nucleic acids (such as RNA and DNA), lipids, and metabolites. The membrane of exosomes is composed primarily of a phospholipid bilayer, similar to the cellular plasma membrane.[9]

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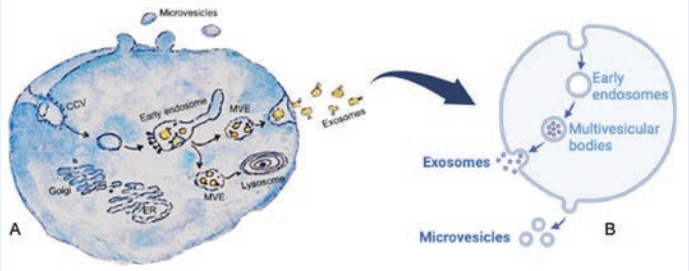
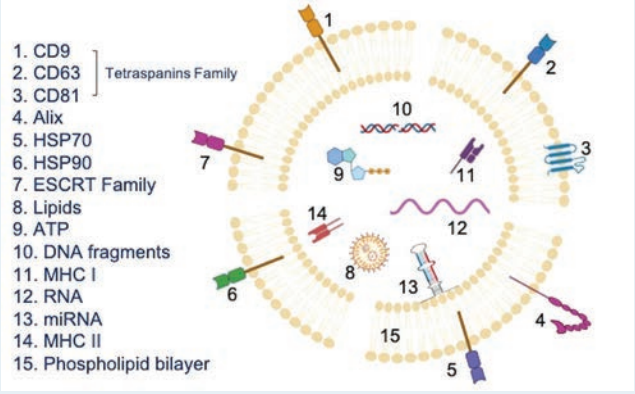
Exosome biogenesis begins with the endosomal membrane's inward budding, forming a multivesicular endosome (MVE) within the cell. These MVEs can then fuse with lysosomes for degradation or the plasma membrane for release into the extracellular environment as exosomes.[10] These MVEs can follow different pathways; either they fuse with lysosomes to be degraded, or they fuse with the plasma membrane to be released into the extracellular medium as exosomes or microvesicles (MV).[10] Unlike MVs, exosomes are formed as intracellular vesicles (ILVs) within early (or primary) endosomes. However, the existence of early endosomes forming MVs cannot be ruled out (Figure 1).[11]

FIGURE 1. Release of microvesicles and exosomes. Note the clathrin associated with vesicles at the plasma membrane (clathrin-coated vesicles - CCV), or bilayered clathrin coats at endosomes. The arrows represent the direction of transport of lipids and proteins between organelles and MVEs, and the direction of secretion of exosomes.
CCV = clathrin-coated vesicles; MVE = multivesicular endosome; ER = endoplasmic reticulum.



Cellular origin and physiological state determine the composition of exosomes. Many common protein markers can be found in exosomes, such as the tetraspanin family (CD9, CD63, CD81), the heat shock protein family (HSP70, HSP90), Alix, TSG101, and numerous other proteins linked to endosomal sorting complexes required for transport (ESCRT). These protein families are directly associated with exosome biogenesis and sorting.[11-13] Numerous other molecules also enrich exosomes, such as mRNA, miRNA, lncRNA, and DNA fragments. Some of the lipids present in exosomes include cholesterol, sphingomyelin, and phosphatidylcholine. Furthermore, they may also carry metabolites such as ATP or NAD+ (Figure 2).[14]

FIGURE 2. Numerous molecules enrich exosomes.



Understanding the biogenesis and composition of exosomes is essential for elucidating their roles in intercellular communication as well as their potential applications in diagnostics and therapeutics across a wide range of fields, including dermatology.[15]

INTERCELLULAR EXCHANGE OF EXOSOMES

As crucial players in intercellular communication, exosomes facilitate the exchange of biomolecules between neighboring or distant cells. When secreted by one cell and subsequently absorbed by another, they transfer their cargo—proteins, nucleic acids, lipids, and metabolites. This transfer of biomolecules via exosomes allows for the transmission of important signals and genetic information between cells.[9,16]

Depending on the cargo transported, exosomes can interfere with several cellular processes in recipient cells, such as gene expression, protein synthesis, and signaling pathways. This intercellular exchange mediated by exosomes has implications for numerous physiological and pathological processes. For example, it is involved in immune responses, tissue regeneration, cancer progression, and neurological functions.[17,18]

Understanding the mechanisms underlying intercellular exchange via exosomes is important for elucidating their roles in health and disease. Additionally, harnessing this process may have potential applications in therapeutic interventions for various medical conditions.[9]

ROLE OF EXOSOMES IN IMMUNE REGULATION

Exosomes play a pivotal role in immune regulation by mediating intercellular communication between various immune cells and other cell types. These tiny extracellular vesicles carry a diverse cargo of biomolecules, including proteins, lipids, RNA, and DNA, which can influence the behavior and function of immune cells.[19]

Dendritic cells (DCs) secrete exosomes that carry major histocompatibility complex (MHC) molecules, thus playing a crucial role in intercellular communication and modulation of the immune response with significant implications for the immune response. These exosomes can be taken up by other cells of the immune system, such as T cells, leading to the presentation of antigens and the activation of an immune response.[20] Exosomes derived from activated immune cells, because they contain signaling molecules, can activate or modulate immune responses. For example, T cell-derived exosomes can carry cytokines or costimulatory molecules that affect the function of other T cells or antigen-presenting cells (APCs).[21]

Certain exosomes have been found to suppress the activity of immune cells. Exosomes secreted by tumors can stimulate immunosuppressive effects on immune cells, such as lymphocytes and natural killer cells (NK cells), promoting tumor evasion.[22,23] Exosomes released during inflammation can carry bioactive lipids and inflammatory mediators that can propagate or resolve inflammatory responses in tissues.[24,25]

Exosomes also facilitate communication between immune and non-immune cell types, such as endothelial cells or epithelial cells in tissues.[18]

THERAPEUTIC POTENTIAL OF EXOSOMES IN DERMATOLOGY

Exosomes have garnered significant interest in dermatology due to their therapeutic potential in a number of skin conditions. Some potential applications of exosomes in dermatology include wound healing, skin rejuvenation, hair regeneration, inflammatory skin conditions, and drug delivery (Figure 3).[1,9]

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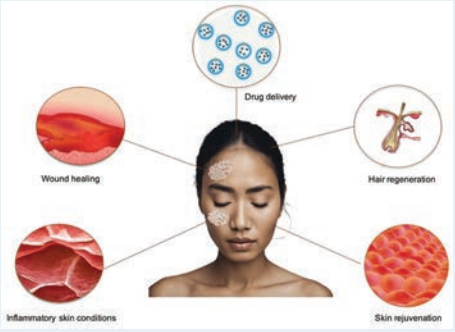
FIGURE 3. Some potential applications of exosomes in dermatology.



Studies have shown that exosomes secreted by mesenchymal stem cells (MSCs) can promote wound healing by stimulating cell proliferation, migration, and angiogenesis. They can also modulate the immune response and reduce inflammation, contributing to improved wound repair.[26,27] Exosomes derived from fibroblasts or other skin cells contain growth factors and proteins that can stimulate collagen production, improve skin elasticity, and aid in reducing signs of aging such as wrinkles and fine lines.[3,28] Exosomes promote hair growth because they stimulate the proliferation of hair follicle cells and regulate the hair growth cycle.[29,30]

FIGURE 4. Exosomes anti-inflammatory effects on skin diseases.

These microvesicles have been studied for their potential anti-inflammatory effects. Furthermore, exosomes have been studied for their potential anti-inflammatory effects in conditions such as psoriasis, eczema, and atopic dermatitis (Figure 4). They can modulate immune responses and reduce inflammation within the skin.[31] Exosomes also can be engineered to carry specific payloads, such as therapeutic drugs or nucleic acids, targeted at treating skin disorders such as melanoma or other forms of skin cancer.[32,33]

MODERATING FACTORS OF EXOSOME ACTIVITY IN DERMATOLOGY

The therapeutic potential of exosomes in dermatology is influenced by several moderating factors, including those noted below.[34]

SOURCE AND ISOLATION METHOD

The source of exosomes (such as mesenchymal stem cells, fibroblasts, or immune cells) and the method used to isolate exosomes can impact their composition and activity. Standardized isolation methods are essential to ensure consistent potency and safety.[35] According to Gao et al, so far, the methods for exosome isolation are constantly improving.[36]

Unfortunately, low exosome yield is an obstacle to therapeutics in clinical practice. According to a study by Gurunathan et al, less than 1µg of exosome proteins can be collected from 1ml of in vitro culture medium.[35] Methods to increase exosome production use biochemical strategies such as stimulating exosome release by stimulating donor cells with lipopolysaccharide (LPS), bone morphogenetic protein 2 (BMP-2), hypoxia-inducible factor 1-alpha (HIF-1α) and interferon-gamma (IFN-α) and tumor necrosis factor-alpha (TNF-α); physical strategies such as hypoxia, heat stress, and starvation; mechanical strategies including shear stress and 3D culture; and instrumental strategies such as hollow fiber bioreactors and stirred tank bioreactors.[37]

The difficulty in isolating exosomes is mainly due to their heterogeneity in terms of size, content, surface markers, and source. However, current isolation and purification techniques are based on their size, surface markers, or immunoaffinity.[38] All currently available techniques for exosome isolation have advantages and disadvantages.[39]

The gold standard for exosome extraction is ultracentrifugation, a technique that requires minimal reagents and expertise. However, it is a time-consuming process that requires expensive equipment and has low efficiency, and the co-separation of lipoproteins limits its use on a large scale. In 1998, Zitvogel et al presented a protocol that is still used today, where the supernatant containing isolated and cultured donor cells from which exosomes will be extracted is ultracentrifuged at 3,000 × g for 20 minutes at room temperature, followed by ultracentrifugation at 10,000 × g for 30 minutes at 4°C to remove cellular debris.[41] The supernatant is again ultracentrifuged at 100,000 × g for 1 hour at 4°C to generate a pellet containing exosomes.

The immunoaffinity chromatography isolation technique consists of separation based on the specific binding of antibodies and ligands. It is fast and provides high purity, specificity, and yield. However, the antigen/protein coupling used needs to be expressed on the surface of the exosomes.[42] Other exosome isolation methods have already been described in the literature, such as the use of commercial kits, polyethylene glycol/polymer-based EV enrichment, and size fractionation.[1] Regarding size-based isolation techniques, especially ultrafiltration and size exclusion chromatography, both are fast and suitable for large-scale applications; however, pore-clogging with loss of exosomes and low purity may occur, which prevents the popularization of these methods.[9]

No technique is perfect; however, combining the above techniques with others, such as those based on precipitation and microfluidics, may be a solution to meet both exosome isolation and purification needs.

DOSE AND ADMINISTRATION

The optimal dose of exosomes for specific dermatological applications has yet to be determined. The route of administration (topical, intradermal injection, etc.) also affects their bioavailability and efficacy.[43]

Storage and transportation are crucial steps to ensure that exosomes remain stable and can perform their activities. Proper handling, storage conditions, and shelf-life determination are necessary.[44] Exogenous administration of exosomes may trigger immune responses in some individuals due to differences in donor-derived antigens or other factors. The clinical application of exosomes depends on understanding their immunogenic potential.[45]

Assessing the safety profile of exosome-based therapies is critical to avoid adverse effects such as hypersensitivity reactions, unintended cellular interactions, or exposure

to infectious agents.[46] As with any emerging therapeutic modality, regulatory oversight significantly ensures the quality, safety, and efficacy of exosome-based products intended for dermatological use.[32]

These moderating factors highlight the need for rigorous research to optimize the use of exosomes in dermatology while addressing critical considerations related to their production, characterization, delivery methods, safety profile assessment, and regulatory standards.[26]

EXOSOME RECEPTORS ON TARGET CELLS

The interaction of exosomes with target cells occurs through surface receptors, with subsequent recognition by signaling pathways.[9] Exosomes are enriched with tetraspanin proteins such as CD9, CD63, and CD81, which can interact with integrins and other cell surface molecules on target cells to facilitate exosome uptake.[47]

The integrin family of cell adhesion molecules plays a role in exosome binding and internalization into target cells. Integrins recognize specific ligands present on the exosome surface.[48] Tumor susceptibility gene 101 (TSG101) is an ESCRT-I protein involved in multivesicular body (MVB) biogenesis and is present on the surface of some exosomes. It may interact with certain cellular receptors.[49]

Exosomes can bind to HSPGs, abundantly expressed on the cell surface or extracellular matrix, facilitating their uptake by recipient cells.[50]

Certain types of exosomes carry ligands for toll-like receptors (TLRs), which can activate inflammatory responses or modulate immune functions upon interaction with TLR-expressing cells.[35] Carbohydrate-binding proteins such as lectins have been identified as potential receptors for exosomes, mediating their interaction with glycoproteins or glycolipids on target cells.[51]

These interactions between exosome-derived ligands and specific receptors on the surfaces of recipient cells determine the uptake mechanisms, intracellular trafficking, and subsequent biological effects of exosomes within the target tissues. Understanding these receptor-mediated processes is important for harnessing the therapeutic potential of exosomes in dermatology and other medical applications.

ANALYSIS AND CHARACTERIZATION OF EXOSOMES

Exosomes can be analyzed and characterized using various techniques to better understand their composition, function, and potential therapeutic applications.[52] The morphology and size of exosomes can be visualized using transmission electron microscopy (TEM) or scanning electron microscopy (SEM). This provides their structural characteristics.[53]

To identify and analyze the particle size distribution of extracellular vesicles (EVs), including exosomes, a widely used and sensitive technology known as nanoparticle tracking analysis (NTA) is used. With this technology, it is possible to identify the characteristic movement of particles in liquid suspension according to Brownian motion. For example, the trajectory of the particles within a given volume is recorded by a camera that captures the scattered light as the laser illuminates the particles. The NTA software collects data on several particles simultaneously. This technology uses the Stokes-Einstein equation to measure the concentration and diameter of the particles. Thus, with NTA it is possible to directly observe EVs or exosomes in a solution. Conventional NTA and fluorescent NTA (fl-NTA) are currently used for exosome analysis.[54] Dynamic light scattering (DLS) can provide information about the size distribution and polydispersity of exosomes by analyzing how they scatter light as a result of Brownian motion.[55] Immunoblotting (western blotting) for specific exosomal markers, such as CD9, CD63, CD81, or TSG101, can confirm the presence of exosomes in isolated samples.[56,57] The flow cytometry technique allows for quantitative analysis of individual exosomes based on surface markers using fluorophore-labeled antibodies.[58]

Proteomic analysis using mass spectrometry can reveal the protein composition of exosomes, providing insight into their cargo and potential biological functions.[59] Next-generation sequencing techniques can be used to analyze the RNA content within exosomes, including microRNAs, mRNAs, and other non-coding RNAs.[60]

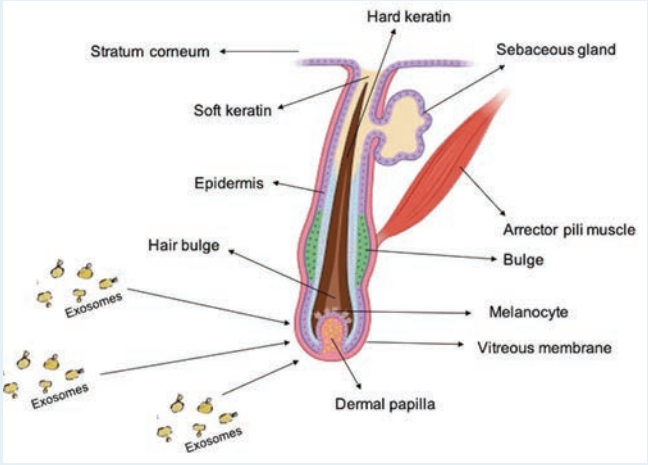
Analyzing the lipid composition within exosomes provides information about their membrane structure and potential signaling roles associated with lipid components.[61] These may include uptake studies utilizing fluorescently labeled or genetically modified exosomes to determine their internalization by target cells or bioassays to evaluate specific biological functions induced by the interaction between exosomal cargo molecules and recipient cells.[62]

By employing these various analytical techniques in combination with functional assays, researchers can comprehensively characterize the molecular content, biophysical properties, uptake mechanisms, and functional effects of exosomes—all critical aspects for advancing our understanding of these extracellular vesicles in health and disease contexts.

EXOSOMES PROMOTE HAIR GROWTH

Studies have demonstrated that exosome therapy can lead to increased hair density and thickness, making it a promising treatment for conditions such as androgenetic alopecia and other forms of hair loss.[8,64] According to the study by Cheng et al, exosomes stimulate hair growth, as they are enriched with various growth factors and proteins that act directly on hair follicle cells (Figure 5).[29] Additionally, exosome therapy

FIGURE 5. Exosomes can stimulate hair follicle cells and promote the proliferation of new hair.



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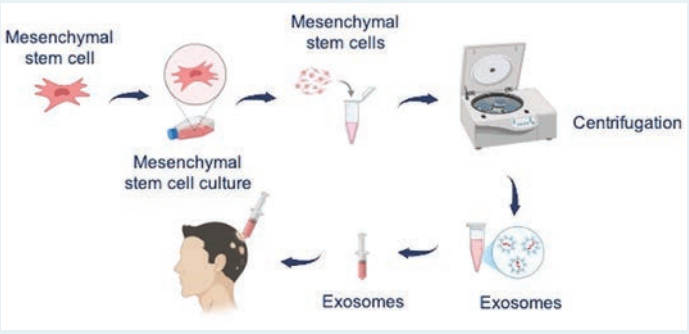
is also being explored as a potential option for improving the results of hair transplantation procedures. Overall, the use of exosomes in promoting hair growth shows significant potential and may offer a non-invasive and effective approach for addressing some types of hair loss concerns.[65]

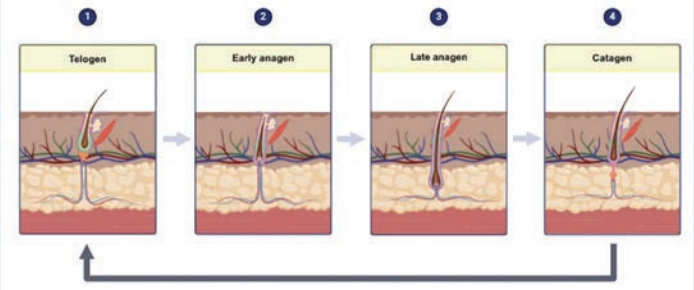
Clinical applications with exosomes derived from mesenchymal stem cells (MSC-exosomes) represent an innovative and promising approach for the treatment of several conditions, including dermatological ones (Figure 6).[66] MSC-exosomes contain potent cytokines and growth factors that restore the hair follicle.[67,68] The study by Rajendran et al demonstrated that MSCs induce the proliferation and migration of human dermal papilla cells and the secretion of vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1).[69]

FIGURE 6. Isolation of mesenchymal stem cells exosomes.



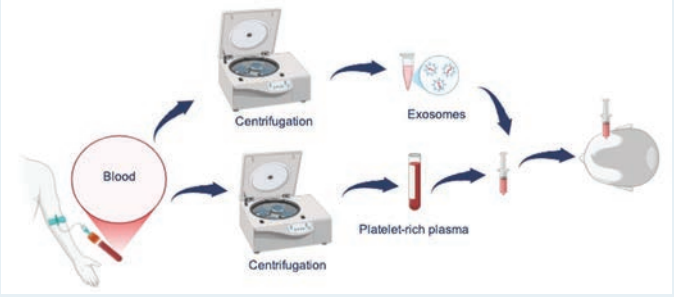
In vitro, dermal papilla exosomes were able to accelerate the onset of the anagen phase of the hair follicle and delay the catagen phase, concomitantly with the increased expression of beta-catenin and sonic hedgehog (Shh) growth factors (proteins that play a crucial role in cellular communication during embryonic development and in the maintenance of tissues in adult organisms).[70] Numerous histological and morphological changes occur during the hair follicle and shaft growth cycle. These changes characterize the phases of the cycle: 1) telogen (resting), 2) early anagen (proliferation and growth), 3) late anagen, 4) catagen (Figure 7), and finally, 5) the exogen phase (shedding hair).[71]

FIGURE 7. The hair follicle and shaft growth cycle.



Exosome use is being explored as a potential technique to enhance the results of hair transplantation procedures, and platelet-rich plasma (PRP) has gained prominence as a therapeutic option for hair growth, especially in cases of androgenetic alopecia and other forms of hair loss.[72] PRP extracted from the patient's blood enriched with autologous exosomes, when injected into the patient's scalp, has been reported to stimulate hair follicles and promote hair growth (Figure 8).[64] This combination can further enhance the regenerative effect on hair follicles.[64] Growth factors contained in exosomes, such as platelet-derived growth factor (PDGF), one of the most important growth factors in the human body, TGF-B, VGEF, EGF, and FGF, stimulate the proliferation and differentiation of hair follicle cells. In addition, this combination can promote angiogenesis, increasing local blood flow and nutrient supply to hair follicles.[69] By facilitating intercellular communication, exosomes promote hair growth. Thus, the PRP/exosome combination may improve the efficacy of hair growth stimulation, improve hair density, reduce recovery time, protect hair follicles from oxidative stress, and minimize side effects. The number of sessions prescribed is usually 3-6, spaced 4-6 weeks apart.[64]

FIGURE 8. Combination of platelet-rich plasma and exosomes in hair transplantation.



Adverse effects usually resolve within 24-48 hours after treatment and include mild scalp pain at the injection site. Scalp exosome injections are minimally invasive procedures that can be performed in the office; monthly sessions are required for treatment efficacy and maximum hair restoration. Exosomes can be applied directly to hair grafts before they are transplanted into the scalp, which may help improve the survival and growth of transplanted hair follicles.[65]

Some clinics now offer topical scalp treatment with exosome-containing solutions before or after hair transplantation to stimulate hair growth and reduce inflammation. The microneedling technique is performed by making small lesions in the skin using fine needles, stimulating collagen production and improving the absorption of topical treatments. Combining microneedling with topical exosome therapy may facilitate better penetration of exosomes into the scalp for improved results. A preclinical study by Hamed et al demonstrated the benefits of using microneedles (MNs) for exosome inoculation for hair regeneration.[73] In a study with mice, de Yang et al described a drug delivery system (MSC-exosomes and a molecular drug, UK5099) mediated by a patch with removable MNs based on hair-derived keratin.[74] Transdermal therapy with this system increased drug efficiency using a reduced dose and promoted hair growth within six days after two applications. Direct injection of exosomes into balding or thinning areas of the scalp is another potential technique under investigation for promoting new hair growth.[65]

POTENTIAL LIMITATIONS OF EXOSOME THERAPY IN HAIR TRANSPLANTATION

The efficacy of exosome therapy for promoting hair growth and improving transplant success rates may vary among individuals, and the specific factors influencing its effectiveness are still being researched. Therefore, it may be challenging

to standardize the production, quality, and concentration of exosomes for consistent outcomes across different patients and treatments.[64,75] Other limitations include the following:

- The regulatory approval process for exosome-based therapies is still evolving, and there may be regulatory hurdles to overcome before widespread clinical use in hair transplantation.[76]
- The ideal parameters for exosomes, including mode of delivery, frequency of sessions, type, and concentration, have yet to be studied and determined for hair growth and hair transplantation.
- The lack of standardization and agreement on optimal parameters can lead to variability in efficacy and safety, including the risk of adverse effects.
- The long-term effects of exosome therapy on transplanted hair follicles and surrounding tissues have not been fully elucidated, and more research is needed to assess the sustainability of results over time.[27,65]
- The cost-effectiveness of incorporating exosome therapy into routine hair transplantation procedures has yet to be fully evaluated against existing treatments.[77]

It is essential to consult with a qualified medical professional or researcher with expertise in this area for the most up-to-date information on the potential limitations and considerations when using exosomes for hair growth and in hair transplantation therapy.[78]

CONCLUSION

The use of exosomes in dermatology, particularly in the context of hair growth and hair transplantation, shows potential. Exosomes have been found to contain growth factors and other signaling molecules that can promote tissue regeneration and hair growth. Studies have demonstrated their ability to enhance the survival of transplanted hair follicles and improve overall transplant success rates. However, there are still several limitations and considerations to address, including efficacy variability among individuals, challenges in standardization, unknown optimal parameters, regulatory approval processes, long-term effects, and cost-effectiveness. Further research is warranted to determine the full scope of exosome therapy's benefits in growth and hair transplantation and its long-term outcomes. Despite these limitations, exosome therapy holds promise as a potentially valuable addition to dermatological treatments for hair restoration.

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