SYSTEMATIC REVIEWS

Therapeutic potential of stem cell-derived exosomes in hair regeneration: A systematic review

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Abstract

BACKGROUND
Exosome-based therapies represent a promising approach for hair regeneration. Unlike conventional treatments such as minoxidil and finasteride, exosomes deliver bioactive cargo that can stimulate dermal papilla cells, enhance angio-genesis, and modulate inflammatory pathways. However, variability in exosome sources, isolation techniques, and dosing protocols limits their clinical translation.

AIM
To synthesize findings from *in vitro*, preclinical and clinical studies, and to evaluate the efficacy, mechanisms, and challenges associated with exosome-based hair restoration therapies.

METHODS
A literature search was conducted using multiple databases (PubMed/Medline, Embase, Scopus, and Web of Science) employing terms for exosomes and hair regeneration for articles published in English to February 2025, following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

RESULTS
A total of 27 studies (three *in vitro*, three pre-clinical, 18 with both *in vitro* and pre-clinical component and three clinical) met the pre-defined search and inclusion criteria and were included in this review.

CONCLUSION
Exosome-based therapies hold immense promise for hair regeneration by leveraging their ability to modulate key signaling pathways and enhance hair follicle regeneration. While *in vitro* and preclinical studies demonstrate consistent

efficacy across diverse exosome sources, methodological heterogeneity and a limited number of clinical studies warrant further clinical research to realize their full clinical potential for hair regeneration.

Core Tip: This review synthesizes findings from *in vitro*, preclinical, and clinical studies to evaluate the efficacy, mechanisms, and challenges associated with exosome-based hair restoration therapies. A total of 27 studies met the pre-defined search and inclusion criteria and were included in this review. Exosome-based therapies hold immense promise for hair regeneration by leveraging their ability to modulate key signaling pathways and enhance hair follicle regeneration. While *in vitro* and preclinical studies demonstrate consistent efficacy across diverse exosome sources, methodological heterogeneity and limited number of clinical studies warrant further clinical research to realize their full clinical potential for hair regeneration.

INTRODUCTION

Hair loss, or alopecia, is a widespread condition affecting millions of individuals worldwide, with significant physical, psychological, and economic implications[1]. It is estimated that androgenetic alopecia alone impacts up to 50% of men and 25% of women by the age of 50, contributing to an expanding market for hair loss treatments[2]. Beyond its cosmetic concerns, hair loss can lead to scarring, inflammation, and profound emotional distress, reducing overall quality of life[3, 4]. The global burden of alopecia extends to healthcare costs and lost productivity, further highlighting the need for effective and long-lasting treatments[5-7].

Hair loss manifests in various forms, including progressive hair thinning, increased shedding, or complete bald patches, depending on the underlying cause[8]. Androgenetic alopecia, commonly known as male or female pattern baldness, results from genetic predisposition and hormonal influences[9]. In contrast, autoimmune conditions such as alopecia areata occur when the immune system mistakenly attacks hair follicles, leading to patchy hair loss[1,9,10]. Other causes include telogen effluvium, which results from metabolic stress, hormonal imbalances, or medication use, and Tinea capitis, a fungal infection of the scalp. Trichorrhexis nodosa, characterized by dry, brittle hair, is often associated with underlying scalp infections, while alopecia totalis manifests as complete body hair loss[11-13]. In addition to the physical symptoms, individuals with hair loss frequently experience psychological consequences, including anxiety, depression, and social withdrawal, with studies reporting a high prevalence of depression among affected individuals, particularly women[3,14].

Several treatment modalities have been developed to combat hair loss, ranging from pharmaceutical interventions to surgical procedures. Food and Drug Administration-approved medications such as minoxidil and finasteride have been widely used, though their effectiveness is limited[15,16]. Minoxidil works by stimulating hair follicles through potassium channel activation, but long-term use has been associated with paradoxical hair shedding and scalp irritation[17,18]. Finasteride, a 5α-reductase inhibitor, is effective in some cases but carries risks of sexual dysfunction and mood disorders, particularly in men[19,20]. Alternative therapies such as herbal compounds - quercitrin, proanthocyanidins, and astragaloside IV - have been explored for their ability to modulate key hair growth signaling pathways, including protein kinase B (AKT), insulin-like growth factor 1, and vascular endothelial growth factor (VEGF)[21-24]. However, these treatments often provide only temporary relief and do not consistently stimulate new hair follicle formation.

For patients seeking more definitive solutions, hair transplant surgery remains an option. While effective, it is invasive, expensive, and limited by donor hair availability[25,26]. Less invasive approaches such as microneedling and low-level laser therapy have shown some promise in stimulating hair growth, particularly when combined with minoxidil, though clinical evidence remains inconclusive[27,28]. Given these limitations, regenerative medicine has emerged as a promising field for hair restoration, leveraging biologics such as platelet-rich plasma, stem cells, and growth factor-based therapies to enhance hair follicle regeneration[29-31]. These treatments capitalize on bioactive molecules - including cytokines, extracellular vesicles, and exosomes - that modulate cellular signaling, reduce inflammation, and promote tissue repair[32,33].

Among these biologics, exosomes have garnered increasing attention as potential therapeutic agents for hair loss. Exosomes are lipid bilayer vesicles that play a critical role in intercellular communication by transporting proteins, RNAs, and microRNAs (miRNAs)[34]. Recent studies suggest that exosome-based therapies may effectively stimulate hair follicle stem cells, induce the Wnt/β-catenin signaling pathway, and promote hair regrowth[33,35,36]. Dermal papilla

cell-derived exosomes in particular can accelerate the transition from the resting phase (telogen) to the active growth phase (anagen) of the hair cycle[33,37,38]. Despite these promising findings, challenges such as the standardization of exosome isolation methods and the need for robust clinical trials remain hurdles to widespread clinical application.

The primary objective of this systematic review is to evaluate the current body of evidence on exosome-based therapies for hair regeneration. Specifically, we aim to document findings from basic science/*in vitro* investigations, pre-clinical studies, and clinical trials assessing the efficacy and safety of exosomes for hair restoration. Additionally, we summarize on-going registered clinical trials investigating exosome-based interventions in hair loss treatment.

MATERIALS AND METHODS

Search strategy

A systematic search was conducted across PubMed/Medline, Embase, Scopus and Web of Science databases for articles published in English prior to February 2025. The Preferred Reporting Items for Systematic Reviews and Meta-analyses statement and guidelines were followed, using the following search terms: ('exosome' OR 'small extracellular vesicle' OR 'small EV' OR 'microsome' OR 'endosome' OR 'secretome' OR 'extracellular vesicle' OR 'vesicle' OR 'microvesicle' OR 'ectosome') AND ('pilus' OR 'pili' OR 'hair' OR 'triches' OR 'trich' OR 'capillus' OR 'capilli' OR 'pilosity' OR 'follicle' OR 'shaft' OR 'cortex' OR 'cuticle' OR 'medulla' OR 'anagen' OR 'catagen' OR 'telogen') AND ('regeneration' OR 'rejuvenation' OR 'restoration' OR 'repair' OR 'regrowth' OR 'revitalization' OR 'revitalization'). All basic science, preclinical, and clinical studies using the aforementioned terms for exosomes for the purpose of hair regeneration were included. There were no control groups or alternative treatments used for comparison purposes, nor were there any specific outcomes or metrics that were assessed or measured.

To minimize the risk of bias, the first two authors discussed and reviewed all selected articles, references and excluded articles from the study. Any disagreements among authors were resolved by the last author, who made the final decision on inclusion or exclusion. In addition, on-going clinical studies involving the use of exosomes for the purpose of hair regeneration, registered on publicly available clinical trial repositories (ClinicalTrials.gov, Clinical Trials Registry - India, and Chinese Clinical Trial Register using the aforementioned search terms were documented.

RESULTS

Study selection

Our initial literature search uncovered 1810 articles potentially relevant to the search question. A total of 508 duplicates were eliminated, and the remaining 1302 articles were screened according to their abstracts, of which 1156 were excluded. The full text was reviewed for the remaining 146 articles, and 119 were excluded due to wrong outcomes (36 articles), wrong indications (35 articles), wrong intervention (22 articles) and wrong study design (26 articles). A total of 27 studies met our pre-defined search and inclusion criteria and were included in this review (Figure 1).

In vitro studies

Three *in vitro* studies met our search criteria and are included in this review. They are summarized in Table 1.

Pre-clinical studies

Three pre-clinical studies met our search criteria and are included in this review. They are summarized in Table 2.

Studies with both in vitro and pre-clinical component

Eighteen studies with both *in vitro* and pre-clinical component met our search criteria and are included in this review. They are summarized in Table 3.

Clinical studies

Three clinical studies met our search criteria and are included in this review. They are summarized in Table 4.

On-going clinical studies

Five clinical trials were registered on ClinicalTrials.gov. They are summarized in Table 5. No clinical trials were found on Clinical Trials Registry - India and Chinese Clinical Trial Register.

DISCUSSION

The current study investigated the therapeutic potential of exosomes for hair regeneration. All *in vitro*, pre-clinical and clinical studies using exosomes for hair regeneration were included. A total of 27 studies (three *in vitro*, three pre-clinical, eighteen with both *in vitro* and pre-clinical component and three clinical) fulfilled the scope of our manuscript. Five on-going clinical trials, registered on ClinicalTrials.gov, were also identified.

Table 1 Summary of the main findings of included *in vitro* studies involving exosomes for hair regeneration

Ref.	Title	Country	Source of exosomes	Groups included in study	Results/key outcomes
Kazi *et al*[72], 2022	Dermal papilla cell-derived extracellular vesicles increase hair inductive gene expression in adipose stem cells *via* β-catenin activation	Japan	Dermal papilla cell-derived extracellular vesicles	Control group: ASCs without treatment; CAO1/2FP group: ASCs treated only with CAO1/2FP; DPC-EVs group: ASCs treated with 5 µg/mL of DPC-EVs and CAO1/2FP; P4 DPC-EVs group: ASCs treated with 5 µg/mL of early-passage (P4) DPC-EVs and CAO1/2FP; P5 DPC-EVs group: ASCs treated with 5 µg/mL of late-passage (P5) DPC-EVs and CAO1/2FP	Cell proliferation: P4 DPC-EVs significantly increased ASC proliferation compared to P5 DPC-EVs ($P < 0.01$); optimal concentration of 5 µg/mL DPC-EVs enhanced proliferation without toxicity Gene & protein expression: P4 DPC-EVs upregulated *VCAN*, *α-SMA*, *OPN*, and *NCAM* genes in ASCs ($P < 0.05$); western blot confirmed increased β-catenin and VCAN expression in treated ASCs MiRNA regulation: P4 DPC-EVs contained higher levels of mir-195-5P and mir-218-5P, both of which regulate hair follicle induction; mir-214-5P (a type of inhibitor of keratinocyte proliferation) was lower in P4 DPC-EVs compared to P5 Exosome uptake & characterization: TEM analysis showed that DPC-EVs were 80-170 nm in diameter; CD63 and TSG101 confirmed as exosome markers *via* western blot; fluorescence microscopy demonstrated efficient DPC-EV uptake by ASCs
Nilforoushzadeh *et al*[73], 2020	Human hair outer root sheath cells and platelet-lysis exosomes promote hair inductivity of dermal papilla cell	Iran	HHORSCs and PL exosomes	Control group: hDPCs cultured without exosomes; HHORSC-Exo group: hDPCs treated with 25, 50, 100 µg/mL HHORSC-derived exosomes; PL-Exo group: hDPCs treated with 25, 50, 100 µg/mL PL-derived exosomes	Cell proliferation: HHORSC-Exo significantly increased hDPC proliferation compared to control and PL-Exo groups; MTS assay confirmed higher metabolic activity in HHORSC-Exo-treated Migration & inductive capacity: Transwell migration assay showed increased hDPC migration in HHORSC-Exo-treated cells compared to controls; PL-Exo had a less significant effect in both migration and proliferation analyses compared to HHORSC-Exo Gene & protein expression: HHORSC-Exo treatment upregulated ALP (by 2.1-fold), VCAN (by 1.7-fold), and α-SMA (by 1.3-fold) compared to control; flow cytometry confirmed high expression of VCAN (77%) and α-SMA (55.2%) in hDPCs Exosome characterization & internalization: Nanoparticle tracking analysis showed HHORSC- and PL-derived exosomes were 30-150 nm in size; western blot confirmed the presence of CD9, CD63, and CD81 in both HHORSC- and PL-Exos; fluorescence microscopy demonstrated efficient uptake of exosomes by hDPCs, with PL-Exo showing higher internalization efficiency (59.93%) than HHORSC-Exo (47.73%), but had weaker biological effects
Shieh *et al*[74], 2022	Bio-pulsed stimulation effectively improves the production of avian mesenchymal stem cell-derived extracellular vesicles that enhance the bioactivity of skin fibroblasts and hair follicle cells	Taiwan	Bio-pulsed AMSC-sEVs and control AMSC-sEVs were isolated from the bio-pulsed AMSC CM and control AMSC CM	Control group: HSFs without treatment; HFDPCs treated with control AMSC-sEV; HFDPCs treated with AMSC-sEVs, treatment with the bio-pulsed AMSC-sEVs	Furthermore, the bio-pulsed AMSC-sEVs, especially at the concentration of 70 µg/mL, enhanced wound healing in the HSFs within 24 hours

HHORSCs: Human hair outer root sheath cells; PL: Platelet lysis; AMSC: Avian-derived mesenchymal stem cell; sEVs: Small extracellular vesicles; CM: Conditioned medium; ASCs: Adipose-derived stem cells; DPC: Dermal papilla cell;

EVs: Extracellular vesicles; hDPCs: Human dermal papilla cells; HSFs: Heat shock transcription factors; HFDPCs: Hair follicle dermal papilla cells; VCAN: Versican; α-SMA: Alpha-smooth muscle actin; OPN: Osteopontin; NCAM: Neural cell adhesion molecule; miRNA: MicroRNA; TEM: Transmission electron microscopy; TSG101: Tumor susceptibility gene 101; MTS: 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; ALP: Alkaline phosphatase.

Table 2 Summary of the main findings of included pre-clinical studies involving exosomes for hair regeneration

Ref.	Title	Country	Sources of exosomes	Treatment groups	Main study outcomes
Rosalina *et al*[75], 2023	Placenta extract-loaded novasome significantly improved hair growth in a rat *in vivo* model	Indonesia	Bovine PE-loaded novasomes	Control group: No treatment Minoxidil group: Treated with 2% minoxidil solution PE-liposome group: Treated with PE-loaded liposomes PE-novasome group: Treated with PE-loaded novasomes	Hair growth acceleration: The PE-novasome group showed earlier and more even hair growth compared to other groups. By day 14, the control group still had incomplete hair coverage, while all the treatment groups had full coverage. Hair length & diameter: At week 4, the PE-novasome group had the longest hair (14.19 mm), followed by PE-liposome (12.54 mm), minoxidil (12.05 mm), and control (8.50 mm). Hair diameter was significantly thicker in the PE-novasome group (120.68 μm) compared to PE-liposome (90.06 μm), minoxidil (49.98 μm), and control (38.59 μm). Anagen-telogen ratio: PE-novasome group had the highest anagen/telogen ratio (4.25), followed by PE-liposome (3.41), minoxidil (2.66), and control (1.88). Hair weight evaluation: Hair weight on day 28 was highest in the PE-novasome group (128.6 mg), significantly greater than PE-liposome (110.7 mg), minoxidil (104 mg), and control (83.4 mg). Novasome characterization & stability: PE-loaded novasomes had 155.0 nm particle size, polydispersity index of 0.139, and entrapment efficiency of 79.60%. Transmission electron microscopy confirmed non-aggregating, oligolamellar nanovesicles. Stable at 4 °C for 90 days with minimal changes in size and entrapment efficiency
Zöller *et al*[39], 2018	Immunoregulatory effects of myeloid-derived suppressor cell exosomes in mouse model of autoimmune alopecia areata	Germany	MDSCs isolated from bone marrow cells of healthy donor mice	Control group: Mice with alopecia areata receiving no treatment MDSC-Exo group: AA mice treated with MDSC-derived exosomes MDSC group: AA mice treated with MDSCs SADBE group: AA mice treated with squaric acid dibutylester, a known therapeutic agent for AA MDSC group: AA mice treated with MDSCs	Hair growth acceleration: MDSC-Exo-treated mice showed partial hair regrowth, preventing the progression of alopecia areata. MDSC-Exo homing was the strongest in activated immune cells. Live imaging confirmed exosome uptake in skin-draining lymph nodes and near hair follicles. Histological analysis: H&E staining showed increased Treg infiltration in MDSC-Exo-treated mice. T helper cell proliferation was significantly reduced, and cytotoxic T-cell activity was suppressed. Immunomodulation & gene expression: FoxP3 (Treg marker) and arginase 1 mRNA levels increased in MDSC-Exo-treated mice. Treg expansion was a dominant feature, supporting immune tolerance in AA. Cytotoxic activity of T cells was suppressed, reducing inflammation. Exosome characterization & targeting: MDSC-Exo were 30-100 nm in diameter, confirmed *via* transmission electron microscopy. Flow cytometry showed that MDSC-Exo preferentially targeted Tregs, macrophages, and NK cells. Exosome uptake exceeded the binding of MDSCs themselves, suggesting stronger immunoregulatory effects. *In vivo* distribution & effects: MDSC-Exo were detected in lymphoid tissues and near hair follicles 8-48 hours after injection. Repeated MDSC-Exo injections reduced inflammatory cytokines (IL-1β, IL-6) and increased IL-10 expression
Mao *et al* [46], 2024	Exosomes derived from umbilical cord mesenchymal stem cell promote hair regrowth in C57BL6 mice through upregulation of the	China	Umbilical cord mesenchymal stem cells	Blank group: No treatment Model group: Injected with dihydrotestosterone solution (AGA induction)	Hair growth acceleration: Model group had significantly shorter and thinner hairs compared to the blank group. Exosome hydrogel-treated mice showed longer hair length, greater hair diameter, and more hair follicles than the model group. Histological analysis: H&E staining revealed increased hair follicle number and size in the exosome group compared to the model group. *AR* expression: Model group exhibited significantly higher AR mRNA and protein levels, which were reduced in the exosome hydrogel group. HFSC markers: K15 and CD200 expression increased in the exosome group, indicating improved

RAS/ERK signaling pathway	Positive control group: Treated with 5% minoxidil solution Exosome hydrogel group: Treated with hUCMSC-derived exosome hydrogel	stemness of HFSCs. PCNA expression (a marker of proliferation) was significantly upregulated in exosome-treated mice. Molecular mechanism (transcriptomics & pathway analysis): KEGG analysis identified the RAS/ERK pathway as significantly activated in the exosome group. Exosome treatment upregulated p-Raf, p-MEK1/2, p-ERK1/2, and RAS expression, confirming ERK/MAPK pathway activation. Western blot showed reduced expression of AR and increased expression of MAPK-related proteins in exosome-treated mice

PE: Placenta extract; MDSCs: Myeloid-derived suppressor cells; hUCMSCs: Human umbilical cord mesenchymal stem cells; Treg: Regulatory T-cell; AR: Androgen receptor; HFSC: Hair follicle stem cell; PCNA: Proliferating cell nuclear antigen; H&E: Hematoxylin and eosin; NK: Natural killer; IL: Interleukin; KEGG: Kyoto Encyclopedia of Genes and Genomes; ERK: Extracellular signal-related kinase; MAPK: Mitogen-activated protein kinase.

Table 3 Summary of the main findings of included studies with both *in vitro* and pre-clinical component involving exosomes for hair regeneration

Ref.	Title	Country	Sources of exosomes	Groups in study	Results/key outcomes
Xiong *et al*[61], 2024	Bioinspired engineering ADSC nanovesicles thermosensitive hydrogel enhance autophagy of dermal papilla cells for androgenetic alopecia treatment	China, United Kingdom	Adipose-derived stem cell NVs	*In vitro*: (1) Control group: Untreated hDPCs; (2) AGA model: HDPCs cells damaged by DHT; (3) ADSC-NV treatment group; (4) JAM-AOE group; (5) JAM-A interference group; and (6) JAM-A control group. *In vivo*: (1) Model group: Mice injected with DHT to induce AGA; (2) Minoxidil group: Treated with topical minoxidil (positive control); (3) HSF-NVs group: Treated with HSF-NVs; (4) ADSC-NVs group: Treated with ADSC-NVs; (5) JAM-AOE@NV group: Treated with JAM-AOE ADSC NVs; and (6) JAM-AOE@NV Gel group: Treated with JAM-AOE@NV encapsulated in thermo-sensitive hydrogel	Hair growth acceleration: JAM-AOE@NV Gel-treated mice exhibited the highest hair regrowth rate, with significantly greater hair follicle density than other groups. By day 15, ADSC-NVs showed superior hair growth compared to HSF-NVs Histological analysis: H&E staining demonstrated more intact and larger hair follicles in the JAM-AOE@NV Gel group. Ki67 immunofluorescence staining confirmed higher proliferation in JAM-AOE@NV-treated hair follicles Autophagy activation: JAM-AOE@NV treatment increased autophagosome formation in DHT-injured DPCs. LC3-II expression was significantly upregulated, while p62 levels decreased, which confirmed induction of autophagic processes Wnt/β-catenin pathway modulation: β-catenin and cyclin D1 were significantly upregulated, promoting HFSC activation AR & inflammation reduction: JAM-AOE@NV reduced inflammation by suppressing TGF-β1 and IL-6, decreasing the amount of androgen-induced follicular damage. Exosome characterization: NV size: About 110 nm, confirmed *via* TEM. Western blotting identified exosome markers CD63, TSG101, and calnexin. Hydrogel properties & drug release: JAM-AOE@NV Gel exhibited sustained release, achieving 60% release at day 1 and full release at day 4. Hydrogel was biocompatible, with no significant toxicity in dermal papilla cells
Tang *et al*[40],	Baricitinib-loaded EVs promote	China	Mesenchymal stem cells	*In vitro*: (1) Control group: Untreated DPCs; (2) DPCs treated	Enhanced hair regrowth: EV-B group showed the most

2025	alopecia areata mouse hair regrowth by reducing JAK-STAT-mediated inflammation and promoting hair follicle regeneration		derived from human placenta	baricitinib solution; (3) DPCs treated with EVs; and (4) DPCs treated with EV-B. *In vivo*: (1) Control group: Injected with saline; (2) Baricitinib group: Injected with baricitinib solution (86.37 µg/mL); (3) EV group: Injected with EVs (2.48 × 10^{11} particles/mL); and (4) EV-B group: Injected with EV-B (86.37 µg baricitinib + 2.48 × 10^{11} EV particles)	significant hair regrowth compared to all other groups. By day 20, hair fully covered the previously bald area Improved drug delivery: EV-B demonstrated higher delivery efficiency than baricitinib alone, leading to greater therapeutic effects JAK-STAT pathway inhibition: EV-B significantly downregulated IFN-γ, Jak-2, Stat-1, and IL-15, reducing inflammation in the alopecia areata mouse model Wnt/β-catenin pathway activation: EV-B upregulated β-catenin, promoting hair follicle regeneration Synergistic effect: The combination of EVs and baricitinib led to better inflammation control and hair regrowth compared to either treatment alone
Kwak *et al*[76], 2024	Development of pluripotent stem cell-derived epidermal organoids that generate effective extracellular vesicles in skin regeneration	South Korea	iEpiOs	*In vitro*: (1) Control group: PBS only; (2) Cells were treated with 2D-cultured iEpiO-derived EVs; (3) Cells treated with 3D-cultured iEpiO-derived EVs; (4) Cells cultured in full growth medium; and (5) Cells treated with miRNA inhibitors. *In vivo*: (1) Control PBS group: Received 100 µL PBS; (2) 2D-EV group: Received 100 µg of 2D-cultured iEpiO-derived EVs in 100 µL PBS; and (3) 3D-EV group: Received 100 µg of 3D-cultured iEpiO-derived EVs in 100 µL PBS	Wound healing acceleration: 3D-EVs increased wound closure 1.6-fold faster than PBS and 2D-EVs by days 3, 5, and 7 EV yield: 3D-cultured iEpiOs produced 2 × more EVs than 2D cultures Angiogenesis: 3D-EVs contained higher VEGF levels and enhanced endothelial tube formation in HUVECs Cellular proliferation: 3D-EVs significantly upregulated Ki67 and COL1A1 expression in fibroblasts Migration: 3D-EVs promoted fibroblast migration in scratch-wound and transwell assays MiRNA content: 3D-EVs were enriched in miR-31-5p, miR-146a-5p, which regulate proliferation, migration, and differentiation Epidermal regeneration: iEpiOs formed multi-layered epidermal structures, closely mimicking native skin morphology
Shang *et al*[52], 2024	Exosomes derived from mouse vibrissa dermal papilla cells promote hair follicle regeneration during wound healing by activating Wnt/β-catenin signaling pathway	China	Dermal papilla cells from mouse vibrissa follicles	*In vitro*: (1) Fibroblasts without exosomes; (2) Fibroblasts treated with various concentrations of DPC-exos; (3) Fibroblasts treated with the Wnt/β-catenin pathway inhibitor; and (4) Fibroblasts treated with both DPC-Exos and XAV939. *In vivo*: (1) PBS group: Received PBS (control); (2) DPC-Exos group: Received 100 µg of DPC-Exos in 100 µL PBS; (3) XAV939 group: Received Wnt/β-catenin pathway inhibitor (XAV939); and (4) DPC-Exos + XAV939 group: Received DPC-Exos + XAV939	Wound healing acceleration: DPC-Exos enhanced wound closure, with significantly smaller wound areas on days 7 and 10 compared to PBS ($P < 0.05$) Hair follicle regeneration: DPC-Exos increased new hair follicle formation at wound sites compared to control, confirmed by H&E staining Fibroblast proliferation and migration: DPC-Exos promoted fibroblast proliferation and migration in a concentration-dependent manner (10-40 µg/mL)

				Hair-inducing capacity: DPC-Exos-treated fibroblasts significantly upregulated β-catenin, ALP, Lef1, and Noggin, key markers for hair follicle neogenesis
				In vivo hair reconstitution: Exos-treated fibroblasts combined with neonatal mouse ECs induced hair follicle formation in nude mice, comparable to dermal papilla cells
				Collagen deposition: Masson staining showed reduced collagen deposition in the DPC-Exos group, indicating lower fibrosis and improved skin regeneration
				Wnt/β-catenin activation: DPC-Exos upregulated β-catenin and Lef1, while XAV939 inhibited these effects, confirming the pathway's role in hair follicle regeneration
				Effect of Wnt inhibition: XAV939 significantly slowed wound healing, reduced fibroblast activity, and decreased new hair follicle formation, confirming that DPC-Exos act *via* Wnt/β-catenin signaling
Zhang *et al*[62], 2024	Engineered exosomes biopotentiated hydrogel promote hair follicle growth *via* reprogramming the perifollicular microenvironment	China	mDPCs	*In vitro*: (1) NC: PBS group; (2) Group treated with 5 µg/mL minoxidil; (3) Group treated with 20 µg/mL nanoparticles consisting of liposomes and exosomes without minoxidil; and (4) Group treated with 25 µg/mL of engineered exosomes consisting of liposomes and exosomes loaded with minoxidil. *In vivo*: (1) Model group: Received testosterone solution (AGA induction); (2) Minoxidil group: Treated with 5% minoxidil; (3) Gel group: Treated with blank hydrogel (no active components); (4) Gel@MNs group: Treated with hydrogel containing exosomes but no minoxidil; and (5) Gel@MNs group: Treated with hydrogel containing both exosomes and minoxidil	Hair regrowth acceleration: Gel@MNs group showed greater hair coverage and density on day 28 compared to other groups. Hair follicles in Gel@MNs group were larger and more numerous than in the minoxidil group
				Histological analysis: H&E staining confirmed more hair follicle units in Gel@MNs-treated mice compared to other groups. Epidermal thickness was significantly increased in Gel@MNs and Gel@MNs groups
				Angiogenesis and microenvironment changes: CD31-positive blood vessels were more abundant around hair follicles in the Gel@MNs group. VEGF expression was significantly higher in Gel@MNs-treated skin tissues than in untreated AGA skin
				Transcriptomic analysis: RNA-seq revealed that Gel@MNs modulated gene expression, particularly downregulating IL-17 signaling (inflammation suppression). Genes associated with lipid biosynthesis, glucose metabolism, and protein synthesis were regulated after treatment. Circadian rhythm pathway alterations were noted, indicating possible involvement in hair follicle cycling
				Safety and biocompatibility: No significant toxicity was observed in major organs (heart, liver, spleen, lung, kidney). Blood counts (RBC, WBC, PLT, HGB) remained unchanged post-treatment. No allergic reactions (IgE levels unchanged) were detected in Gel@MNs-treated mice

Jiao *et al*[57], 2024	Stimulation of mouse hair regrowth by exosomes derived from human umbilical cord mesenchymal stem cells	China	hUCMSCs	*In vitro*: (1) Control group: Only PBS; and (2) Fibroblasts cultured with hUCMSC-Exos (50 μg/mL, 100 μg/mL, 200 μg/mL). *In vivo*: (1) PBS group: Received PBS (control); and (2) hUCMSC-Exos group: Received 200 μg/mL hUCMSC-derived exosomes	Fibroblast proliferation: Fibroblast proliferation was significantly increased in the hUCMSC-Exos (200 μg/mL) group compared to controls (P = 0.017 at 72 hours) Hair growth acceleration: Mice treated with hUCMSC-Exos showed faster transition into the anagen phase, with thicker skin, larger hair bulbs, and more follicles in the subcutis Hair follicle stem/progenitor cells: Increased expression of CD34, K15, Lgr5, and Lrig1 in hUCMSC-Exos-treated skin (qPCR analysis). Flow cytometry confirmed higher numbers of CD49f$^+$CD34$^+$ and CD34$^-$CD49f$^+$Pcad^hi stem cell populations in treated areas. Immunofluorescence showed elevated Lgr5 expression in epidermal and bulge regions Wnt/β-catenin pathway activation: β-catenin, Lrp5, Wnt5, and Lef1 expression significantly increased in hUCMSC-Exos-treated regions (qPCR analysis). Immunohisto-chemistry revealed higher β-catenin staining in epidermal and follicular regions of treated mice
Li *et al*[50], 2025	Decorin-mediated dermal papilla cell-derived exosomes regulate hair follicle growth and development through miR-129-2-3p/SMAD3/TGF-β axis	China, Japan	Dermal papilla cells derived from angora rabbit vibrissa follicles	*In vitro*: (1) Control-Exos group: DPC-derived exosomes without treatment; (2) DCN-Exos group: DPC-derived exosomes treated with 200 nM rhDCN; (3) SRI-011381 group: Treated with a TGF-β pathway activator (SRI-011381 hydrochloride, 10 μM); (4) MiR-129-2-3p mimic/inhibitor groups: Cells transfected with miR-129-2-3p mimic/inhibitor; and (5) SMAD3 OE/KD groups: Cells with *SMAD3* gene modulation. *In vivo*: Mice injected with fluorescently labelled DPC-Exos	Hair follicle growth: DCN-Exos significantly promoted hair shaft elongation compared to untreated exosomes (P < 0.05) Cell proliferation & apoptosis: DPC proliferation was enhanced following DCN treatment (P < 0.05). MiR-129-2-3p mimic increased HFSC proliferation and reduced apoptosis, whereas its inhibitor had the opposite effect Gene & protein expression: MiR-129-2-3p was significantly upregulated in DCN-Exos compared to control-Exos. SMAD3, E2F4, RBL1, TFDP2, and TGF-β1 were downregulated in the miR-129-2-3p mimic group and upregulated in the inhibitor group. Western blot confirmed lower SMAD3 and TGF-β1 expression in DCN-Exos-treated HFSCs Wnt/TGF-β pathway modulation: β-catenin and LEF1 were upregulated, while SMAD3 and TGF-β1 were downregulated in DCN-Exos-treated HFSCs. SRI-011381 restored SMAD3/TGF-β1 expression, counteracting miR-129-2-3p effects Exosome uptake & function: DiI-labeled DPC-Exos were successfully internalized by HFSCs within 24 hours. Live imaging confirmed *in vivo* uptake of exosomes after dorsal skin injection in mice
Wu *et al*[45], 2024	Hybrid hair follicle stem cell extracellular vesicles co-delivering finasteride and gold nanoparticles for	China	HFSC-derived EVs	*In vitro*: (1) Control group: Untreated cells; (2) HDPCs treated with AuNPs; (3) HDPCs treated with HFSC-derived EV; (4) HDPCs treated with finasteride; (5) HVs group: Fusion vesicles of EVs and	Hair regrowth acceleration: Hybrid/Au@Fi-treated mice had significantly greater hair regrowth coverage on day 11 (23.04% ± 11.17%) and day 14 (53.88% ± 15.25%) than

	androgenetic alopecia treatment			liposomes; and (6) HVs co-loaded with AuNPs and finasteride. *In vivo*: (1) Blank group: No treatment after depilation; (2) Model group: Topically applied 0.1 mL/cm^2 of 0.5% testosterone solution (AGA induction); (3) Minoxidil (Mino) group: Treated with 5% minoxidil solution; (4) AuNPs group: Treated with AuNPs gel; (5) EVs group: Treated with HFSC-derived EVs gel; (6) Fi group: Treated with finasteride-loaded gel; (7) HVs group: Treated with HVs containing EVs and liposomes; and (8) Hybrid/Au@Fi group: Treated with HVs containing AuNPs and finasteride	the minoxidil group (31.92% ± 18.09% on day 14). Regrown hair was thicker and more uniform in the hybrid/Au@Fi group compared to other treatments Histological analysis: H&E staining showed more intact and well-structured hair follicles in the hybrid/Au@Fi group. Bulb diameter was larger in hybrid/Au@Fi-treated mice compared to other treatment groups Microenvironment modulation: CD31-positive blood vessels were significantly increased in hybrid/Au@Fi-treated skin, suggesting enhanced angiogenesis. SOX9 expression was more evenly distributed in hybrid/Au@Fi-treated follicles, indicating a well-maintained follicular niche Cell proliferation & apoptosis: Ki67 (proliferation marker) expression in hair bulbs was significantly higher in hybrid/Au@Fi-treated mice than in the minoxidil group. TUNEL staining showed more controlled apoptosis in the ORS, suggesting healthy hair follicle cycling Exosome stability & drug encapsulation: HVs provided higher follicle retention, storage stability, and finasteride encapsulation efficiency (45.33%) compared to EVs alone. AuNPs mimicked LLLT, stimulating vascularization and follicular activation
Oh *et al*[77], 2024	Improvement of androgenic alopecia by extracellular vesicles secreted from hyaluronic acid-stimulated induced mesenchymal stem cells	South Korea	iMSCs stimulated with HA	*In vitro*: (1) Control group: No testosterone or treatment; (2) HFDPCs treated with 50 μM testosterone; (3) Positive control: HFDPCs treated with 50 μM testosterone and 100 nM finasteride; (4) HFDPCs treated with 50 μM testosterone and 25 μg/mL iMSC-derived EVs; (5) HFDPCs treated with 50 μM testosterone and 25 μg/mL HA-stimulated iMSC-derived EVs; and (6) HFDPCs treated with testosterone and HA-iMSC-EVs and rhDKK-1. *In vivo*: (1) Vehicle control group: Received 50% ethanol + DPBS injections; (2) Testosterone-treated group: Received 0.5% testosterone propionate topically; (3) Finasteride group: Received 0.5% testosterone + 1 mg/kg finasteride injections; (4) iMSC-EVs group: Received 0.5% testosterone + 0.2 mg/kg iMSC-EVs injections; and (5) HA-iMSC-EVs group: Received 0.5% testosterone + 0.2 mg/kg HA-iMSC-EVs injections	Hair growth acceleration: HA-iMSC-EVs significantly restored hair growth in testosterone-induced AGA mice. Hair growth was comparable to the finasteride group on day 27 Anagen phase restoration: Testosterone reduced the anagen ratio (0.53 *vs* 1.55 in normal mice, $P < 0.0001$). HA-iMSC-EVs increased the anagen ratio to 1.19, comparable to finasteride (1.29) AR & Wnt/β-catenin pathway activation: AR expression was significantly reduced in HA-iMSC-EVs-treated mice. β-catenin and phosphorylated GSK3β levels were increased, confirming Wnt/β-catenin pathway reactivation. Immunofluorescence showed increased β-catenin-positive hair follicles in HA-iMSC-EVs-treated skin HFDPC response: Testosterone-induced increases in AR, TGF-β1, and IL-6 were blocked by HA-iMSC-EVs. IGF1, FGF7, and VEGF expression was upregulated, promoting hair growth Exosome characterization: HA-iMSC-EVs were about 135.3 nm in diameter and contained CD63, CD81, and TSG101 markers. Proteomic analysis identified 44 differ-

				entially expressed proteins, linked to ECM interactions, PI3K/AKT signaling, and proteasome function
Chu *et al*[44], 2025	Exosome-derived long non-coding RNA AC010789.1 modified by FTO and hnRNPA2B1 accelerates growth of hair follicle stem cells against androgen alopecia by activating S100A8/Wnt/β-catenin signaling	China	Exosomes derived from human HFSCs	*In vitro*: (1) Control group: HFSCs transfected with NC plasmids or siRNAs; (2) AGA group: HFSCs from androgenetic alopecia patients; (3) AC010789.1 OE group: HFSCs transfected with AC010789.1 OE plasmids; (4) AC010789.1 KD group: HFSCs transfected with si-AC010789.1; and (5) Exosome-treated groups: HFSCs treated with exosomes containing AC010789.1 (Exo-AC010789.1). *In vivo*: (1) Hairless mice injected with Exo-AC010789.1 or Exo-NC; (2) Positive control: Hairless mice treated with 5% minoxidil; (3) Exo-AC010789.1 group: Hairless mice injected with exosomes containing AC010789.1; and (4) Exo-NC group: Hairless mice injected with control exosomes	LncRNA AC010789.1 expression: Downregulated in AGA hair follicle tissues but upregulated in HFSCs from normal scalp tissue HFSC proliferation & migration: AC010789.1 OE increased proliferation and migration, while KD inhibited growth. Exo-AC010789.1 significantly enhanced HFSC proliferation compared to control exosomes ($P < 0.05$) m6A modification & molecular interactions: FTO demethylase suppressed AC010789.1 expression, reducing HFSC growth. hnRNPA2B1 bound to AC010789.1, enhancing its stability and upregulating Wnt/β-catenin signaling Gene & protein expression: AC010789.1 OE upregulated K6HF, Lgr5, and Wnt/β-catenin pathway components (β-catenin, Wnt10b, c-myc). KD of S100A8 reversed AC010789.1-induced HFSC proliferation, confirming its role in hair growth signaling Exosome uptake & function in mice: Exo-AC010789.1 was internalized by HFSCs, leading to increased proliferation and migration. Exo-AC010789.1-treated mice showed significantly more hair regrowth than controls. Immuno-histochemistry confirmed increased K6HF, Lgr5, Wnt10b, and β-catenin expression in hair follicles
Hu *et al*[78], 2024	Exosomes derived from uMSCs promote hair regrowth in alopecia areata through accelerating human hair follicular keratinocyte prolif-eration and migration	China	HUCMSCs	*In vitro*: (1) Human hair follicle KCs treated with PBS; and (2) KCs treated with various concentrations of exosomes. *In vivo*: (1) PBS group: Injected with 100 μL PBS (control); (2) UMSC-Exos group: Injected with 100 μL of 30 μg UMSC-derived exosomes	Hair regrowth acceleration: On day 14, the UMSC-Exos group achieved about 95% hair coverage, compared to about 70% in the PBS group. Hair follicle density and skin thickness were significantly higher in the UMSC-Exos group ($P < 0.05$) Exosome uptake & function: DiI-labeled UMSC-Exos were internalized by hair follicle KCs *in vitro* within 24 hours. Injected UMSC-Exos integrated into mouse hair follicles after 24 hours Hair follicle regeneration: H&E staining showed a higher number of anagen-stage hair follicles in the UMSC-Exos group. Western blot confirmed increased expression of FGF-7, BMP-4, and VCAN, key factors for hair follicle development KC proliferation & apoptosis: Ki67-positive KCs increased to about 70% in the UMSC-Exos group, compared to about 45% in controls. TUNEL staining showed decreased KC apoptosis in UMSC-Exos-treated cells ($P < 0.05$) Wound healing & migration: KCs treated with UMSC-

					Exos exhibited faster migration in a wound scratch assay
Liu *et al*[48], 2024	Combatting ageing in dermal papilla cells and promoting hair follicle regeneration using exosomes from human hair follicle dermal sheath cup cells	China	Human hair follicle DSCCs	*In vitro*: (1) Control group: Normal DPCs; (2) H$_2$O$_2$ group: DPCs treated with 600 μmol/L H$_2$O$_2$ to induce senescence; (3) H$_2$O$_2$ + ExoDSCCs (P3) group: Senescent DPCs treated with exosomes from P3 DSCCs; (4) Long-generation DPCs (P10) group: Aged DPCs from hair follicles in bald areas; and (5) P10 + ExoDSCCs (P3) group: Aged DPCs treated with exosomes from P3 DSCCs. *In vivo*: (1) Control group: Normal DPCs combined with neonatal mouse ECs; (2) Senescent DPC group: Senescent DPCs + neonatal mouse ECs; (3) ExoDSCCs group: Senescent pre-treated with ExoDSCCs and neonatal mouse ECs; and (4) ECs group: Neonatal mouse ECs alone	DPC proliferation & migration: ExoDSCCs (P3) significantly increased cell viability and proliferation in both H$_2$O$_2$-treated and P10 DPCs ($P < 0.01$). Scratch wound healing assay confirmed enhanced migration of senescent DPCs after ExoDSCCs (P3) treatment Senescence marker expression: SA-β-Gal staining showed a significant reduction in senescent cells after ExoDSCCs (P3) treatment ($P < 0.05$). p16, p21, and p53 expression levels were reduced, indicating delayed cellular ageing Hair follicle induction markers: ALP and VCAN expression were upregulated in ExoDSCCs (P3)-treated DPCs ($P < 0.001$). Hanging drop assay showed that ExoDSCCs (P3)-treated senescent DPCs formed spheroids, mimicking functional dermal papilla aggregates *In vivo* hair follicle regeneration: ExoDSCCs (P3)-treated DPCs successfully induced new hair follicles when co-transplanted with neonatal ECs in nude mice. Untreated senescent DPCs failed to induce hair follicle neogenesis Wnt/β-catenin pathway activation: β-catenin, Wnt7a, Wnt10b, and LEF1 were significantly upregulated in ExoDSCCs (P3)-treated DPCs ($P < 0.01$). GSK-3β phosphorylation (Ser-9) increased, indicating Wnt pathway activation
Chen *et al*[43], 2020	Sustained release of dermal papilla-derived extracellular vesicles from injectable microgel promotes hair growth	China	Human DP-EVs	*In vitro*: (1) NC: PBS group; (2) DP-EVs group: Cells treated with DP-EVs; (3) OSA group: Treated with OSA hydrogel; (4) OSA-EVs group: Treated with DP-EVs encapsulated in OSA hydrogel; (5) DF-EVs group: Treated with dermal fibroblast-derived EVs; and (6) KC-EVs group: Treated with KC-derived EVs. *In vivo*: (1) PBS group: Control group with PBS injection; (2) DP-EVs group: Injected with naked DP-EVs; (3) OSA-EVs group: Injected with OSA-encapsulated DP-EVs; and (4) Minoxidil group: Treated with 3% minoxidil	Hair growth acceleration: OSA-EVs significantly accelerated hair regrowth in depilated mice compared to DP-EVs alone; increased hair follicle density and larger hair bulb diameters observed in OSA-EVs-treated mice Histological analysis: H&E staining showed more anagen-phase follicles in OSA-EVs-treated mice compared to controls Hair matrix cell proliferation: Ki67-positive cells were significantly increased in OSA-EVs-treated follicles ($P < 0.01$); wound healing assays showed enhanced migration of hair matrix cells with OSA-EVs Molecular mechanisms: OSA-EVs upregulated Wnt3a and β-catenin expression, activating the Wnt/β-catenin signaling pathway; BMP2 (inhibitory molecule) was significantly downregulated in OSA-EVs-treated follicles; MMP3 (a hair growth-promoting enzyme) expression was elevated, enhancing ECM remodeling Exosome retention & stability: OSA hydrogels provided sustained release of DP-EVs, ensuring longer bioavail-

Study	Title	Country	Source	Experimental design	Key findings
					ability compared to free DP-EVs; encapsulated DP-EVs were retained in hair follicles for up to 8 days, compared to 3 days for naked DP-EVs; encapsulation protected EV proteins from degradation, maintaining their biological activity
Kim *et al*[79], 2022	Potential of colostrum-derived exosomes for promoting hair regeneration through the transition from telogen to anagen phase	South Korea	Milk-exo	*In vitro*: (1) DPCs without treatment; (2) DPCs treated with various concentrations of colostrum-derived milk exosomes; (3) DPCs treated with exosome-free milk; (4) DPCs pre-treated with DHT (30 µM) and then with Milk-exo; and (5) DPCs pre-treated with DHT and then treated with Exo-free milk. *In vivo*: (1) PBS group: Injected with PBS (control); (2) Exo-free milk group: Injected with milk fraction without exosomes; (3) Milk-exo group: Injected with 200 µg of colostrum-derived exosomes; and (4) Minoxidil group: Topically applied 2.5% minoxidil solution	Hair growth acceleration: Milk-exo significantly promoted hair regrowth in mice, with results comparable to minoxidil treatment; by day 15, the Milk-exo group had the highest hair coverage, reaching about 50%, while the control group had about 25% ($P < 0.0001$) Histological analysis: H&E staining showed more hair follicles in the anagen phase in the Milk-exo group compared to controls; Ki67 staining indicated increased dermal papilla cell proliferation in the Milk-exo-treated mice Telogen-to-anagen transition: Milk-exo accelerated the transition from telogen to anagen phase, evidenced by increased hair bulb size and deeper follicles; CD31 staining showed increased angiogenesis in Milk-exo-treated skin Wnt/β-catenin pathway activation: Western blot analysis showed increased β-catenin and Wnt3a expression in the Milk-exo group; Milk-exo inhibited DHT-induced suppression of β-catenin, preventing hair follicle miniaturization Exosome characterization & stability: Milk-exo were 50-100 nm in size, confirmed by TEM and dynamic light scattering analysis; western blot identified exosomal markers TSG101 and Alix, confirming successful isolation; lyophilized Milk-exo maintained stability and hair growth efficacy after reconstitution
Liang *et al*[49], 2023	Adipose mesenchymal stromal cell-derived exosomes carrying miR-122-5p antagonize the inhibitory effect of dihydrotestosterone on hair follicles by targeting the TGF-β1/SMAD3 signaling pathway	China	ADSCs	*In vitro*: (1) Control group: Normal untreated DPCs; (2) DHT group: DPCs treated with 10^{-5} M DHT; (3) ADSC-Exos group: DPCs treated with 10 µg/mL ADSC-Exos; (4) ADSC-Exos + DHT group: Co-treatment with ADSC-Exos and DHT; (5) Exo-miR-122-5p group: DPCs treated with exosomes enriched in miR-122-5p; and (6) Exo-in-miR-122-5p group: DPCs treated with exosomes with inhibited miR-122-5p. *In vivo*: (1) Control group: PBS only; (2) DHT group to induce hair loss; (3) Mice given DHT + Exo-miR-122-5p; (4) Mice treated with DHT + minoxidil; and (5) Mice treated with DHT and exosomes lacking miR-122-5p	Hair growth acceleration: Exo-miR-122-5p significantly reversed DHT-induced hair follicle miniaturization. Hair bulb size and dermal thickness were restored in Exo-miR-122-5p-treated mice DPC proliferation & migration: Ki67-positive cells increased in ADSC-Exos-treated DPCs compared to the DHT group ($P < 0.05$). Wound healing assay confirmed enhanced DPC migration in the ADSC-Exos group Gene & protein expression: β-catenin and VCAN were upregulated in ADSC-Exos and Exo-miR-122-5p groups ($P < 0.01$). SMAD3 and p-SMAD3 levels were significantly reduced in Exo-miR-122-5p-treated cells, confirming suppression of the TGF-β1/SMAD3 axis. BCL2 expression increased, while Bax (an apoptosis marker) was downregulated, indicating reduced DHT-induced apoptosis

					MiRNA regulation: MiR-122-5p was highly enriched in ADSC-Exos, and luciferase assays confirmed SMAD3 as its direct target. Exo-miR-122-5p reduced SMAD3 levels, rescuing β-catenin expression and DPC proliferation
					In vivo hair growth model: Exo-miR-122-5p-treated mice exhibited significantly greater hair regrowth than DHT-treated controls. Immunofluorescence analysis showed increased β-catenin and reduced SMAD3 in hair follicles of Exo-miR-122-5p-treated mice
Wang *et al*[60], 2023	Treatment of androgenetic alopecia by exosomes secreted from hair papilla cells and the intervention effect of LTF	China	DPC-Exo treated with LTF, a traditional Chinese medicine formulation	*In vitro*: (1) Control group: DPCs without treatment; and (2) DPCs cultured with various LTF concentrations. *In vivo*: (1) Control group: Normal untreated mice; (2) Model group: Mice injected with testosterone propionate to induce AGA; (3) Minoxidil group: Treated with 5% minoxidil solution; (4) LTF group: Treated with LTF herbal extract; and (5) LTF-DPC-Exo group: Treated with exosomes derived from LTF-treated DPCs	Hair growth acceleration: LTF, minoxidil, and LTF-DPC-Exo groups showed significant hair regrowth, while the model group had only localized hair growth. Live imaging confirmed sustained fluorescence signals of exosomes in treated mice, with disappearance in areas of full hair regrowth
					Histological analysis: H&E staining showed denser, larger anagen-phase hair follicles in the LTF-DPC-Exo group. Model group had reduced and miniaturized follicles, indicative of AGA
					Serum hormone levels: Testosterone levels were significantly reduced, and estradiol levels were increased in all treatment groups compared to the model group ($P < 0.01$). LTF-DPC-Exo group had the greatest reduction in androgen levels, suggesting an anti-AGA effect
					Gene & protein expression: LTF-DPC-Exo significantly upregulated VEGF and AKT1, key regulators of hair follicle growth ($P < 0.01$). Caspase-3 (apoptosis marker) expression was significantly downregulated in the LTF-DPC-Exo group, indicating reduced follicular apoptosis. Western blot confirmed increased VEGF and AKT1 levels, with reduced caspase-3 expression
					Molecular mechanism: LTF-DPC-Exo activated the PI3K/AKT pathway, promoting hair follicle regeneration. Inhibition of caspase-3 prevented hair follicle apoptosis, maintaining follicular viability
Wu *et al*[80], 2021	Adipose-derived stem cell exosomes promoted hair regeneration	China	ADSC-Exos isolated from 6-week-old C57BL/6 mice	Control group: Grafted with DCs and ECs only. ADSC-Exos group: Grafted with DCs, ECs, and 50 μg/mL ADSC-Exos	Hair growth acceleration: By week 2, the ADSC-Exos group had significantly more regenerated hairs than the control group ($P < 0.001$). By week 3, the ADSC-Exos group showed uniform, denser hair regrowth compared to the control
					Histological analysis: H&E staining confirmed that ADSC-Exos promoted terminal hair formation, while the control group had immature follicles. Follicle count per vertical section was significantly higher in the ADSC-Exos group *vs* control group (17.70 ± 2.67 *vs* 11.22 ± 2.37, $P < 0.001$)

				Cytokine expression & molecular markers: PDGF and VEGF expression was significantly increased in ADSC-Exos-treated skin ($P < 0.05$), indicating enhanced angiogenesis. TGF-β1 levels were significantly lower in the ADSC-Exos group compared to controls ($P < 0.001$), suggesting reduced fibrosis and improved follicular health
				Exosome characterization: ADSC-Exos were 20-130 nm in diameter, confirmed by TEM. Western blot detected exosome markers CD63, ALX1, and CD9, verifying successful isolation
Zhang *et al*[47], 2016	iTRAQ-based quantitative proteomic comparison of early- and late-passage human dermal papilla cell secretome in relation to inducing hair follicle regeneration	China	Secretome (conditioned media) from early-passage (P3) and late-passage (P9) human DPCs	P3 DPC-CM group: Conditioned medium from early-passage (P3) DPCs. P9 DPC-CM group: Conditioned medium from late-passage (P9) DPCs	Hair growth acceleration: P3 DPC-CM induced hair follicle regeneration in NU/NU mice, with white hair appearing by day 3 post-injection. P9 DPC-CM failed to induce hair regrowth, confirming loss of inductive potential in late-passage DPCs
					Histological analysis: H&E staining showed newly formed hair follicle structures in P3 DPC-CM-treated mice, absent in P9 DPC-CM-treated mice
					Proteomic analysis (iTRAQ-based quantification): 1360 proteins identified, with 213 proteins differentially expressed between P3 and P9 DPC-CM. SDF1, MMP3, Biglycan, and LTBP1 were significantly upregulated in P3 DPC-CM, suggesting key roles in hair follicle regeneration
					Molecular mechanisms: SDF1 (CXCL12) upregulation in P3 DPC-CM promoted Wnt/β-catenin activation, facilitating dermal-epidermal crosstalk for hair follicle induction. MMP3 enhanced Wnt signaling by antagonizing Wnt5b, a non-canonical Wnt inhibitor. Biglycan promoted β-catenin/TCF-mediated transcription *via* LRP6 receptor activation, further stimulating follicle development. LTBP1 was highly expressed in P3 DPC-CM and localized in hair follicles, supporting its role in TGF-β/BMP pathway regulation

ADSC: Adipose mesenchymal stromal cell; hDPCs: Human dermal papillary cells; DHT: Dihydrotestosterone; NV: Nanovesicles; ADSC-NV: Adipose mesenchymal stromal cell nanovesicles; OE: Overexpression; HSF-NVs: Human skin fibroblast nanovesicles; H&E: Hematoxylin and eosin; TGF: Transforming growth factor; IL: Interleukin; TEM: Transmission electron microscopy; TSG101: Tumor susceptibility gene 101; JAK: Janus kinase; STAT: Signal transducer and activator of the transcription; EVs: Extracellular vesicles; EV-B: Baricitinib-loaded extracellular vesicles; IFN: Interferon; iPSC: Induced pluripotent stem cell; iEpiOs: Induced pluripotent stem cell-derived epidermal organoids; miRNA: MicroRNA; PBS: Phosphate buffered saline; COL1A1: Collagen type I alpha 1; VCAN: Versican; DPC: Dermal papillary cell; ALP: Alkaline phosphatase; Lef1: Lymphoid enhancer-binding factor 1; DPC-Exo: Exosomes derived from dermal papilla cell; mDPCs: Mouse dermal papilla cells; RBC: Red blood cell; WBC: White blood cell; PLT: Platelet; HGB: Hemoglobin; IgE: Immunoglobulin E; hUCMSCs: Human umbilical cord mesenchymal stem cells; HFSC: Hair follicle stem cell; qPCR: Quantitative polymerase chain reaction; TFDP2: Transcription factor DP2; SOX9: Sry-box transcription factor 9; AuNPs: Gold nanoparticles; HVs: Hybrid vesicles; ORS: Outer root sheath; LLLT: Low-level laser therapy; iMSCs: Induced mesenchymal stem cells; HA: Hyaluronic acid; AR: Androgen receptor; GSK3β: Glycogen synthase kinase-3β; rhDKK-1: Recombinant human DKK-1; DPBS: Dulbecco's phosphate-buffered saline; IGF1: Insulin-like growth factor 1; FGF7: Fibroblast growth factor-7; VEGF: Vascular endothelial growth factor; ECM: Extracellular matrix; PI3K: Phosphatidylinositol-3-kinase; AKT: Protein kinase B; siRNAs: Small interfering RNAs; KD: Knockdown; NC: Negative control; UMSCs: Umbilical cord mesenchymal stem cells; KCs: Keratinocytes; BMP-4: Bone morphogenetic protein-4; DSCCs: Dermal sheath cup cells; DP-EVs: Dermal papilla cell-derived extracellular

vesicles; OSA: Oxidized sodium alginate; Milk-exo: Bovine colostrum-derived exosomes; ADSC-Exos: Adipose-derived stem exosomes; LTF: Liao Tuo Fang; JAM-AOE: JAM-A overexpression; DCs: Dermal cells; ECs: Epidermal cells; PDGF: Platelet-derived growth factor; ALX1: Aristaless-like homeobox1; SDF1: Stromal-derived factor 1; LTBP1: Latent-transforming growth factor beta-binding protein 1; CXCL12: C-X-C motif chemokine 12; MMP3: Matrix metalloproteinase 3; TCF: T cell factor; LRP6: Lipoprotein receptor-related protein 6; LncRNA: Long noncoding RNA.

Immunomodulation and inflammatory response

Exosomes demonstrate potent immunomodulatory capabilities essential for treating inflammatory hair loss conditions such as alopecia areata. Zöller *et al*[39] found that myeloid-derived suppressor cell-derived exosomes significantly promoted T regulatory cell expansion, decreased pro-inflammatory cytokines [interleukin (IL)-1β, IL-6], and enhanced anti-inflammatory cytokines (IL-10), effectively restoring immune tolerance. Similarly, Tang *et al*[40] showed that baricitinib-loaded extracellular vesicles effectively suppressed Janus kinase-signal transducer and activator of the transcription-mediated inflammation, reducing cytokines, including interferon-γ and IL-15, which are critical mediators of inflammation in alopecia. Collectively, these findings underscore the therapeutic potential of exosomes in resolving follicular inflammation by recalibrating immune responses and restoring a conducive microenvironment for follicular regeneration[33,35,41,42].

Exosome delivery systems and formulation techniques

Optimizing delivery strategies is crucial for translating exosome therapies into clinical applications. Chen *et al*[43] demonstrated that encapsulating dermal papilla cell-derived exosomes within injectable hydrogels significantly enhanced follicular retention, provided sustained release, and extended the anagen phase. Similarly, Chu *et al*[44] reported improved therapeutic outcomes by integrating engineered adipose-derived stem cell nanovesicles into thermosensitive hydrogels, enhancing follicular targeting and stability. Wu *et al*[45] further confirmed that hybrid vesicles encapsulating exosomes, finasteride, and gold nanoparticles considerably improved follicular delivery, bioavailability, and efficacy compared to conventional solutions. These advanced delivery approaches illustrate the importance of developing targeted, stable, and biocompatible exosome formulations to maximize clinical effectiveness.

Cellular sources of exosomes

Cellular origin critically impacts exosome function and therapeutic potential in hair regeneration. Mao *et al*[46] utilized exosomes from umbilical cord mesenchymal stem cells, showing robust promotion of keratinocyte proliferation and reduced apoptosis, translating into significantly improved hair regeneration. Similarly, Zhang *et al*[47] demonstrated that dermal papilla cell-derived exosomes effectively restored hair growth by modulating the perifollicular environment. Rajendran *et al*[37] showed that fibroblast-derived engineered nanovesicles significantly induced hair growth *ex vivo*, while Liu *et al*[48] reported human dermal sheath cup cell-derived exosomes notably reversed dermal papilla cell senescence, underscoring varied cellular sources' regenerative potential in hair regrowth therapy.

MiRNA and other exosomal cargo in hair regeneration

Exosomal cargo, particularly miRNAs, critically regulates hair regeneration *via* precise genetic modulation. Liang *et al*[49] reported that adipose mesenchymal stromal cell-derived exosomes enriched with miR-122-5p antagonized dihydrotestosterone-induced hair follicle suppression by targeting transforming growth factor (TGF)-β1/SMAD3 signaling. Li *et al*[50] found that decorin-modified dermal papilla cell-derived exosomes enhanced hair follicle proliferation through miR-129-2-3p mediated downregulation of SMAD3 expression. Chu *et al*[44] illustrated that the exosome-derived long non-coding RNA AC010789.1 promoted hair growth by activating S100A8/Wnt/β-catenin signaling. These

Table 4 Summary of the main findings of included clinical studies involving exosomes for hair regeneration

Ref.	Title	Country	Sources of exosomes	Groups in study	Results/key outcomes
Gentile *et al* [29], 2015	The effect of platelet-rich plasma in hair regrowth: A randomized placebo-controlled trial	Italy, India, Turkey (multicentric study)	Autologous micrografts containing EVs derived from human follicle mesenchymal stem cells	MPHL group: 40 males (Norwood-Hamilton stages I-III vertex); FPHL group: 20 females (Ludwig stages I-II)	HD increase: FPHL group: HD increased by 28 ± 4 hairs/cm^2 after 12 months (P = 0.0429). MPHL group: HD increased by 30 ± 5 hairs/cm^2 after 12 months (P = 0.0012) Trichoscopic analysis: Baseline HD (T0): 114 ± 5 hairs/cm^2 (FPHL), 108 ± 3 hairs/cm^2 (MPHL). Post-treatment HD (T4, 12 months): 142 ± 4 hairs/cm^2 (FPHL), 138 ± 4 hairs/cm^2 (MPHL). No significant changes in vellus HD, hair thickness, or anagen/telogen ratio Physician's global assessment: 70% of patients (42/60) reported improved global scalp coverage (P = 0.045) Patient satisfaction: 80% of patients (48/60) reported a good level of satisfaction (P = 0.021) *In vitro* exosome analysis: EVs were 95.9-123.2 nm in size, with concentrations ranging from 10^8 to 10^{10} particles/mL Transmission electron microscopy confirmed lipid bilayer vesicle morphology. Fluorescence microscopy showed EV uptake by fibroblasts, confirming cellular interaction
Lee *et al*[51], 2024	The efficacy of adipose stem cell-derived exosomes in hair regeneration based on a preclinical and clinical study	South Korea	Adipose stem cell derived exosomes	*In-vitro* groups: HDPCs treated with ASC-exosomes (8 μg or 40 μg); *ex-vivo* groups: Human hair follicles treated with ASC-exosomes (8 μg or 40 μg) or 20 μmol/L minoxidil; clinical groups: 30 patients with androgenetic alopecia treated with ASC-exosomes (ASCE + HRLV®) over 24 weeks	*In vitro* & *ex vivo* findings: (1) hDPC proliferation: ASC-exosomes increased hDPC proliferation in a concentration-dependent manner (P < 0.05) compared to controls; (2) Hair follicle growth: Hair shaft elongation was significantly greater in the ASC-exosome 40 μg group than in controls (P = 0.03); (3) Gene & protein expression: ALP, VCAN, β-catenin, and LEF-1 mRNA levels were upregulated in ASC-exosome-treated hDPCs (P < 0.05). Western blot confirmed increased β-catenin and phosphorylated GSK3β, indicating Wnt/β-catenin pathway activation; and (4) Immunostaining: Ki67 and β-catenin expression was highest in ASC-exosome-treated follicles, suggesting enhanced cell proliferation Clinical findings: (1) HD increase: Baseline: 158.03 ± 16.48 hairs/cm^2. Week 12: 161.90 ± 17.78 hairs/cm^2 (P = 0.033). Week 24: 166.14 ± 19.57 hairs/cm^2 (P < 0.001); (2) Global photographic assessment: Week 12: 31.03% of patients showed slight improvement, 3.45% showed marked improvement (P = 0.023). Week 24: 41.38% had slight improvement, 10.34% had marked improvement (P = 0.004); (3) Subjective **s**atisfaction: 52.72% of patients reported improved HD (P < 0.001). 55.17% noted reduced daily hair loss (P = 0.003). 58.62% reported thicker hair strands (P < 0.001); and (4) Adverse **r**eactions: Mild scalp tingling and erythema were observed but resolved quickly. No severe adverse effects reported
Lueangarun *et al*[81], 2024	Rose stem cell-derived exosomes for hair regeneration enhancement *via* noninvasive electro-poration in androgenetic alopecia	Thailand, South Korea	RSCEs	Single case study: 54-year-old male with Norwood-Hamilton scale V androgenetic alopecia	Hair growth improvement: After three treatment sessions, the patient showed increased HD and thickness. Significant regrowth observed by the 6th and 12th sessions, with continued improvement three months post-treatment Dermoscopy & clinical evaluation: Dermoscopic images showed increased HD and shaft thickness after six and twelve treatment sessions Exosome characterization: RSCEs were 100-200 nm in diameter, confirmed by nanoparticle tracking analysis and cryo-electron microscopy. Proteomic analysis identified 206 proteins, including cell membrane components, enzymes, and RNA-binding proteins. RSCEs contained *Let-7* family miRNAs, miR-8485, miR-574-5p, and miR-1246, which are linked to cell proliferation and inflammation regulation

	Mechanism of action: RSCEs activated the Wnt/β-catenin signaling pathway, promoting dermal papilla proliferation and follicular development. Reduced inflammation and oxidative stress, supporting hair regeneration
	Treatment protocol: 5 mL of lyophilized RSCEs (20 mg) applied *via* electroporation every 3 weeks for 12 sessions. Electroporation enhanced exosome penetration, avoiding the need for invasive injections
	Adverse events & safety: No serious adverse effects reported

EVs: Extracellular vesicles; RSCEs: Rose stem cell-derived exosomes; MPHL: Male pattern hair loss; FPHL: Female pattern hair loss; hDPCs: Human dermal papilla cells; ASCs: Adipose-derived stem cells; HD: Hair density; ALP: Alkaline phosphatase; VCAN: Versican; LEF-1: Lymphoid enhancer-binding factor 1; GSK3β: Glycogen synthase kinase-3β; miRNAs: MicroRNAs.

Table 5 On-going clinical trials registered on ClinicalTrials.gov, Clinical Trials Registry - India, and Chinese Clinical Trial Register till February 2025, evaluating the safety and/or efficacy of exosomes for hair regeneration

Study identifier	Title of the study	Source of exosomes	Study phase; estimated enrollment (*n*)	Primary outcome measure(s)	Recruitment status	Study location(s)
NCT06571799	Study evaluating the efficacy and safety of BENEV exosome regenerative complex+ for self-perceived thinning hair	Adipose tissue stem cell-derived exosomes	Not applicable; *n* = 30	Change in terminal hair counts, change in vellus hair counts, change in total hair counts (time frame: Baseline to day 120 or end of study visit)	Completed	United States
NCT05658094	Exosome effect on prevention of hair loss	Human amniotic mesenchymal stem cells-derived exosomes	Not applicable; *n* = 20	Change in mean total hair density (hair/cm^2) (time frame: 0, 3 and 6 months), visual assessment before and after (time frame: 6 months)	Unknown	Iran
NCT06482541	Efficacy and safety of AGE ZERO™ exosomes to treat men and women with androgenetic alopecia	Wharton's jelly mesenchymal stem cell-derived exosome	Phase I; *n* = 100	Hair count, hair thickness, hair color (time frame: Evaluated on monthly visits for a year)	Not yet recruiting	United States
NCT06539273	Exosome treatment in androgenetic alopecia	Foreskin-derived mesenchymal stromal cells derived exosome	Phase III; *n* = 30	Hair density (time frame: 4 and 12 weeks)	Completed	Turkey
NCT06697080	Umbilical cord-derived mesenchymal stem cell exosomes on hair growth in patients with androgenetic alopecia	Umbilical cord-derived mesenchymal stem cell exosomes	Not applicable; *n* = 50	Hair diameters changed over time (time frame: 0 days, 1 month, 3 months, 6 months)	Active, not recruiting	China

findings underscore the potent regenerative effects of exosomes, heavily influenced by their unique cellular sources and miRNA content, emphasizing the necessity of source-specific characterization to achieve consistent clinical outcomes.

Exosome characterization and standardization

A significant limitation in the current body of literature - and consequently in this review - is the substantial methodological heterogeneity across relevant studies. Variability exists in several key domains, including exosome isolation techniques, dosing regimens, and outcome measures. This lack of standardization limits the comparability of findings across studies and introduces uncertainty regarding the reproducibility of therapeutic effects. Moreover, inconsistent
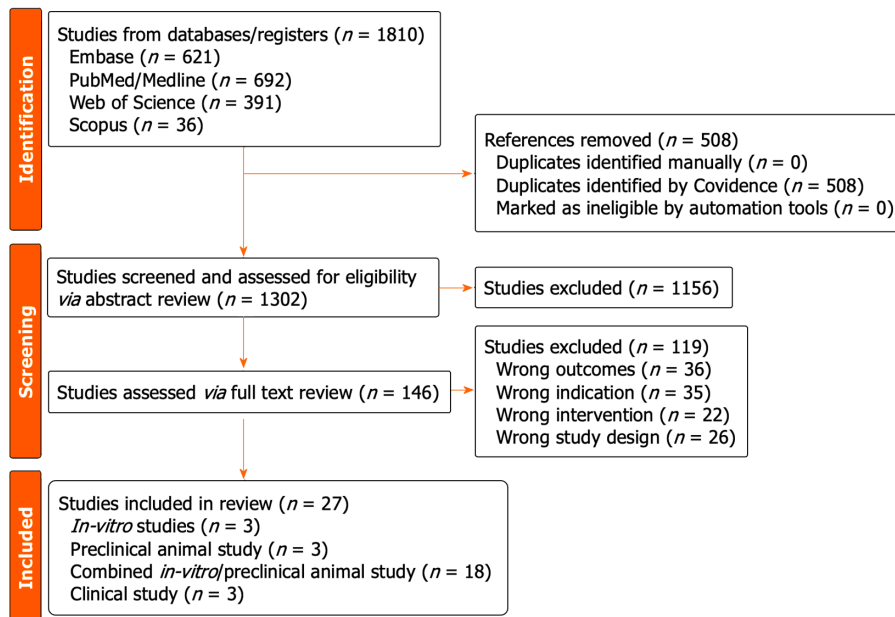
Figure 1 A PRISMA flow diagram outlining the record identification and selection process.

reporting of exosome characterization data further complicates efforts to draw definitive conclusions. As a result, the generalizability of the preclinical and early clinical findings remains limited, and the translation of these therapies into standardized clinical protocols is hindered.

A crucial challenge in exosome-based hair regeneration therapy is the lack of standardized characterization methods, hindering reproducibility and comparability across studies. Consistency in exosome size, protein markers, cargo profiling, and bioactivity assessment is necessary for clinical translation. Studies by Lee *et al*[51], Hu *et al*[38], and Liang *et al*[49] consistently utilized nanoparticle tracking analysis, electron microscopy, and western blotting for exosomal markers (CD63, tumor susceptibility gene 101, Alix), illustrating the importance of systematic characterization. Nevertheless, variations in isolation techniques and analytical methods across studies underscore the urgent need for universally accepted standardization protocols to ensure reproducible, high-quality exosome preparations capable of consistent therapeutic outcomes.

Future directions in exosome standardization
One of the most important limitations hindering the clinical translation of exosome-based hair regeneration therapies is the lack of standardized methodologies for exosome isolation, characterization, and bioactivity assessment. As noted in our review, while many studies have demonstrated promising regenerative effects of exosomes derived from various cellular sources, the absence of universally accepted criteria for defining and validating exosomal preparations makes it difficult to compare results across studies or establish reproducible protocols for clinical application, especially considering country-specific regulatory protocols.

Exosome isolation methods vary widely across the literature, ranging from ultracentrifugation and size-exclusion chromatography to polymer-based precipitation and microfluidic-based separation[36,52]. Each technique offers distinct advantages and limitations in terms of yield, purity, and scalability. For example, ultracentrifugation remains the most commonly used approach, but it often results in co-isolation of protein aggregates and other vesicular contaminants, leading to decreased homogeneity of exosomal contents[53]. Furthermore, size-exclusion chromatography and immunoaffinity capture offer greater specificity but are less scalable for therapeutic production[54].

Characterization of exosomes similarly lacks standardization. While many studies report using nanoparticle tracking analysis, transmission electron microscopy, and western blotting to identify canonical exosome markers, there is no consensus on the minimal set of criteria required to confirm the identity or integrity of therapeutic exosomes. Moreover, few studies report quantitative measures of cargo content (*i.e.*, specific miRNAs) or functional assays to assess biological activity. As a result, it is very difficult to determine whether the therapeutic effects observed in the studies are due to the exosomal cargo itself or artifacts from the isolation process.

Fortunately, efforts have recently been made to address these gaps. The International Society for Extracellular Vesicles has written and proposed the Minimal Information for Studies of Extracellular Vesicles guidelines, which suggest standardized criteria for the isolation, characterization, and reporting of extracellular vesicle studies. These recommendations encourage and allow researchers to validate particle identity, assess purity, and provide detailed methodological transparency, as they realized the necessity for a standardized exosome processing method[55].

Molecular pathways beyond Wnt/β-catenin (i.e., TGF-β/SMAD, phosphatidylinositol-3-kinase/AKT)
Exosomes modulate several intracellular signaling cascades, of which we found Wnt/β-catenin and TGF-β to be among the most critical and consistent in regulating hair follicle regeneration[35]. The Wnt/β-catenin pathway is a well-

established regulator of the anagen (growth) phase in the hair cycle. Activation of this pathway promotes proliferation and differentiation of dermal papilla cells and hair follicle stem cells, both of which are essential for initiating new follicular growth[56]. Studies included in this review have demonstrated that exosomes derived from adipose-derived stem cells, dermal papilla cells, and mesenchymal stromal cells can upregulate β-catenin and its downstream effectors, thereby increasing activation of the follicle and proliferative capability of the relevant matrix cells[44,52,57].

The TGF-β/SMAD pathway, on the other hand, has dual and context-dependent roles. While TGF-β1 is generally associated with catagen induction and follicular regression, exosomes enriched with specific miRNAs inhibit TGF-β1 or its downstream mediator SMAD3, thereby preventing premature follicle apoptosis. By rebalancing this pathway, exosomes may help sustain the anagen phase and promote healthier follicular environments[58,59].

Beyond the Wnt/β-catenin pathway, exosomes modulate multiple signaling cascades crucial for hair follicle regeneration. Liang *et al*[49] identified exosomal miR-122-5p's ability to suppress TGF-β1/SMAD3 signaling, counteracting dihydrotestosterone-mediated hair follicle miniaturization. Additionally, Wang *et al*[60] demonstrated that dermal papilla cell-derived exosomes activated the phosphatidylinositol-3-kinase/AKT pathway, significantly upregulating VEGF and downregulating apoptosis mediator caspase-3, resulting in improved follicle viability. Further, Chu *et al*[44] highlighted that exosome-derived long noncoding RNA AC010789.1 activated the S100A8/Wnt pathway, underscoring the intricate interplay between various pathways. Collectively, these findings illustrate exosomes' broad therapeutic potential through targeted modulation of diverse, complementary signaling networks critical for hair regeneration.

Scaffold and biomaterial integration (i.e., hydrogels, nanocarriers)

Recent research has investigated the use of biomaterials and scaffold systems to enhance the therapeutic potential and application of exosomes in hair regeneration. Chen *et al*[43] highlighted oxidized sodium alginate-based injectable microgels that significantly prolonged the release and retention of dermal papilla-derived extracellular vesicles, maintaining their biological activity and optimizing their efficacy. Similarly, Xiong *et al*[61] introduced thermosensitive hydrogels encapsulating JAM-A-overexpressing adipose mesenchymal stromal cell nanovesicles, which increased stability, ensured controlled release, and significantly enhanced dermal papilla cell proliferation and autophagy activation. Wu *et al*[45] developed hybrid exosomes combined with finasteride-loaded gold nanoparticles within vesicles, substantially improving follicular delivery and bioavailability. These advanced biomaterial-integrated exosome formulations clearly indicate their potential to augment exosome therapeutic efficiency, suggesting crucial implications for enhancing clinical applicability.

Long-term safety and efficacy considerations

Despite promising results, the long-term safety and durability of exosome-based hair regeneration therapies remain insufficiently studied. Lee *et al*[51] reported that patients treated with adipose-derived stem cell-derived exosomes did not experience any severe adverse effects, though mild scalp tingling was noted. Zhang *et al*[62] confirmed that there was no systemic toxicity in major organs following exosome administration in animal models, yet long-term biodistribution and potential off-target effects remain unclear. Wu *et al*[45] demonstrated that encapsulating exosomes in hybrid vesicles improved stability and biocompatibility, reducing degradation risks. While no studies reported immune rejection, rigorous clinical trials are essential to assess prolonged safety, immune responses, and sustained efficacy over time.

While short-term safety data from preclinical and early-phase clinical studies suggest that exosome-based therapies are generally well-tolerated, the long-term risks associated with their use remain insufficiently studied. In our review, we noted that clinical trials have reported minimal adverse effects, such as mild scalp tingling or localized irritation following administration of adipose- or dermal papilla cell-derived exosomes[51]. Additionally, even though animal models have not demonstrated evidence of systemic toxicity or immune rejection, the absence of long-term follow-up and rigorous post-treatment monitoring limits our understanding of potential delayed adverse outcomes[45,62].

One of the primary safety concerns involves the biological complexity and heterogeneity of exosome cargo[63]. Exosomes carry a range of molecules - including miRNAs, proteins, and lipids - which can affect various signaling pathways and can potentially influence cellular behavior[64]. The potential for adverse side effects including oncogenic activation or immune dysregulation cannot be ruled out, particularly with increased frequency and dosage. Furthermore, batch-to-batch variability and inconsistencies in isolation methods may lead to unpredictable therapeutic profiles, as we have previously described[65].

Optimal dosing treatment protocols

Determining the optimal dosing and treatment regimen for exosome-based hair regeneration remains an unresolved challenge. Studies vary widely in exosome concentrations, frequencies, and delivery methods, making direct comparisons difficult. Zhang *et al*[62] showed that higher concentrations of dermal papilla-derived exosomes (200 μg/mL) enhanced follicle proliferation, whereas lower doses had limited effects. Lee *et al*[51] reported that multiple sessions over 24 weeks improved hair density, suggesting that repeated administrations may be necessary for sustained results. However, excessive dosing risks immune activation or unintended signaling disruptions. Establishing standardized dosing guidelines through controlled clinical trials is essential for optimizing efficacy while ensuring safety.

Combination therapies

Integrating exosome therapy with complementary treatments may enhance hair regeneration outcomes by targeting multiple biological pathways. Several studies suggest that microneedling, pharmacological agents, and growth factor delivery can amplify exosome efficacy. Wu *et al*[45] demonstrated that hybrid vesicles co-delivering exosomes and finasteride enhanced follicular penetration and prolonged therapeutic effects compared to exosomes alone. Similarly,

Wang *et al*[60] found that combining exosomes with traditional Chinese medicine (Liao Tuo Fang) improved VEGF expression and hair follicle proliferation. Microneedling, which is known to stimulate dermal papilla activation, could further enhance exosome uptake[35,66]. Future studies should explore optimized combination protocols for maximum therapeutic synergy[67,68].

Clinical translation challenges and potential solutions

Despite promising preclinical data, translating exosome therapies into clinical practice remains complex. Key barriers include lack of large-scale human trials, variability in exosome isolation, and uncertain long-term effects. Lee *et al*[51] highlighted the absence of standardized dosing regimens, while Wu *et al*[45] emphasized the need for optimized delivery systems to enhance follicular uptake. Additionally, regulatory uncertainties slow clinical adoption. Potential solutions include developing GMP-compliant production methods, conducting multicenter trials, and integrating exosome therapies with existing dermatological treatments. Addressing these challenges is crucial for ensuring safe, scalable, and effective clinical implementation of exosome-based hair regeneration therapies[69-71].

Limitations of current animal models

Animal models play a crucial role in exosome research for hair regeneration, yet they often fail to fully replicate human hair follicle biology. Most studies, including those by Wu *et al*[45] and Zhang *et al*[47], rely on murine models, which lack human-like follicular cycling and immune responses. While rodent models provide insights into exosome-induced follicular proliferation, they do not account for androgen-driven miniaturization seen in androgenetic alopecia. Large-animal models, such as pigs, may offer better translational relevance. Future research must focus on developing humanized models or organoid-based systems to improve predictive validity for clinical applications.

Limitations of clinical studies

One of the primary limitations in the current body of literature is the extremely limited number of published clinical studies evaluating exosome-based therapies for hair regeneration. Of the studies included in this review, only three met eligibility criteria and each had small cohorts, varying methodologies, and short-term follow-up. The current evidence reported does not allow for forming strong conclusions regarding safety, efficacy, or long-term outcomes of exosome-based therapies for hair regeneration. This is particularly important as these therapies begin to attract increasing clinical interest and patient demand increases. Without larger, well-designed randomized trials, there remains a risk of premature clinical application based on early-stage data that may not hold up under more rigorous testing. Furthermore, the lack of standardized dosing protocols, manufacturing consistency, and long-term safety data compounds the uncertainty.

Exosome therapy shows some promise for hair regeneration, but there are many limitations that hinder its widespread clinical use. First, the lack of standardized protocols for exosome isolation, purification, and dosage makes treatment outcomes inconsistent. Additionally, the potential for immune reactions or unwanted side effects remains unclear due to limited long-term studies. Scalability and cost are also major concerns, as high-quality exosome production is expensive and complex. Furthermore, regulatory hurdles pose challenges, as exosome-based therapies require rigorous safety and efficacy testing before approval.

A key limitation of this review is the absence of formal statistical analysis or meta-analytic synthesis of the included studies. Due to substantial heterogeneity in study designs, exosome sources, outcome measures, and reporting formats, quantitative comparison or pooling of effect sizes across studies was not feasible. Most studies reported qualitative or semi-quantitative outcomes without standardized metrics, further limiting our ability to perform a rigorous comparative analysis. While we aimed to provide a comprehensive overview of current findings, future research in this field would benefit from greater methodological consistency and standardized reporting, which would enable meaningful statistical evaluation and evidence-based comparison of therapeutic efficacy across different exosome-based interventions. Lastly, while early research is promising, robust clinical trials with large patient populations are needed to confirm its long-term benefits and mechanisms in hair regeneration[71].

CONCLUSION

Exosome-based therapies hold immense promise for the treatment of hair loss by leveraging their ability to modulate key signaling pathways and enhance hair follicle regeneration. While pre-clinical studies demonstrate consistent efficacy across diverse exosome sources, methodological heterogeneity and the limited amount of clinical data highlight the need for further research. Addressing these challenges through standardized protocols, early-phase, adequately powered, randomized clinical trials with longer follow-up, and combinatorial approaches will be critical in realizing the full potential of exosome therapies in clinical practice.

FOOTNOTES

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