

Exosome-based therapy for androgenetic alopecia: a systematic review of preclinical mechanisms and efficacy

Adniana Nareswari¹✉, Paramasari Dirgahayu², Ratih Puspita Febrinasari³

¹Department of Dermatology Venereology, Faculty of Medicine, Sebelas Maret University, Central Java, Indonesia. ²Department of Parasitology, Faculty of Medicine, Sebelas Maret University, Central Java, Indonesia. ³Department of Pharmacology, Faculty of Medicine, Sebelas Maret University, Central Java, Indonesia.

Abstract

Androgenetic alopecia (AGA) is a progressive hair disorder with a substantial psychosocial impact. Current therapies have variable efficacy and adherence challenges. Exosomes are emerging as regenerative candidates. We systematically appraised preclinical (in vivo / in vitro) evidence on exosome-based intervention for AGA following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, searching PubMed and Scopus. Eligible studies evaluated exosome or extracellular vesicle interventions in androgen-related alopecia models. Of 352 records, 16 studies met inclusion criteria, most employing male C57BL/6 mice with testosterone or dihydrotestosterone (DHT) induction alongside assays in dermal papilla cells (DPCs) and hair follicle stem cells. Sources include mesenchymal stem cell derived, DPC-derived, platelet-rich plasma derived, and engineered/primed exosomes, predominantly delivered via local intradermal/subcutaneous routes or topical microneedles/hydrogels over 2 to 4 weeks. Across studies, exosomes improved hair coverage and density, anagen/telogen ratio, follicle diameter, dermal thickness, and proliferation markers, while reducing apoptosis; mechanistic signals consistently showed reactivation of Wnt/ β -catenin and down-modulation of TGF- β /SMAD3, with additional angiogenic support, anti-inflammatory effects, and mitigation of oxidative stress, and adverse signals were minimal in animals. Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) appraisal indicated generally low risk with common concerns regarding blinding and allocation concealment. Overall, exosome therapy demonstrates compelling preclinical efficacy for AGA via multi-target regenerative mechanisms.

Keywords: androgenetic alopecia, exosomes, extracellular vesicles, hair regeneration, dermal papilla

Received: 28 November 2025 | Returned for modification: 4 June 2026 | Accepted: 2 July 2026

Introduction

Androgenetic alopecia (AGA) is a progressive condition characterized by miniaturization of hair follicles. It is estimated to affect up to 80% of men and 50% of women over age 50. In men, it manifests as a characteristic pattern of baldness in the vertex and frontotemporal areas, whereas in women it often presents as diffuse hair thinning at the crown of the head. In addition to physical manifestations, AGA can have significant psychosocial impacts, affecting self-esteem, body image, and social interactions. The pathogenesis of AGA is a multifactorial interaction of genetic and hormonal factors. Dihydrotestosterone (DHT), produced from testosterone via the enzyme 5- α -reductase, plays a central role. DHT binds to the androgen receptor (AR) in dermal papilla cells (DPCs), triggering a series of molecular events that shorten the anagen (growth) phase and prolong the telogen (resting) phase, ultimately leading to hair follicle shrinkage. Genetic factors, including polymorphisms in the AR gene and other genes involved in hair growth pathways, also significantly influence individual susceptibility. Recent evidence also suggests that low-grade inflammation around the hair follicles contributes to the pathogenesis of AGA (1, 2).

The main Food and Drug Administration (FDA)-approved therapies, topical minoxidil and oral finasteride, have limitations. Minoxidil is a vasodilator that prolongs the anagen phase, but its effects are often temporary and require lifelong use. Finasteride, a 5- α -reductase inhibitor, is effective in reducing DHT levels but can cause unwanted side effects such as sexual dysfunction and gynecomastia (3, 4). Other regenerative therapies, such as platelet-rich

plasma (PRP) and hair transplantation, also have drawbacks. PRP plasma exhibits high variability in results, and hair transplantation is invasive and expensive, and it does not prevent further loss of non-transplanted hair follicles (5–7). Exosomes (30–150 nm), a type of extracellular vesicle (EV), carry protein and microRNA (miRNA) cargo that can reprogram recipient cells, offering a cell-free regenerative strategy potentially overcoming safety and logistical hurdles of cell therapies. Stem cell-derived exosomes have been shown to possess remarkable capabilities in tissue regeneration, including promoting cell proliferation, angiogenesis, and immune modulation (8–11). This potential makes exosomes ideal candidates for innovative therapies for AGA, offering a more natural and comprehensive approach. We systematically reviewed preclinical evidence on exosome-based AGA interventions, summarizing efficacy, mechanisms, safety, and gaps.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure replicability and reproducibility (12). The review protocol was not prospectively registered, and no external funding influenced the design, data collection, or reporting process.

Search strategy and search terms

A comprehensive literature search was conducted using the Pub

✉ Corresponding author: adnianaanawari@student.uns.ac.id

Med and Scopus databases to identify relevant studies published between January 2015 and November 2025. The search strategy followed Medical Subject Headings (MeSH) terminology combined with Boolean operators to maximize coverage. The keywords used included (“exosomes” OR “extracellular vesicles”) AND (“androgenetic alopecia” OR “hair loss” OR “hair regeneration”) OR (“stem cell-derived exosomes”) AND (“AGA” OR “hair growth”) OR (“exosomes” AND “dermal papilla cells” AND “proliferation”). The selection process adhered strictly to the PRISMA framework, encompassing the stages of identification, removal of duplicates, title and abstract screening, full-text evaluation, and final inclusion. Two independent reviewers (A. N. and P. D.) conducted all stages of screening and selection, and any disagreements were resolved by consensus with a third reviewer to ensure objectivity and minimize bias.

Eligibility criteria

The inclusion criteria encompassed experimental preclinical studies conducted either *in vivo* using animal models or *in vitro* using cell culture systems relevant to AGA. Eligible studies involved the administration of exosomes or EVs, regardless of their origin, dosage, delivery route, or modification method. Studies were considered relevant if they investigated androgen-induced alopecia models, particularly those employing testosterone propionate (TP) or DHT induction in mice, or used cell models derived from human or murine DPCs and hair follicle stem cells (HFSCs). Only studies published in English or Indonesian, available as full text, and published within the designated 10-year period (2015–2025) were included. Studies were excluded if they were conducted in humans, designed as case reports, case series, or reviews, or did not involve exosome-based interventions. Nevertheless, the reference lists of review articles were manually screened to identify additional eligible primary studies not captured in the initial database search.

Data extraction

Data were extracted independently by two reviewers using a standardized data extraction form to ensure consistency and minimize transcription errors. Extracted information included the author’s name, year of publication, study design, animal strain or cell type, method of alopecia induction, details of exosome isolation and administration (source, dosage, delivery route, and treatment duration), and principal outcomes related to hair growth or follicle regeneration. Mechanistic data such as modulation or molecular pathways—for example, wntless related integration site (Wnt) / β -catenin, transforming growth factor beta (TGF- β) / SMAD3, or vascular endothelial growth factor (VEGF) / cluster of differentiation (CD31)—were recorded, along with any reported adverse events or abnormal findings. In cases of disagreement, the two reviewers discussed discrepancies and reached consensus through verification of the original article.

Risk of bias assessment

The methodological quality and internal validity of the animal studies included were evaluated using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias tool (13). This tool, adapted from the Cochrane Collaboration framework, assesses multiple domains of potential bias specific to

animal research, including sequence generation, baseline comparability, allocation concealment, random housing, blinding of caregivers and outcome assessors, completeness of outcome data, selective outcome reporting, and other potential sources of bias. Each domain was rated as having a low, high, or unclear risk of bias.

Data synthesis

Given the substantial heterogeneity among the studies included regarding animal species, exosome source, dose, delivery route, treatment duration, and measured outcomes, a qualitative narrative synthesis was employed instead of a meta-analysis. The synthesis integrated findings related to hair regrowth, follicular morphology, and molecular mechanisms while highlighting consistent biological pathways involved in the therapeutic action of exosomes. The data were organized thematically to reflect the main mechanistic domains, including proliferation, apoptosis, angiogenesis, inflammation, oxidative stress, and stemness preservation.

Results and discussion

Data extraction

The study selection process is illustrated in Figure 1, which presents the PRISMA 2020 flow diagram summarizing the identification, screening, and inclusion phases of the systematic review. A total of 352 records were retrieved from the two electronic databases searched. After full-text review, 16 studies met all inclusion criteria and were incorporated into the qualitative synthesis. Each of these studies provided *in vivo*, *in vitro*, or combined preclinical evidence on the therapeutic potential of exosomes or extracellular vesicles in androgenetic alopecia models.

Risk of bias assessment

The methodological quality of the studies included was evaluated using the SYRCLE Risk of Bias (RoB) tool, which assesses bias domain adapted from the Cochrane framework for animal research. The overall summary of assessment is presented in Figure 2A, and the detailed study-level distribution across individual bias domains is shown in Figure 2B.

Overall, the majority of studies demonstrated a low risk of bias in most domains evaluated, suggesting adequate internal validity and reliable methodological execution. Domains such as random group allocation, baseline group similarity, reporting of dropouts, freedom from selective outcome reporting, and absence of other biases were consistently rated as low risk across nearly all studies. This indicates that most experiments were conducted with proper control of confounding factors and transparency in reporting outcomes.

However, certain methodological concerns were identified. The domains related to blinding procedures—specifically, blinded group allocation, blinded intervention, and blinded outcome assessment—showed a mix of unclear and high risk of bias because several studies did not explicitly state whether investigators or assessors were blinded during treatment administration and data evaluation. Similarly, the random housing and random outcome assessment domains were occasionally rated as unclear, suggesting that allocation concealment and randomization during housing or data analysis were not always adequately described.

Despite these limitations, the overall methodological quality of the studies included remains acceptable, with most exhibiting low risk in key areas that influence study validity.

Study subject

A total of sixteen experimental studies met the inclusion criteria and were analyzed in this review (Table 1). The majority of these investigations employed C57BL/6 mice as experimental subjects, accounting for more than 80% of all animal studies included. Almost all used male mice with dorsal hair depilation to synchronize the hair growth cycle before treatment, allowing consistent evaluation of anagen induction and hair regrowth. A few studies utilized other strains, such as C57BL/6N and BALB/c, but these were less frequent and primarily served as complementary models. In addition to animal experiments, several studies incorporat-

ed human-derived cell models to strengthen mechanistic insights. Human DPCs were the most frequently used, appearing in more than 60% of the studies included, often employed to validate in vivo findings through proliferation, migration, and gene expression assays. Other commonly used cell types included HFSCs, human umbilical vein endothelial cells (HUVECs), fibroblasts, and macrophage cell lines (RAW264.7). The combination of in vivo mouse models and in vitro human or murine cell assays was particularly prominent in recent publications (2023–2025), reflecting a trend toward integrated mechanistic and phenotypic validation of exosome-based therapies for androgenetic alopecia (3, 14–28).

The C57BL/6 mouse strain is widely regarded as the standard model for hair cycle research due to its highly synchronized follicular cycling after birth. Following depilation, dorsal skin in these mice predictably transitions from telogen (resting) to anagen (growth) phase, which is easily monitored by visual skin

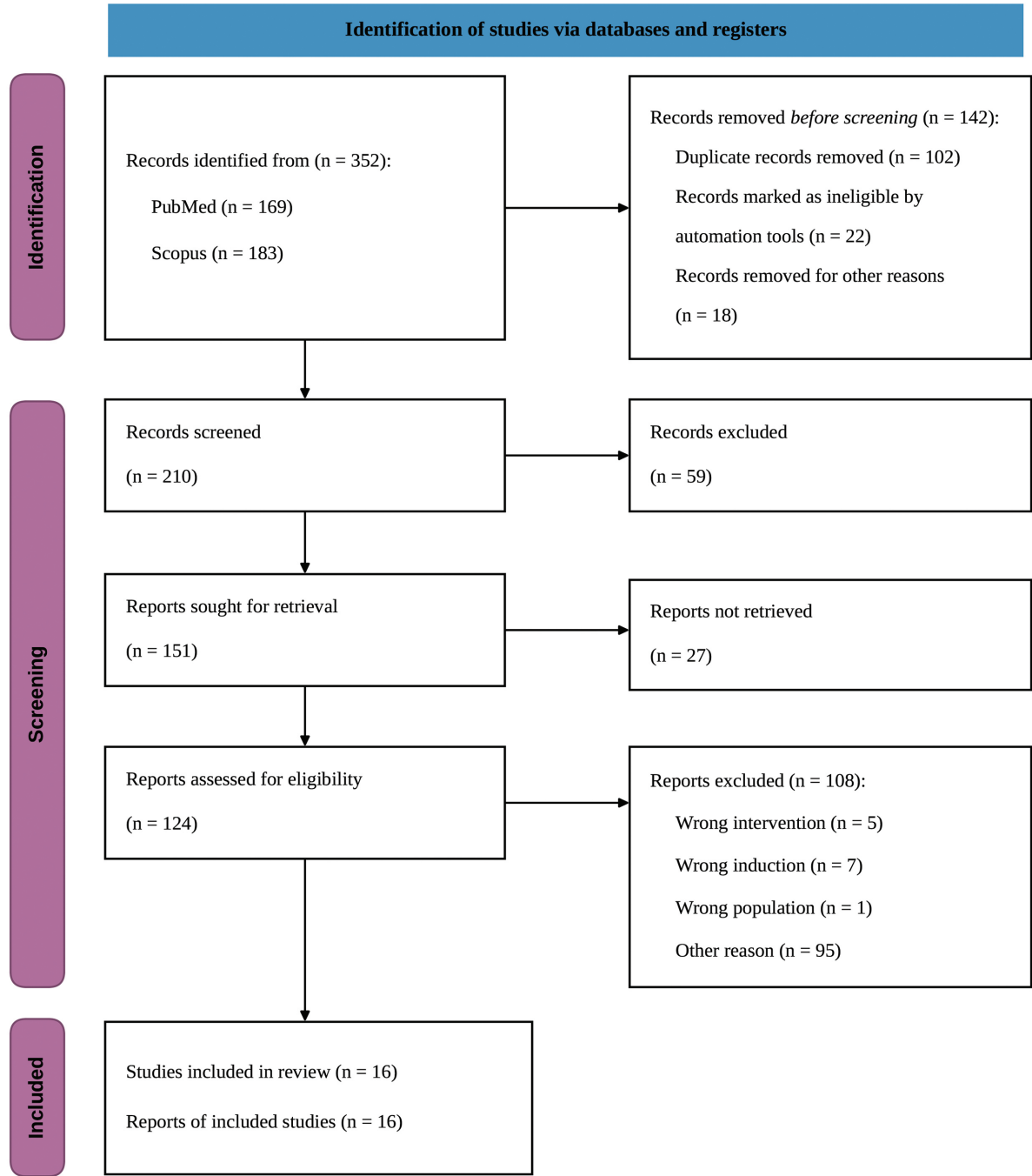


Figure 1 | PRISMA 2020 flow diagram of study selection.

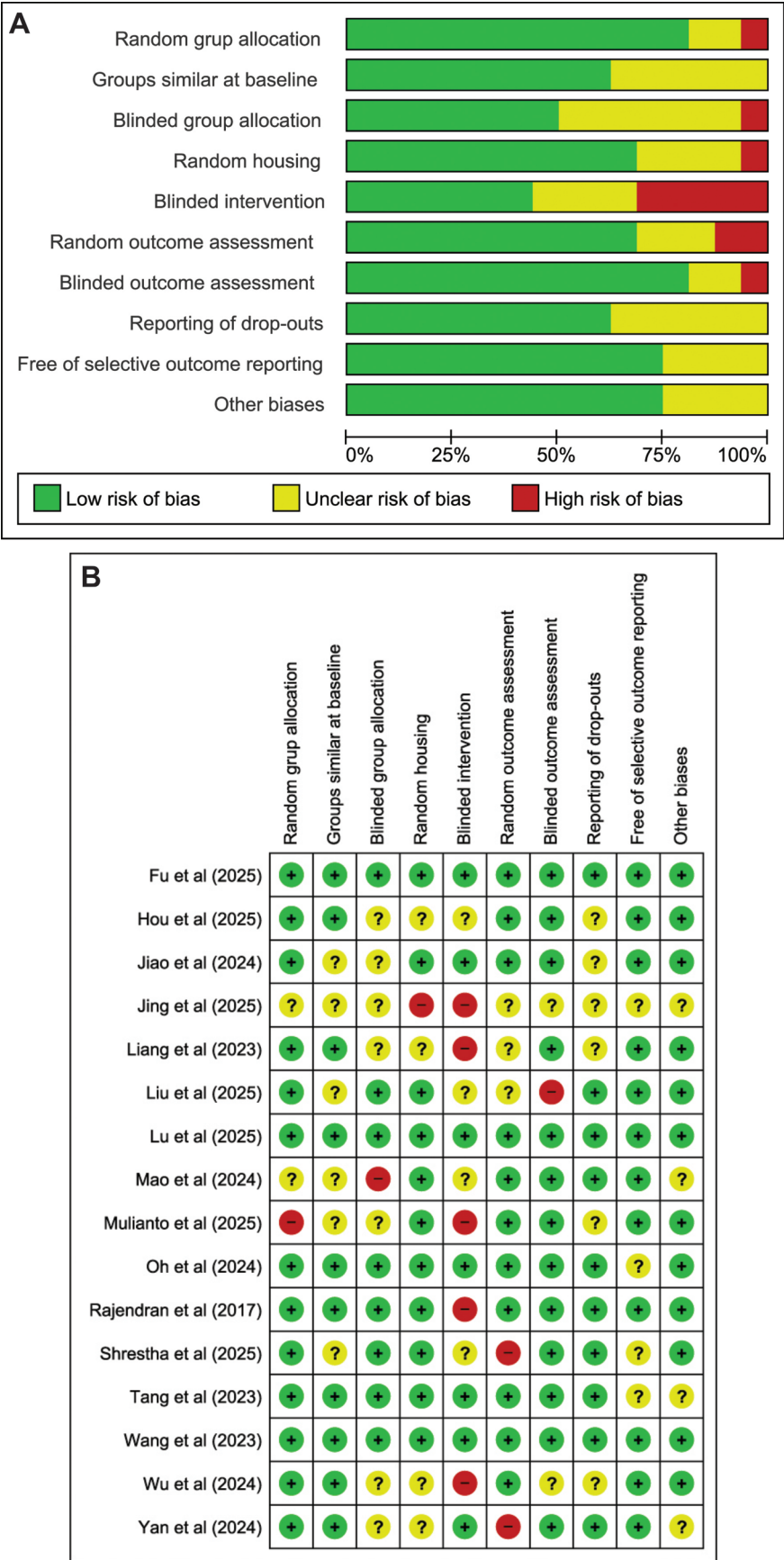


Figure 2 | Risk of bias assessment using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool. (A) Summary chart showing the overall percentage of studies classified as having low (green), unclear (yellow), or high (red) risk of bias across ten methodological domains. Most domains, including random allocation, baseline comparability, outcome reporting, and other biases, demonstrated predominantly low risk. Higher or unclear risks were primarily observed in domains related to blinding and random housing. (B) Study-level risk of bias matrix for all sixteen included studies, displaying the judgment of each bias domain per study. Most studies exhibited low risk of bias, though a few demonstrated unclear or high risk in blinding and randomization-related criteria.

pigmentation changes. This synchronization allows precise timing of interventions, allowing controlled delivery of exosomes or other treatments and facilitating consistent documentation of hair regrowth. Furthermore, strains such as C57BL/6 and BALB/c are inbred, providing genetic homogeneity that enhances reproducibility and minimizes biological variability across experiments. These characteristics make them ideal for preclinical testing, mechanistic studies, and drug screening (29–36).

The architecture and cycling properties of mouse hair follicles are structurally analogous to those in humans, and their response to androgens (such as DHT or TP) reliably mimics key features of human AGA, including follicle miniaturization, delayed anagen, and hair density loss. Mice are cost effective, are easy to house and handle, and yield ample numbers for statistical analysis. Their small size and established genome further allow for genetic modification and *in vivo* mechanistic exploration (29–36).

Androgenetic alopecia model

Nearly all studies included in this review employed an androgen-induced model of alopecia to replicate the pathophysiological features of human AGA. The most frequently used induction agent was TP, administered either subcutaneously or topically at doses ranging from 0.5 to 5 mg/kg/day for 21 to 28 consecutive days. This approach effectively induces follicular miniaturization and delayed anagen onset. The second most common induction method involved DHT, administered via intradermal, subcutaneous, or intraperitoneal routes at concentrations between 0.5 and 30 mg/kg, typically given daily or every 2 to 3 days over a period of 1 to 4 weeks. Successful establishment of AGA was verified through characteristic findings, including absence of hair regrowth, miniaturized follicles, reduced dermal thickness, delayed anagen entry, and suppressed cellular proliferation markers such as Ki67 or proliferating cell nuclear antigen (PCNA). A minority of studies adopted non-androgen-dependent models, in which alopecia was induced through depilation or telogen synchronization without hormonal manipulation. These models, reported in studies such as those by Jiao et al. (17), Rajendran et al. (24), and Shrestha et al. (25), were primarily utilized to evaluate regenerative mechanisms rather than androgen-specific pathways (3, 14–28).

TP is used as an induction agent by mimicking the human endocrine environment. While being administered (commonly subcutaneously or topically), TP is absorbed and locally converted to DHT by the enzyme 5 α -reductase present in skin and hair follicles. DHT is the more potent androgen responsible for AGA. Increased local DHT results in activation of AR in DPCs, suppression of Wnt/ β -catenin signaling, shortened anagen (growth) phase and accelerated transition to catagen/telogen, miniaturization of hair follicles, and reduced hair density—hallmarks of AGA pathophysiology. This androgen-driven model provides a physiologically relevant framework for studying the molecular and regenerative effects of exosome therapy. It allows for controlled modulation of androgen signaling and recapitulates the gradual, progressive follicular suppression observed in human disease. As such, TP and DHT-induced mouse model remain the gold standard for preclinical evaluation of novel interventions targeting androgen-mediated hair loss (31, 37).

Intervention and outcomes

Exosome source types include mesenchymal stem cell-derived

exosomes (MSC-Exos), with the most frequent source from adipose tissue, umbilical cord, or bone marrow. Others include DPC-derived exosomes (DPC-Exos); PRP-derived exosomes (PRP-Exos), especially in 2025 studies; and modified/engineered exosomes loaded with microRNA (miR-122-5p), drugs (curcumin or finasteride), growth factors (VEGF-A, Wnt family member 10B [WNT10B], or fibroblast growth factor 7 [FGF7]), or functional materials (selenium nanozyme or gold nanoparticles). Hypoxia-primed or rapamycin-primed MSC exosomes also emerged as promising methods to improve exosome potency and stability. Less common but notable alternatives included milk-derived extracellular vesicles (mEVs) and hybrid vesicles combining exosomes with liposomal carriers (3, 14–28).

The delivery route was a key determinant of efficacy and tissue penetration. Subcutaneous administration was the predominant approach, accounting for approximately 70% of studies, followed by intradermal injections designed to mimic clinical mesotherapy or PRP protocols. Topical nanocarrier systems, including microneedle patches, hydrogels, and liposome-based formulations, were increasingly utilized in recent studies (2024–2025) to enhance localized delivery and prolong exosome retention. The typical treatment duration ranged from 2 to 4 weeks, with repeated administration either daily or every 2 to 3 days. Localized systems such as hydrogels or microneedle platforms required fewer doses—typically three to four administrations at 3-day intervals—and some experimental protocols explored the efficacy of single-dose injections with sustained results; for example, Shrestha et al. (25) and Yan et al. (28).

Percentages and fractions reported in this and the following paragraph are calculated over the 15 studies for which comparable quantitative data could be extracted; the remaining study of the 16 included did not report outcomes in a form that permitted tabulation alongside the others. Across nearly all studies included, exosome therapy produced robust improvements in hair regrowth. Quantitatively, 100% of studies reported visible enhancement in hair coverage, density, and shaft diameter, and 80% demonstrated significant increases in the anagen/telogen (A/T) ratio. Approximately 60% observed increased dermal thickness, and 73% documented elevated proliferation markers (Ki67 and PCNA) in follicular keratinocytes or DPCs. Indicators of apoptosis reduction—including decreased terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) positivity and caspase-3 expression—were reported in 40% of studies, whereas angiogenic enhancement (increased VEGF and CD31) appeared in 53%. Comparative analyses revealed that, in two-thirds ($\approx$ 67%) of studies, exosome-based interventions were superior or equivalent to minoxidil or finasteride, establishing their strong preclinical therapeutic potential (3, 14–28).

Dominant pathogenesis mechanisms are as follows. AR-Wnt/ β -catenin axis suppression (androgen-induced β -catenin blockade) was identified in 13/15 studies (87%). The TGF- β /SMAD3 pathway result in apoptosis and growth suppression was found in 7/15 studies (47%). Inflammation (interleukin [IL]-6, tumor necrosis factor- α [TNF- α], microinflammation in follicle milieu) was identified in 6/15 studies (40%). Reactive oxygen species (ROS) accumulation was found in 4/15 studies (27%), predominantly newer studies with nanozyme-loaded EVs. Angiogenesis impairment such as microvascular rarefaction and VEGF downregulation was identified in 5/15 studies (33%). Stemness loss in HFSCs (reduced CD200, K15, Lgr5/6, etc.) was found in 5/15 studies (33%). Immune system/immune cell contributions were iden-

tified in 2/15 studies (13%); these are not a dominant aspect, but an emerging one (3, 14–28).

As explained previously, exosome therapy in AGA thus works via multi-pronged molecularly targeted mechanisms including activating Wnt/ β -catenin, inhibiting TGF- β /SMAD3, reducing inflammation and apoptosis, promoting angiogenesis, mitigating oxidative stress, and preserving stemness and proliferation signaling, providing a fundamentally regenerative, cell-free approach beyond conventional drugs (3, 14–28). Exosomes, especially those derived from MSCs, DPCs, and modified/engineered sources, carry bioactive proteins, mRNAs, and microRNAs (e.g., Wnt3a, Wnt10b, miR-181a-5p, and miR-22-5p) that directly activate the canonical Wnt/ β -catenin pathway in DPCs and hair follicle stem cells. Exosome cargo activates Wnt ligands and inhibits glycogen synthase kinase-3 β (GSK3 β), preventing phosphorylation and degradation of β -catenin. This results in β -catenin nuclear translocation, which upregulates the target genes required for follicle entry into anagen (growth phase), cell proliferation (Ki67, PCNA), matrix production, restoration of follicle proliferation, reversal of DHT/AR-induced β -catenin blockade, and robust hair regrowth (14, 24, 38, 39).

Exosomes, notably those enriched with miR-122-5p and other regulatory microRNAs, counteract the DHT-induced upregulation of TGF- β 1/SMAD3 in DPCs and matrix cells. miR-122-5p in exosome cargo binds to SMAD3 mRNA, reducing its translation and thereby suppressing the downstream pro-apoptotic signaling. This leads to decreased caspase-3 activation and reduced follicular apoptosis. In TGF pathways, this maintains follicular viability, prevents miniaturization, and sustains the anagen phase (39). Exosomes suppress the expression of inflammatory cytokines (IL-6, TNF- α) released by damaged or androgen-stressed DPCs and surrounding skin cells. Exosome cargo (miRNAs and anti-inflammatory proteins) inhibits the NF- κ B pathway and inflammatory gene transcription. It promotes M2 macrophage polarization, increasing anti-inflammatory microenvironment. This pathway reduces microinflammation, prevents perifollicular fibrosis/scarring, and supports regenerative repair (38, 40).

Exosomes are loaded with angiogenic factors (VEGF, FGF7, and WNT10B), as seen in engineered variants (e.g., EX104), and they stimulate vascular endothelial cell function in the follicular niche. Exosome upregulation of VEGF and CD31 enhances new capillary formation and promotes proliferation, migration, and tube formation in endothelial cells. This restores microvascular supply, supports active hair follicle metabolism, and accelerates regrowth and density (3, 38, 41).

Exosome components neutralize excess ROS in skin/hair follicle cells. Exosomes increase glutathione protein expression and decrease matrix metalloproteinases (MMP) involved in ROS-induced damage. They augment cell survival and collagen synthesis via phosphorylated extracellular signal regulated kinase (P-ERK) and signal transducer and activator of transcription (STAT6) pathways. As antioxidants, exosomes preserve hair follicle integrity, prevent atrophy, and support robust regrowth under stress conditions (40). Exosomes upregulate HFSC markers (K15, Lgr5, and CD200), enhancing self-renewal and differentiation potential. Activation of the rat sarcoma virus oncogene homologue (RAS) / extracellular signal regulated kinase (ERK) / mitogen activated protein kinase (MAPK) signaling pathway by exosome cargo up-regulates stemness-associated gene expression, which prevents AR-induced stem cell exhaustion and supports entry into anagen. This mechanism maintains the stem cell pool, allowing sustained cycles of hair regeneration.

Exosome-derived factors (e.g., VEGF and miR-129-2-3p) activate PI3K/AKT signaling. Enhanced AKT1 phosphorylation leads to increased cell survival, growth, and anti-apoptotic mechanisms. Direct inhibition of caspase-3 results in decreased follicular apoptosis and improved viability. This activation fosters follicle regeneration and prevents premature cell death. Supporting data show that proteomic and transcriptomic analysis of exosomes confirms enrichment for growth/regenerative factors, and proven ability to modulate gene expression in DPCs/HFSCs. Other studies state that engineered exosomes (e.g., EX104) with optimized cargo outperform conventional therapies in murine AGA models and show enhanced follicle regeneration, capillary density, and proliferation.

Other findings and safety considerations

Across the studies included, exosome-based interventions showed favorable safety profiles and excellent biocompatibility. Most experiments reported no systemic toxicity, with animals maintaining stable body weight, normal grooming behavior, and preserved organ histology upon microscopic examination. Local adverse effects were minimal; for example, studies utilizing PRP-Exos occasionally noted mild transient erythema or swelling at injection sites, which resolved spontaneously without intervention or histologic damage.

Formulation approaches also contributed to safety and sustained efficacy. The incorporation of exosomes into hydrogel matrices was found to slow degradation, extend local retention, and prolong therapeutic action. Similarly, milk-derived mEVs showed high scalability, low immunogenicity, and good tissue compatibility, supporting their potential as an affordable, mass-producible delivery system. Modified or engineered vesicles, including selenium nanozyme-encapsulated exosomes (Se-HEVs) and synthetic hybrid EVs (engineered EVs), maintained favorable biosafety while demonstrating superior regenerative efficacy in promoting follicular proliferation and angiogenesis.

However, several translational challenges were acknowledged. The murine hair cycle is highly synchronized and significantly shorter than in humans, which may lead to exaggerated regrowth responses and limit clinical extrapolation. Moreover, only a few studies considered economic feasibility and production scalability, particularly in comparison to established therapies such as minoxidil and finasteride, which remain more cost effective and widely accessible. Despite these challenges, the consistent demonstration of safety and efficacy across multiple preclinical models strongly supports the translational potential of exosome-based therapies for androgenetic alopecia (3, 14–28).

Study limitations

The main limitation is translational gaps between animal models and human disease. Although mouse hair cycles can be synchronized and manipulated for assessment, species differences mean that the results may not fully reflect human AGA pathophysiology and treatment responses. In addition, exosome sources, dosing, delivery methods, and regimens varied widely among studies, making direct comparison and standardization difficult. Some engineered or modified exosomes showed enhanced effects. Few studies systematically evaluated long-term safety, cost-effectiveness, and practicality compared to conventional therapies such as minoxidil and finasteride. High variability and lack of large-scale

randomized controlled human trials limit certainty regarding the efficacy, optimal administration, and reproducibility of exosome-based AGA treatment.

Conclusions

Exosome therapy demonstrates strong potential as a novel and effective regenerative approach for the treatment of AGA, as evidenced by consistent findings across preclinical in vivo and in vitro studies. Exosomes derived from MSCs, DPCs, and PRP markedly promote hair regrowth through multifaceted biological mechanisms, primarily by reactivating the Wnt/ β -catenin signaling pathway and suppressing the TGF- β /SMAD3 axis. Beyond restoring follicular proliferation, exosomes exert anti-apoptotic,

anti-inflammatory, angiogenic, antioxidant, and stemness-preserving effects, collectively supporting follicular regeneration and prolongation of the anagen phase. These cell-free vesicles thus offer a biologically targeted, minimally invasive, and potentially safer alternative to conventional pharmacologic treatments such as minoxidil and finasteride.

Future research should focus on standardizing exosome isolation and characterization, optimizing dose and delivery routes, and conducting controlled clinical trials to confirm safety, reproducibility, and long-term efficacy in human androgenetic alopecia. There is need for more rigorous implementation and explicit reporting of randomization and blinding procedures to further minimize potential bias.

References

- Li H, Cai H, Li P, Zeng Y, Zhang Y. Assessing causality between androgenetic alopecia with depression: a bidirectional Mendelian randomization study. *Clin Cosmet Investig Dermatol*. 2025;18:445–51.
- Sakhiya J, Sakhiya D, Modi M, Gandhi S, Daruwala F. Prevalence, severity and associated factor of androgenetic alopecia in the dermatology outpatient clinic: a retrospective study. *Indian J Clin Exp Dermatol*. 2019;5:280–7.
- Liu Y, Liu Y, Zhao J, Deng T, Ben Y, Lu R, et al. Subcutaneous injection of genetically engineered exosomes for androgenic alopecia treatment. *Front Bioeng Biotechnol*. 2025;13:1614090.
- Ntshingila S, Oputu O, Arowolo AT, Khumalo NP. Androgenetic alopecia: an update. *JAAD Int*. 2023;13:150–8.
- Yuan J, He Y, Wan H, Gao Y. Effectiveness of platelet-rich plasma in treating female hair loss: a systematic review and meta-analysis of randomized controlled trials. *Skin Res Technol*. 2024;30:e70004.
- Paichitrojjana A, Paichitrojjana A. Platelet rich plasma and its use in hair regrowth: a review. *Drug Des Devel Ther*. 2022;16:635–45.
- Gentile P, Garcovich S, Bielli A, Sciolli MG, Orlandi A, Cervelli V. The effect of platelet-rich plasma in hair regrowth: a randomized placebo-controlled trial. *Stem Cells Transl Med*. 2015;4:1317–23.
- Aguiar Koga BA, Fernandes LA, Fratini P, Sogayar MC, Carreira ACO. Role of MSC-derived small extracellular vesicles in tissue repair and regeneration. *Front Cell Dev Biol*. 2022;10:1047094.
- Lee YJ, Shin KJ, Chae YC. Regulation of cargo selection in exosome biogenesis and its biomedical applications in cancer. *Exp Mol Med*. 2024;56:877–89.
- Asgari R, Rashidi S, Soleymani B, Bakhtiari M, Mohammadi P, Yarani R, et al. The supportive role of stem cells-derived exosomes in the embryo implantation process by regulating oxidative stress. *Biomed Pharmacother*. 2025;188:118171.
- Emanuelli C, Shearn AIU, Angelini GD, Sahoo S. Exosomes and exosomal miRNAs in cardiovascular protection and repair. *Vascul Pharmacol*. 2015;71:24–30.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol*. 2021;134:103–12.
- Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol*. 2014;14:43.
- Fu Y, Han YT, Xie JL, Liu RQ, Zhao B, Zhang XL, et al. Mesenchymal stem cell exosomes enhance the development of hair follicle to ameliorate androgenetic alopecia. *World J Stem Cells*. 2025;17:102088.
- Hou C, Wang S, Li Z, Huang Q, Jiang Y, Zhou X, et al. Curcumin-primed milk-derived extracellular vesicles remodel hair follicle microenvironment for the treatment of androgenetic alopecia. *Regen Biomater*. 2025;12:rbaf051.
- Wu X, Huang X, Zhu Q, Zhang J, Hu J, Song Y, et al. Hybrid hair follicle stem cell extracellular vesicles co-delivering finasteride and gold nanoparticles for androgenetic alopecia treatment. *J Control Release*. 2024;373:652–66.
- Jiao Y, Sun QM, Shen YC, Li QS, Piao YJ, Gong L. Stimulation of mouse hair regrowth by exosomes derived from human umbilical cord mesenchymal stem cells. *Acta Histochem*. 2024;126:152184.
- Jing S, Liu Y, Wang B, Zhou H, Zhang H, Siwakoti P, et al. Microneedle-mediated hypoxic extracellular vesicle-encapsulated selenium nanoparticles delivery to treat androgenetic alopecia. *J Control Release*. 2025;381:113597.
- Liang Y, Tang X, Zhang X, Cao C, Yu M, Wan M. Adipose mesenchymal stromal cell-derived exosomes carrying MIR-122-5p antagonize the inhibitory effect of dihydrotestosterone on hair follicles by targeting the TGF- β 1/SMAD3 signaling pathway. *Int J Mol Sci*. 2023;24:5703.
- Lu C, Ding Y, Zhang R, Du Y, Bi L, Zhao M, et al. Platelet-rich plasma-derived exosomes stimulate hair follicle growth through activation of the Wnt/ β -catenin signaling pathway. *Regen Ther*. 2025;29:435–46.
- Mao Y, Liu P, Wei J, Xie Y, Zheng Q, Hu X, et al. Exosomes derived from umbilical cord mesenchymal stem cell promote hair regrowth in C57BL6 mice through up-regulation of the RAS/ERK signaling pathway. *J Transl Int Med*. 2024;12:478–94.
- Mulianto N, Julianto I, Irawanto ME, Dharmawan N, Monica PW, Oktaviani T. Comparative study on therapeutic efficacy of minoxidil and platelet-rich plasma exosome in androgenetic alopecia mice models. *Int J App Pharm*. 2025;89–92.
- Oh HG, Jung M, Jeong SY, Kim J, Han S, Kim H, et al. Improvement of androgenic alopecia by extracellular vesicles secreted from hyaluronic acid-stimulated induced mesenchymal stem cells. *Stem Cell Res Ther*. 2024;15:287.
- Rajendran RL, Gangadaran P, Bak SS, Oh JM, Kalimuthu S, Lee HW, et al. Extracellular vesicles derived from MSCs activates dermal papilla cell in vitro and promotes hair follicle conversion from telogen to anagen in mice. *Sci Rep*. 2017;7:15560.
- Shrestha M, Nguyen TT, Kausar R, Chaudhary D, Puspitasari IF, Jiang HL, et al. Enhancing hair regrowth using rapamycin-primed mesenchymal stem cell-derived exosomes. *Theranostics*. 2025;15:6938–56.
- Tang X, Cao C, Liang Y, Han L, Tu B, Yu M, et al. Adipose-derived stem cell exosomes antagonize the inhibitory effect of dihydrotestosterone on hair follicle growth by activating Wnt/ β -catenin pathway. *Stem Cells Int*. 2023;2023:1–20.
- Wang G, Wang Z, Zhang J, Shen Y, Hou X, Su L, et al. Treatment of androgenetic alopecia by exosomes secreted from hair papilla cells and the intervention effect of LTF. *J Cosmet Dermatol*. 2023;22:2996–3007.
- Yan W, Liu J, Xie X, Jin Q, Yang Y, Pan Y, et al. Restoration of follicular β -catenin signaling by mesenchymal stem cells promotes hair growth in mice with androgenetic alopecia. *Stem Cell Res Ther*. 2024;15:439.
- Orasan MS, Roman II, Coneac A, Muresan A, Orasan RI. Hair loss and regeneration performed on animal models. *Clujul Med*. 2016;89:327–34.
- Bran EL, Pérez LP, Esteban PT, Morales MLG. Hair growth stimulated by allogenic adipose-derived stem cells supplemented with ATP in a mouse model of dihydrotestosterone-induced androgenetic alopecia. *Stem Cell Res Ther*. 2025;16:292.
- Fu D, Huang J, Li K, Chen Y, He Y, Sun Y, et al. Dihydrotestosterone-induced hair regrowth inhibition by activating androgen receptor in C57BL6 mice simulates androgenetic alopecia. *Biomed Pharmacother*. 2021;137:111247.
- Sundberg JP, Taylor D, Lorch G, Miller J, Silva KA, Sundberg BA, et al. Primary follicular dystrophy with scarring dermatitis in C57BL/6 mouse substrains resembles central centrifugal cicatricial alopecia in humans. *Vet Pathol*. 2011;48:513–24.
- Woo MJ, Kang HY, Paik SJ, Choi HJ, Uddin S, Lee S, et al. The in vivo and in vitro effects of Terminalia bellirica (Gaertn.) Roxb. fruit extract on testosterone-induced hair loss. *J Microbiol Biotechnol*. 2023;33:1467–74.
- Wang WH, Ramos R, Tai KY, Wu YS, Chang TY, Yan JY, et al. Studying hair growth cycle and its effects on mouse skin. *J Invest Dermatol*. 2023;143:1638–45.
- Anjum MA, Zulfiqar S, Chaudhary AA, Rehman IU, Bullock AJ, Yar M, et al. Stimulation of hair regrowth in an animal model of androgenic alopecia using 2-deoxy-D-ribose. *Front Pharmacol*. 2024;15:1370833.
- Lee BH, Lee JS, Kim YC. Hair growth—promoting effects of lavender oil in C57BL/6 mice. *Toxicol Res*. 2016;32:103–8.

37. Lee HJ, Hong GL, Kim KH, Kim YJ, Kim TW, Jung JY. Therapeutic potentiality of Celtis choseniana Nakai on androgenic alopecia through repression of androgen action and modulation of Wnt/ β -catenin signaling. *Nat Prod Sci.* 2023;29:31–7.
38. Poddar N, Aratikatla A, Gupta A. Therapeutic potential of stem cell-derived exosomes in hair regeneration: A systematic review. *World J Stem Cells.* 2025;17:108519.
39. Li J, Zhao B, Dai Y, Zhang X, Chen Y, Wu X. Exosomes derived from dermal papilla cells mediate hair follicle stem cell proliferation through the Wnt3a/ β -catenin signaling pathway. *Oxid Med Cell Longev.* 2022;2022:9042345.
40. Norouzi F, Aghajani S, Vosoughi N, Sharif S, Ghahremanzadeh K, Mokhtari Z, et al. Exosomes derived stem cells as a modern therapeutic approach for skin rejuvenation and hair regrowth. *Regen Ther.* 2024;26:1124–37.
41. Lyu L, Cai Y, Zhang G, Jing Z, Liang J, Zhang R, et al. Exosomes derived from M2 macrophages induce angiogenesis to promote wound healing. *Front Mol Biosci.* 2022;9:1008802.

Table 1 | Summary of studies included on exosome-based therapy for androgenetic alopecia.

Study	Subject	AGA model	Intervention	Outcomes	Pathogenesis highlighted	Other
Fu et al. (2025) (14)	Male C57BL/6 mice, human DPCs	TP 5 mg/kg, s.c. daily for 4 weeks on dorsal depilated skin, confirmed by lack of hair regrowth	hADSC-Exos, 100 µg/ml, subcutaneously into skin via microneedle daily, started day 1 with TP for 21 days	↑ hair regrowth score vs TP group; at 21 days, similar anagen follicles as minoxidil group. In vitro: ↑ DPC proliferation/migration, rescued DHT-inhibited DPC growth, enhanced Wnt3a and β-catenin, ↓ GSK3β	DHT shortens anagen via AR in DPCs and inhibits Wnt/β-catenin, exosomes (via CDC42/Wnt/β-catenin) re-activate pathway, stimulate DPCs.	No significant adverse effects in mice, comparable to minoxidil in efficacy, uses standardized isolation, cell-free therapy
Hou et al. (2025) (15)	Male C57BL/6 mice, skin, cells	Topical testosterone (0.5% in 50% ethanol), high dose (200 µL/cm ²), daily for 27 to 28 days, dorsal depilated area, successful by delayed skin darkening and hair coverage	Cur-mEVs subcutaneous multi-point injection, 2,000 µg/ml mEVs / 250 µg/ml curcumin, 200 µL, every other day for 13 days	↓ time to skin darkening, ↑ hair coverage and density, ↑ hair diameter, ↑ anagen follicles, faster reversal of androgen suppression than curcumin or mEVs alone. ↓ IL-6, TNF-α; ↑ SOX9, Wnt3a/β-catenin; ↓ TGF-β1	Androgen induces β-catenin degradation and TGF-β1 (inhibitor), inflammation central to pathogenesis, curcumin-mEVs restore Wnt/β-catenin, ↓ TGF-β1 and inflammation	No organ toxicity, stable body weight, safe, highly scalable (from milk)
Wu et al. (2024) (16)	C57BL/6 mice, cell lines (DP, HFSC, HUVEC)	Topical testosterone (0.5% in ethanol, 0.1 ml/cm ²), daily for 14 days after depilation, validated by lack of regrowth	Hybrid vesicles (HFSC EVs fused with liposomes), co-loaded with finasteride (topical), and gold nanoparticles (mimic phototherapy), topical gel, once daily	At 14 days: blank (N/A), minoxidil 32% area regrowth, hybrid/Au@FI 54% (superior), thicker shafts, ↑ skin/hair bulb thickness, ↑ anagen. In vitro: HDPC migration ↑, DPC/HUVEC viability ↑.	Microenvironment repair: cell signaling (EVs), 5α-reductase inhibition (finasteride), activation of growth/angiogenesis (EVs, gold NP)	Storage stable, no cytotoxicity / side effects, superior to minoxidil alone
Jiao et al. (2024) (17)	C57BL/6 mice, fibroblast cultures	Depilation-induced spontaneous regrowth (not androgen-based), dorsal region, compared to PBS	hUCMSC-Exos (umbilical cord MSC exosomes), 200 µg/ml, s.c. injection daily for 14 to 21 days, compared to PBS	↑ hair regrowth, thicker skin, ↑ anagen, ↑ proliferation (CCK8), markers (K15, Lgr5, Lgr6, CD34, Lrig1, Wnt5, Lef1, Lrp5, β-catenin); ↑ CD34+CD49f+ cells FACS	hUCMSC-Exos upregulate Wnt/β-catenin, stimulate s.c. proliferation/differentiation (key anagen activators).	No side effects noted, not an androgen-based AGA model, focused on regenerative boost
Jing et al. (2025) (18)	C57BL/6 mice, HHDPs, HUVECs, RAW264.7	Topical testosterone (0.2% w/v), daily for 14 days after depilation, dorsal skin, successful by no regrowth	Microneedle patch with hypoxic EVs (from DPSCs) loaded with selenium nanozyme (Se-HEVs), 100 µg/ml, applied every 3 days for four doses (days 1, 4, 7, 10)	↑ hair density, ↑ follicle diameter/shaft, ↑ anagen %, ↓ ROS/inflammation (↑ M2/M1 ratio), ↑ CD31 (angiogenesis), ↑ SOX9, ↑ Ki67, ↑ CK19 (mature follicles); in vitro: ↓ ROS, apoptosis, ↑ VEGF	AGA features: oxidative stress, microvascular damage, inflammation; Se-HEVs rescue by ROS scavenging, promote angiogenesis, resist androgen.	No histological toxicity, biocompatible, zenith hair regrowth outperforms minoxidil group
Liang et al. (2023) (19)	Human cells (DPCs, HF, in vitro), in vivo C57BL/6 mice	DHT (105 mol/l) exposure for cells, in vivo, subcutaneous DHT injection after hair removal (dose in solution, detailed in figures)	Adipose-derived mesenchymal stromal cell exosomes (ADSC-Exos), enriched in miR-122-5p, 50 µg/ml, subcutaneous injection or in vitro	ADSC-Exos promoted DPC/HF proliferation, reversed DHT inhibition, increased β-catenin, versican, BMP2, decreased TGF-β1/SMAD3, increased hair coverage and anagen dermal thickness, larger bulbs, restored β-catenin, reduced SMAD3	DHT upregulates TGF-β/SMAD3, downregulates β-catenin/versican; miR-122-5p in exosomes targets SMAD3, blocks DHT effect, activates Wnt/β-catenin for hair growth.	No apparent adverse effects, miR-122-5p other potential targets not excluded, minoxidil compared as positive control
Liu et al. (2025) (3)	Mice (C57BL/6), in vitro human and murine DPCs	Subcutaneous DHT injection (30 mg/kg), after depilation, every 3 days, recapitulated miniaturized follicles and suppressed proliferation (validated by controls and molecular readouts)	Subcutaneous engineered exosomes (EX104) from HEK-293 cells, loading human/mouse VEGFA, WNT10B, FGF7, 0.1 ml/dose, every 3 days, mock exosome and topical minoxidil as controls	EX104 reversed miniaturization, increased hair coverage (> 70%), increased number/diameter of follicles, higher Ki67+ (proliferation), increased CD31+ (angiogenesis), reduced TNF-α, increased β-catenin, higher anagen/telogen ratio	DHT triggers AR, DKK1, IL-6 increases, suppresses LEF1, Wnt; EX104 recovers proliferative, angiogenic, and Wnt/β-catenin homeostasis, suppresses negative regulators.	EX104 outperformed minoxidil in capillary/angiogenesis and proliferation, no mention of adverse effects, only murine models for in vivo

Table 1 | Continued.

Study	Subject	AGA model	Intervention	Outcomes	Pathogenesis highlighted	Other
Lu et al. (2025) (20)	Human DPCs (in vitro), mice (C57BL/6, in vivo)	Not directly stated for in vivo mouse model, but dorsal hair synchronized in telogen by depilation, negative control and treatments compared	Platelet-rich plasma–derived exosomes (PRP-Exos), isolated from activated platelet-rich plasma, subcutaneous injection in mice ($\approx 200 \mu\text{g}$ total), in vitro in DPCs (5, 10, 50 $\mu\text{g}/\text{ml}$)	Increased proliferation, migration, cell cycle S+G2/M, higher β -catenin, Lef-1, decreased SFRP1, increased skin thickness, follicle diameter, higher anagen/telogen ratio, higher Ki67+/ β -catenin+ cells, TUNEL revealed reduced apoptosis	Activates Wnt/ β -catenin signaling in DPCs, promotes cell cycle, suppresses apoptosis; PRP-Exos rich in growth factors/VEGF	No side effects reported, minoxidil used as control, similar results but PRP-Exos led to greater skin thickening, exosome source is autologous/human
Mao et al. (2024) (21)	Mice (C57BL/6)	DHT (1 mg daily, i.p.) $\times$ 17 days after depilation, successful: model group had shorter/thinner hair, less follicles, higher AR in skin	Umbilical cord mesenchymal stem cell exosome hydrogel (local topical application, 1 ml, twice daily, dose not stated per weight), minoxidil (5%) as positive control	Exosomes increased hair length, diameter, follicle number vs. model, restored AR to baseline, increased CD200, K15 (HFSC stemness), increased PCNA (proliferation); transcriptomics: upregulated RAS/ERK/MAPK pathway	DHT-induced AGA: upregulation of AR, loss of HFSC stemness, reduced proliferation; exosomes restore stemness via RAS/ERK pathway, suppress AR.	Exosome hydrogel slowed protein degradation, enhanced effectiveness vs. exosome alone not tested, no adverse effects, minoxidil reversed AR but did not upregulate ERK/MAPK like exosomes
Mulianto et al. (2025) (22)	Mice (14 BALB/c, AGA model)	8-week-old male mice, subcutaneous testosterone 0.1 ml daily for 10 days on dorsal skin, induction based on prior studies, AGA confirmed	1. Minoxidil 5% (topical, two sprays, 2 ml twice daily, 3 weeks), 2. PRP-exosome (0.1 ml intradermal injection on days 11, 18, 25)	PRP-Exo group: hair follicle density $68.61 \pm 7.64 / \text{mm}^2$; minoxidil: $40.14 \pm 11.60 / \text{mm}^2$ ($p = 0.0007$); anagen:telen ratio PRP-Exo 0.34 ± 0.04 , minoxidil 0.22 ± 0.02 ($p = 0.0009$); PRP-Exo $>$ minoxidil for both metrics	Hair loss linked not only to androgen sensitivity but also microinflammation and immune cell role. PRP-Exo via growth factors, cytokines, exerts regenerative effect.	PRP-Exo effects lasted longer, mild local side effects, mouse cycle more synchronized than human, caution in translating to humans, minoxidil is more affordable.
Oh et al. (2024) (23)	Mice (C57BL/6N, AGA model), in vitro DPCs	Topical 0.5% testosterone propionate daily for 27 days, confirmed AGA phenotype (dorsal hair shaving prior), also in vitro DPCs + testosterone	1. Vehicle, 2. testosterone only, 3. finasteride (1 mg/kg s.c. every other day), 4. iMSC-EV 5. HA-iMSC-EV (0.2 mg/kg s.c. every other day)	HA-iMSC-EVs reversed testosterone-induced reduction of anagen ratio (1.19 in HA-iMSC-EV group, 0.53 in AGA, 1.29 in finasteride), improved β -catenin and reduced AR protein; in vitro, HA-iMSC-EVs reduced AR and inflammatory markers, increased growth factors (IGF1, FGF7, VEGF).	Androgen-induced AR activation inhibits Wnt β -catenin; HA-iMSC-EVs block AR, activate β -catenin, re-activate anagen via blocking GSK3 β -mediated β -catenin degradation.	HA-iMSC-EV effect comparable to finasteride, iMSC-EV (non-primed) insignificant, no notable side effects, limited by non-human model and possible immune contributions.
Rajendran et al. (2017) (24)	Mice (C57BL/6, telogen-anagen model), human DPCs	Not a classical AGA model, synchronized telogen by dorsal hair clipping/shaving in mice, no androgen induction	PBS (control), MSC-EV (mouse bone marrow, intradermal 200 μg every two days, 28 days), minoxidil (3% topical)	MSC-EV group: earlier anagen entry (darkening of dorsum at day 11), $> 60\%$ hair regrowth day 18, full regrowth by day 27 (like minoxidil). Increased dermal thickness, upregulated Wnt3a/Wnt5a, versican, VEGF, IGF-1 in mouse skin and DP cells. In vitro, DP proliferation, migration, and VEGF/IGF-1 secretion increased.	MSC-EVs stimulate DP cell proliferation/migration and upregulate Wnt/ β -catenin pathway, promote telogen anagen conversion via growth factors.	No significant toxicity observed, effect in non-androgen-driven model, not a direct AGA model, effects equal to minoxidil in healthy telogen-anagen transition

Table 1 | Continued.

Study	Subject	AGA model	Intervention	Outcomes	Pathogenesis highlighted	Other
Shrestha et al. (2025) (25)	Mice (C57BL/6, depilation model), dermal fibroblasts	No AGA or androgen induction, hair synchronized by depilation (shaving, depilatory cream, 3 days)	REXO (exosome from rapamycin-primed adipose MSCs, 100 µg intradermal, single dose, n = 6), CEXO (unprimed exosomes, same dose), PBS	REXO treated mice: faster and more complete hair regrowth by day 15 (vs. CEXO, control); higher density and size of follicles in histology; in fibroblasts, REXO boosted Wnt/β-catenin pathway genes, autophagy markers, VEGF-A/PDGF-B, and increased cell proliferation.	REXO upregulates Wnt β-catenin, autophagy, and growth factors in target cells; priming with rapamycin enhances exosome bioactivity.	No AGA model, focus on cell proliferation/regeneration, not androgen response, translation to human AGA not direct, no adverse effects in mice, need mechanistic studies
Tang et al. (2023) (26)	Human hair follicles, DPCs, C57BL/6 mice	DHT (10 ⁻⁵ mol/L); in vivo observation period of 21 days, with delayed anagen phase confirmed by lack of hair regrowth and follicular miniaturization	ADSC-Exos (5–20 µg/ml in DPC cultures and 5–80 µg/ml in human hair follicle organ cultures); in mice, a total volume of 300 µL was administered subcutaneously across 12 dorsal injection sites at 48-h intervals	↑Proliferation, migration, and hair-inducibility markers in DPCs; ↑Ki67+ matrix cells (up to 77.8% vs. 32.1% control); ↑skin thickness, ↑hair follicle number; effect equal/superior to minoxidil; restored anagen phase after DHT suppression	DHT upregulates AR, inhibits Wnt/β-catenin in DPCs, triggers apoptosis and miniaturization. Exosomes reactivate Wnt/β-catenin, antagonizing DHT and stimulating DPCs.	No significant adverse effects, concentration-dependent effect, optimal range established for different models, cell-free therapy with clear mechanisms
Wang et al. (2023) (27)	Female C57BL/6 mice, mouse DPCs	TP 5 mg/kg, s.c. for 28 days after depilation, validated by hair loss, skin pathology	DPC-EXO (exosomes from DPCs treated with Liao Tuo Fang herbal compound), 0.2 ml LTF-DPC-EXO s.c. daily × 7 to 15 days, topical LTF or minoxidil as comparators	Significant hair regrowth vs model; at 42 days, ↑hair length and follicle number in exosome group (5.35 mm/37 follicle average vs. 4.2 mm/16 in model, control 6.5 mm/41); ↑VEGF, AKT1, ↓CASP3 (mRNA/protein)	DHT induces apoptosis (↑CASP3), anti-angiogenesis (↓VEGF); exosomes activate PI3K/AKT, upregulate VEGF/AKT1, suppress apoptosis, repair microenvironment.	Safe, no organ toxicity, herbal modulation of exosome cargo, comparable/superior to minoxidil and LTF alone, cell-free, storable, scalable avenue
Yan et al. (2024) (28)	Male C57BL/6 mice, mouse DPCs/HFSCs	DHT (0.5 mg/d s.c.) daily for 1 week post-depilation, validated delayed anagen, skin atrophy	hUC-MSCs (human umbilical cord mesenchymal stem cells); 1 × 106 intradermal (multiple sites), single injection post-DHT	↑Hair regrowth rate, ↑skin thickness (quantified), ↑anagen proportion, ↑follicle density; ↓DPC apoptosis (TUNEL, Casp3 expression), ↑HFSC proliferation (Ki67); DHT+MSC group similar to normal controls	DHT induces DPC apoptosis, blocks Wnt/β-catenin, disrupts paracrine (VEGF, FGF7) for HFSCs; MSCs restore Wnt/β-catenin via Wls → β-catenin → Myc, promote growth factor secretion, suppress apoptosis.	No significant adverse events, mechanistically validated by pathway inhibition and gene knockdown, standardized source and protocols

ADSC-Exos = adipose-derived mesenchymal stromal cell exosomes, AGA = androgenetic alopecia, AR = androgen receptor, A/T ratio = anagen/telogen ratio, Au@Fi = gold nanoparticles co-loaded with finasteride, BMP2 = bone morphogenetic protein 2, CASP3 = caspase-3, CCK8 = Cell Counting Kit-8, CCNA1 = cyclin A1, CCND1 = cyclin D1, CD31 = platelet endothelial cell adhesion molecule, CD34 = stem/progenitor cell marker, CDK4 = cyclin-dependent kinase 2 and 4, CEXO = exosome from conventional (unprimed) adipose MSCs, CK19 = cytokeratin 19, Cur-mEVs = curcumin-primed milk-derived extracellular vesicles, DHT = dihydrotestosterone, DKK1 = Dickkopf-related protein 1, DPC(s) = dermal papilla cell(s), DPC-EXO = exosomes from dermal papilla cells, ERK/MAKP = extracellular signal-regulated kinase/mitogen-activated protein kinase, EV = extracellular vesicle, FACS = fluorescence-activated cell sorting, FGF7 = fibroblast growth factor 7, finasteride = an oral anti-androgen drug, GSK3β = glycogen synthase kinase 3 beta, hADSC-Exos = human adipose-derived stem cell exosomes, HA-IMSC-EV = hyaluronic acid-induced mesenchymal stem cell exosome, HF = hair follicle, HFSC = hair follicle stem cell, hUCMSC-Exos = human umbilical cord mesenchymal stem cell exosomes, HUVEC = human umbilical vein endothelial cell, i.p. = intraperitoneal, IGF1 = insulin-like growth factor 1, iMSC-EV = induced mesenchymal stem cell exosome, K15 = keratin 15, Ki67 = a proliferation marker, LEF1 = lymphoid enhancer-binding factor 1, Lgr5 = leucine-rich repeat-containing G-protein coupled receptor 5, Lgr6 = leucine-rich repeat-containing G-protein coupled receptor 6, Lrig1 = leucine-rich repeats and immunoglobulin-like domains protein 1, LTF = Liao Tuo Fang, M2/M1 = macrophage polarization status, mEVs = milk-derived extracellular vesicles, minoxidil = a topical hair regrowth drug, Myc = cellular Myc proto-oncogene, PBS = phosphate-buffered saline, PCNA = proliferating cell nuclear antigen, PDGF-B = platelet-derived growth factor subunit B, PRP-Exos = platelet-rich plasma-derived exosomes, q2d = every two days, RAS = rat sarcoma viral oncogene homolog, RAW264.7 = smooth muscle macrophage cell line, REXO = exosome from rapamycin-primed adipose MSCs, s.c. = subcutaneous, Se-HEVs = selenium nanosome-encapsulated hypoxic extracellular vesicles, SFRP1 = secreted frizzled-related protein 1, SMAD3 = mothers against decapentaplegic homolog 3, SOX9 = SRY-box transcription factor 9, TGF-β1 = transforming growth factor-beta 1, TP = testosterone propionate, TUNEL = terminal deoxynucleotidyl transferase dUTP nick end labeling, VEGF = vascular endothelial growth factor, w/v = weight/volume, Wls = Wntless, Wnt3a = Wnt family member 3A, Wnt5a = Wnt family member 5A, β-catenin = beta-catenin.