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REVIEW ARTICLE

Systematic review of exosome treatment in hair restoration: Preliminary evidence, safety, and future directions

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Abstract

Background: Exosomes are small extracellular vesicles with potential roles in modulating the hair growth cycle and are an emerging therapy for patients with alopecia. In recent years, researchers have made significant progress in deciphering the network of cellular interactions and signaling pathways mediated by the transfer of exosomes. This has opened the door to a wide range of potential therapeutic applications with an increasing focus on its application in precision medicine.

Aim: To evaluate current published evidence, both preclinical and clinical, on the use of exosomes for hair restoration.

Methods: In January 2023, a systematic search was conducted using PubMed, Embase, and the Cochrane Library. Records were identified, screened, and assessed for eligibility as per the PRISMA guideline.

Results: We identified 16 studies (15 preclinical and 1 clinical) showing varying degrees of efficacy using exosomes derived from sources including adipose-derived stem cells (ADSCs) and dermal papilla cells (DPCs). Applications of exosomes isolated from ADSCs (ADSC-Exo) and DPCs have shown early promising results in preclinical studies corroborated by results obtained from different model systems. Topical ADSC-Exo has been tried successfully in 39 androgenetic alopecia patients demonstrating significant increases in hair density and thickness. No significant adverse reactions associated with exosome treatment have been reported thus far.

Conclusions: Although current clinical evidence supporting the use of exosome treatment is limited, there is a growing body of evidence suggesting its therapeutic potential. Further studies are warranted to define its mechanism of action, optimize its delivery and efficacy, and to address important safety concerns.

KEYWORDS
alopecia, exosomes, hair, regenerative medicine

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1 | INTRODUCTION

Hair loss attributed to non-scarring alopecia, such as androgenetic alopecia (AGA) or alopecia areata (AA), represents a significant source of disease and psychological burden to patients of all ages.[1,2] There is a need for new and innovative therapies that offer sustained hair regrowth over extended durations with minimal side effects.

Previous studies have shown the potential efficacy of stem cell therapies derived from the adipose tissue in inducing significant hair growth in AGA and AA patients; similar results were also observed using extract of secreted proteins containing exosome and other extracellular vesicles (EVs).[3,4]

Exosomes are small (30–150 nm) cargo-delivering EVs that mediate intercellular communications, they are characterized by a phospholipid bilayer with specific surface markers and cargos that affect cell signaling and gene expression (e.g., cytokines, growth factors and regulatory microRNAs [miRNAs]).[5] Although its exact mechanism of action is unclear; it is suspected that exosomes, through modulations of paracrine signaling, can mediate the crosstalk between epithelial cells and mesenchymal cells during the hair growth cycle.[6] For example, exosomes derived from dermal papilla cells (DPCs; DPC-Exos) were shown to upregulate the Wnt/β-catenin pathway in outer root sheath cells (ORSCs), resulting in the telogen-to-anagen transition in mice.[7]

The present review covers the current landscape of exosome treatment in hair restoration, with a focus on preclinical, clinical, and safety data reported thus far in the literature. Issues concerning the safety of exosome treatment, as well as future directions, are discussed.

2 | MATERIALS AND METHODS

An electronic search was conducted in January 2023 using PubMed, Embase (Ovid), and the Cochrane Library, without date or language restrictions. We aimed to investigate published evidence pertaining to the use of exosomes for hair growth. Items identified using the following search/MeSH terms were combined: "exosome," "alopecia," "hair follicle," "dermal papilla cell," "root sheath," and "Wnt pathway." Reference sections of relevant review articles were screened for additional records. Deduplication and screening of identified records were performed using Rayyan (https://www.rayyan.ai/). Studies were excluded if a mixture of EVs was used, and if the observed effects could not be attributed to the exosome fraction; for instance, studies examining the effects of nanovesicles produced through serial cell protrusions were excluded as it may contain cellular organelles and proteins not associated with exosomes.[8] This review was designed in concordance with the PRISMA guideline.[9]

3 | RESULTS AND DISCUSSION

Following the initial identification of 255 search results, 16 articles were eligible for data extraction (Figure 1). Of the 15 preclinical studies, information on source, content and target of exosomes, as well as any observed genotypic and/or phenotypic effects are summarized in Table 1; each data entry was sorted based on the model system used (i.e., in vitro, in vivo, or ex vivo). Results from 1 clinical study of 39 patients are summarized in Table 2. No randomized or controlled trials were found.

3.1 | Preclinical evidence

Favorable effects have been observed using exosomes derived from a variety of cell types, this includes exosomes derived from mesenchymal stem cells such as adipose-derived stem cells (ADSCs) observed to increase hair growth and dermis thickness in vivo, potentially through paracrine regulation of DPCs as demonstrated in vitro (Table 1).[10–12,19] Similar functions were observed for DPC-Exos; most notably, DPC-Exos purified from three-dimensional cell culture induced human hair follicle growth (Table 1).[13] This result corroborated findings of previous in vivo studies demonstrating hair growth effects including the acceleration of the telogen-to-anagen transition in mice, potentially through the upregulation of fibroblast growth factor and β-catenin pathways.[7,13,20] DPCs may function as a paracrine regulator of hair follicle stem cells (HFSCs) and ORSCs.[7,13–15] Interestingly, another in vitro study showed that exosomes isolated from human ORSCs exhibited similar effects vice versa in DPCs (Table 1).[17]

Other potential sources of exosomes include myeloid-derived suppressor cells and amniotic fluid stem cells (Table 1).[21,22] Exosomes purified from platelet lysis or platelet-rich plasma (PRP) did not appear to be effective in vitro.[12,17] The addition of fisetin (a plant extract), as well as the use of bovine colostrum as an alternative exosome source, may increase the production of exosomes in cell culture systems (Table 1).[16,18] Moreover, the use of a microneedle patch loaded with exosomes may improve the efficacy of topical formulations (Table 1).[23]

Regulation of the hair growth cycle observed in preclinical studies may be attributed to the delivery of miRNAs, which are short strands of non-coding RNA molecules with regulatory functions in gene expression (Figure 2). Variable effects, such as promoting or inhibiting hair growth, can be seen depending on the type of miRNA delivered. A previous in vitro study reported migration of DPCs to the proximity of HFSCs during the telogen phase, which led to the uptake of $CD63^+$ DPC-Exos.[25] Sequencing analysis of DPC-Exos identified 111 differentially expressed miRNAs, with miR-22-5p exhibiting inhibitory effects on hair growth through the downregulation of the *LEF1* gene.[25] In contrast, miR-181a-5p and miR-218-5p found in DPC-Exos were shown to induce hair growth in vitro and in vivo, respectively (Table 1; Figure 2).[14,20]

3.2 | Clinical evidence

Exosomes are currently not approved by the U.S. Food and Drug Administration (FDA) to treat hair disorders. In a case series, records

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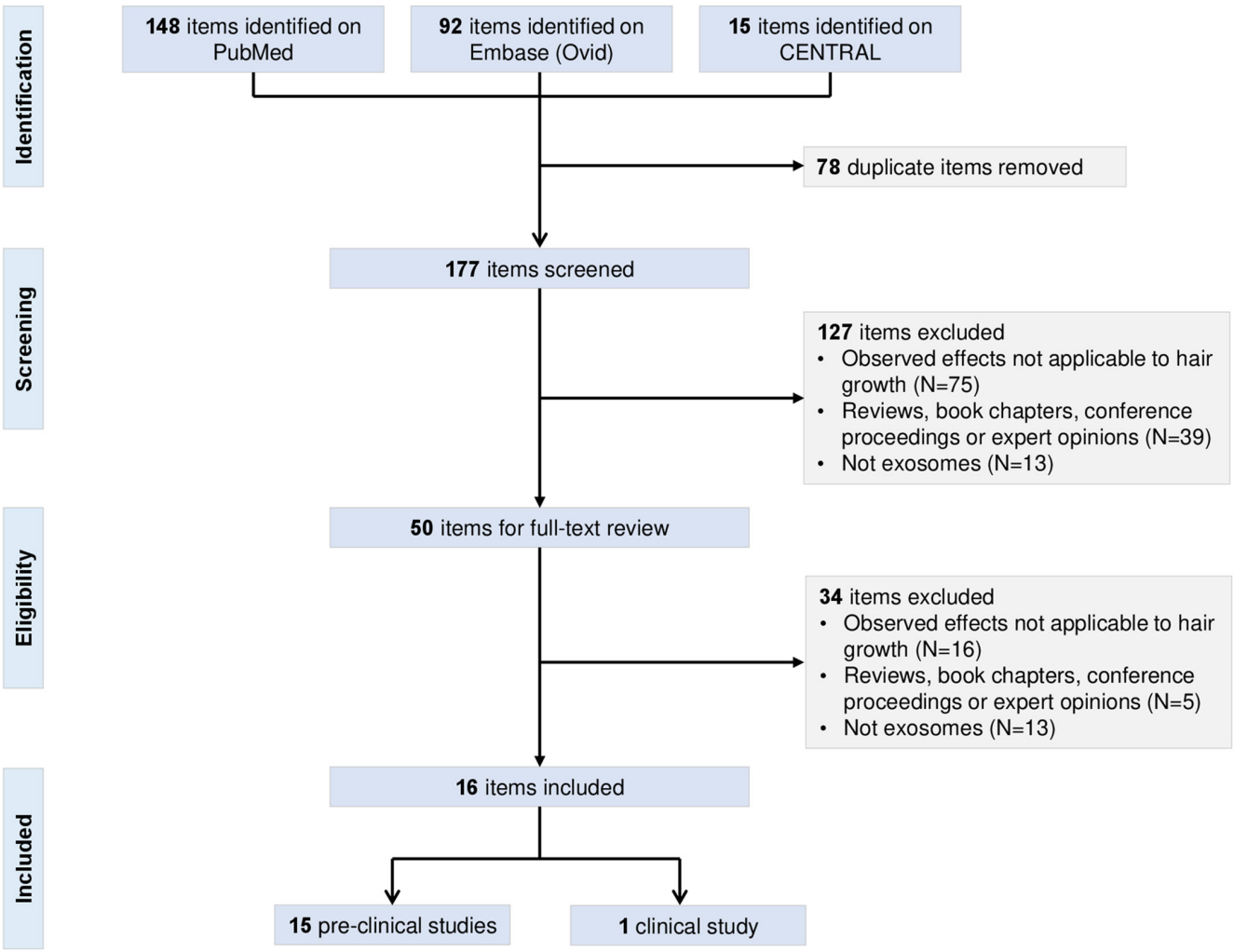

FIGURE 1 Overview of the systematic search. CENTRAL, Cochrane Central Register of Controlled Trials.

of 39 AGA patients with mild to moderate hair loss who received exosome treatment were reviewed (Table 2).[24] Exosomes purified from ADSCs were applied topically (>6×10^{10} particles/vial); each application was administered with a microneedle roller once weekly for 12 weeks.[24] At follow-up, significant improvements in hair density (146.6 hairs/cm^2 vs. 121.7 hairs/cm^2) and hair thickness (61.4 μm vs. 52.6 μm) were observed. There were no age-or hair loss duration-dependent effects on treatment response. However, the possibility of spontaneous hair regrowth could not be excluded in this study due to lack of control.

Nonetheless, these results corroborated the findings of another case series study using intradermal biologic injection containing EVs.[26] After one course of treatment, 64.5% (20/31) of patients reported hair growth at follow-up; trichoscan assessment in 11 responders showed an increase in hair density between 11.1% and 24.2%.[26] However, the effects observed in this study can not be attributed to the exosome fraction as the patients had received injections containing a mixture of EVs. Another open-label, single-arm study examining the effects of placental mesenchymal cell–derived exosomes in alopecia patients is ongoing (ClinicalTrials.gov; NCT05658094).

3.3 | Safety

There is scarce information on the safety of exosome treatment in patients experiencing hair loss. Safety data on topical exosome treatment are available from two studies of 39 AGA patients and 25 patients treated for acne scars.[24,27] No serious adverse reactions were reported in AGA patients after exosomes derived from ADSCs were applied topically once weekly for a total of 12 treatment sessions (Table 2).[24] In another double-blinded study, 25 patients with acne scars were randomized to receive topical applications of either a 30% gel of ADSC-Exo or a control gel.[27] Treatment was given twice a day for 2 days. At follow-up, symptoms including pain, erythema, edema, and dryness were reported with both ADSC-Exo treatment and control, which resolved within 5 days.[27] An average downtime of 4.1 days was associated with topical ADSC-Exo treatment, which was significantly shorter compared with patients who received the control gel (4.3 days); one case of mild hyperpigmentation was also reported.[27]

The safety of subcutaneous injections was assessed in a case series of 31 AGA patients who received biologic treatment derived from human bone marrow mesenchymal stem cells (MSCs), which contains a mixture of EVs in addition to exosomes.[26] Patients were

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TABLE 1 Summary of preclinical evidence on the use of exosomes in hair restoration.

Source	Content	Target	Observed genotypic effects	Observed phenotypic effects	Ref.
In vitro results					
ADSC	-	DPC	• Downregulation of miR-22 and TNF-α signaling pathways	• Increase in cell proliferation and migration • Protection against H_2O_2-induced apoptosis	[10]
	-	DPC	• Upregulation of β-catenin and MMP3	• Increase in cell proliferation and migration • Increase in the number of $Ki67^+$ cells • Increase in protein levels of β-catenin and MMP3	[11]
	-	DPC	• Upregulation of hair follicle inductivity markers (ALP, versican, and α-SMA)	• Increase in cell proliferation and migration	[12]
DPC	-	DPC	• Upregulation of growth factors (IGF-1, KGF, and HGF)	• Increase in cell proliferation • Increase in secretion of growth factors (IGF-1, KGF, and HGF)	[13]
	miR-181a-5p	HFSC	• Downregulation of WIF1 and SFRP2 • Upregulation of Wnt/β-catenin signaling pathway (BCL2, CCND1, CTNNB1, and LEF1)	• Increase in cell proliferation • Protection against apoptosis	[14]
	-	HFSC	• Upregulation of Wnt/β-catenin signaling pathway	• Increase in cell proliferation • Protection against apoptosis	[15]
	-	ORSC	-	• Increase in cell proliferation and migration • Increase in protein levels of β-catenin and Shh	[7]
	-	ORSC	• Upregulation of apoptosis regulator (bcl2) • Downregulation of apoptosis regulator (bax)	• Increase in cell proliferation	[13]
HaCaT cell[a]	-	HFSC	• Upregulation of Wnt/β-catenin signaling pathway (AXIN2)	• Nuclear translocation of β-catenin • Increase in the number of $Ki67^+$ cells • Increase in mitochondria activation ($TOMM20^+$ cells) • Increase in the number of cells with active mitochondria	[16]
HHORSC	-	DPC	• Upregulation of hair follicle inductivity markers (ALP, versican, and α-SMA)	• Increase in cell viability, proliferation and migration	[17]
PL	-	DPC	• No or minimal change in hair follicle inductivity markers (ALP, versican, and α-SMA)	• Decrease in cell viability and proliferation	[17]
PRP	-	DPC	• No or minimal change in hair follicle inductivity markers (ALP, versican, α-SMA)	• No or minimal change in cell proliferation	[12]

(Continues)

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TABLE 1 (Continued)

Source	Content	Target	Observed genotypic effects	Observed phenotypic effects	Ref.
Bovine colostrum	-	DPC	-	• Increase in cell proliferation • Protection against the inhibitory effects of DHT on cell proliferation • Increased protein level of β-catenin	[18]
In vivo results					
ADSC	-	C57BL/6 mice	• Upregulation of Wnt/β-catenin signaling pathway (WNT3A, AXIN2) • Downregulation of SFRP1	• Improved hair growth • Increase in hair follicle count and dermis thickness • Increase in the protein level of β-catenin • Loading of exosomes onto a microneedle patch improved hair coverage	[10,11]
	-	Nu/nu athymic nude mice	• Upregulation of PDGF and VEGF • Downregulation of TGF-β1	• Appearance of terminal hairs • Increase in the number of hair follicles compared to control	[19]
DPC	miR-218-5p	C57BL/6 mice	• Upregulation of β-catenin • Downregulation of SFRP2	• Increase in hair growth • Increase in the protein level of β-catenin	[20]
	-	C57BL/6 mice	-	• Accelerate the onset of the anagen phase, delayed the catagen phase • Increase in protein levels of β-catenin and Shh	[7]
	-	C57BL/6 mice	-	• Prolonged anagen phase	[13]
HaCaT cells[a]	-	C57BL/6 mice	-	• Increase in hair growth • Increase in protein levels of β-catenin and Ki67 in $CD34^+$ cells	[16]
hAFSC	-	SD rats	-	• Increase in epidermal layer thickness • Increase in HF count	[21]
MDSC	-	AA-affected C3H/HeJ mice	• Upregulation of FoxP3 and arginase 1 • Downregulation of T cell hyperactivity	• Partial hair regrowth • Increase in Treg proliferation • Mitigated cytolytic activity • Decrease in T helper proliferation	[22]
MSC[b]	-	C57BL/6J mice	-	• Increase in hair density • Fast onset of hair regrowth • Increase in protein levels of β-catenin, K15, CD34, ALP, and PCNA	[23]
Bovine colostrum	-	C57BL/6 mice	-	• Darker skin pigmentation • Increase in hair coverage • Transition to the anagen phase • Increase in the number of $Ki67^+$ cells in hair matrix • Increase in the protein level of β-catenin and Wnt3a	[18]
Ex vivo results					
ADSC	-	Mice HF	-	• Increase in hair length • Increase in the number of $Ki67^+$ cells in hair matrix	[11]
DPC	-	Human HF	-	• Hair shaft elongation • Increase in Ki67 positive cells around the dermal papilla	[13]

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TABLE 1 (Continued)

Source	Content	Target	Observed genotypic effects	Observed phenotypic effects	Ref.
	miR-181a-5p	Rabbit HF	• Downregulation of SFRP2 • Upregulation of Wnt/β-catenin signaling pathway (BCL2, CCND1, CTNNB1, LEF1)	• Hair shaft elongation • Increase in the protein levels of CCND1 and LEF1	[14]

Abbreviations: AA, alopecia areata; ADSC, adipose-derived stem cell; ALP, alkaline phosphatase; AXIN2, axis inhibition protein 2; CCND1, cyclin D1; DHT, dihydrotestosterone; DPC, dermal papilla cell; ERK, extracellular signal-regulated protein kinase; hAFSC, human amniotic fluid stem cell; HF, hair follicle; HFSC, hair follicle stem cell; HHORSC, human hair outer root sheath cell; K15, keratin 15; Ki67, antigen KI-67; LEF1, lymphoid enhancer-binding factor 1; MDSC, myeloid-derived suppressor cell; miR, microRNA; MMP-3, matrix metalloproteinase 3; MSC, mesenchymal stem cell; ORSC, outer root sheath cell; PCNA, proliferating cell nuclear antigen; PDGF, platelet-derived growth factor; PL, platelet lysis; PRP, platelet-rich plasma; SFRP, secreted frizzled-related protein; Shh, sonic hedgehog; TGF-β1, transforming growth factor beta 1; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; WIF, WNT inhibitory factor.

[a]Keratinocytes (HaCaT cells) were treated with fisetin (a plant flavonoid extract).

[b]Exosomes were loaded onto a microneedle patch.

administered 2 or 5 mL of undiluted solutions or up to 8 mL of diluted solutions (1:2–1:5) at alopecic scalp regions.[26] During follow-up, adverse reactions including fever, myalgias, chills, fatigue, or scalp cellulitis were not reported.[26]

A recent study performed safety evaluation of exosomes using in vitro and in vivo models.[28] Exosomes were isolated from human-induced pluripotent stem cells. Tissue-specific localization was identified in the liver, kidneys, brain, and lungs without significant adverse reactions. Specifically, evidence of hemolysis, DNA damage, and cytolytic effects were not observed; there were no abnormal histological findings, along with normal hemocyte, liver and kidney parameters, albeit with elevations in immunoglobulins and circulating $CD8^+$ T cells.[28] Similar results were also reported in another in vivo study of exosomes isolated from mesenchymal stromal cells.[29] However, differences in experimental design hamper the clinical translation of these findings, and there remains an undetermined risk of tumor development and metastasis depending on the source and content of exosomes.[30] Further studies are clearly warranted to fully define the molecular and functional characteristics of exosomes from different sources.

3.4 | Regulatory concerns

The U.S. FDA has issued alerts against the use of exosome products.[31,32] Exosomes are regulated as a drug and as a biologic, none of the marketed products are currently approved by the FDA.[31,32]

Several technical challenges exist that hinder the clinical use of exosomes.[5,33] Owing to its molecular heterogeneity, no consensus has been established to date on methods for the isolation and characterization of exosomes, which limits the reproducibility across studies. To address this issue, a 2018 guideline was introduced by the International Society for EVs on experimental design and special considerations when reporting study results.[34] Although several isolation methods such as ultracentrifugation and ultrafiltration are available, there remains a possibility that the functional profile of exosomes reported previously could be due to other subtypes of EVs. Furthermore, limited detection methods for exosome content associated with specific functions, such as hair regrowth (e.g., miRNA), pose another challenge to its clinical application.[33]

Although described as a "cell-free" therapeutic product which, in theory, decreases the risk of tumorigenesis and infections compared to stem cell therapy, cases of severe infections were reported in 2019 due to substandard manufacturing conditions.[35] Adherence to good manufacturing practice (GMP) is paramount for minimizing risks of contamination in the cell-culture system, such as microbes including *Mycoplasma*, as well as intracellular contents that can trigger the host immune response.[36,37]

3.5 | Future directions

In addition to addressing safety issues concerning the isolation and quality control of exosomes for industrial production, current

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TABLE 2 Summary of clinical evidence on the use of exosomes in hair restoration for AGA.

Source	Regimen	Duration	Patients (*n*)	Baseline hair measurements	Final hair measurements (*p*-value)	Adverse reactions	Ref
ADSC	Scalp application ($>6\times10^{10}$ particles/vial) with microneedle roller QW	12 weeks	39	Mean hair density: 121.7 ± 37.2 hairs/cm^2 Mean hair thickness: 52.6 ± 10.4 μm	Mean hair density: 146.6 ± 39.5 hairs/cm^2 ($p<0.001$) Mean hair thickness: 61.4 ± 10.7 μm ($p<0.001$)	Pricking at the injections site; no serious adverse reactions reported	[24]

Abbreviations: ADSC, adipose-derived stem cell; QW, once weekly.

literature suggests that further improvements can be made to optimize its formulation, regimen, and delivery methods.

As aforementioned, the use of topical formulations may improve patient adherence and satisfaction over intradermal injections owing to fewer required clinic visits, as well as decreased risks of adverse reactions related to pain at the injection site, systemic side effects, and infections. In addition, this may satisfy current regulatory issues.

Incorporating exosome treatment in combination regimens may further improve the clinical outcome. In a mice model study, topical 5% minoxidil applied daily showed synergistic effects with ADSC-Exo.[10] In another study, 11 AGA patients who received autologous ADSC treatment combined with PRP showed more profound reversal of hair loss compared to patients treated with PRP alone (51.6% vs. 21.5%).[38] Exosomes present in PRP may complement the effects of exosome treatment in hair growth.[39] However, two recent studies using PRP- or platelet lysate-derived exosomes reported no significant effects in DPCs (Table 1).[12,17] The authors have attributed the lack of efficacy to the purity of the isolated exosomes; further studies examining alternative isolation methods affecting the physiochemical and functional properties of platelet-derived exosomes maybe warranted.[5,17,34]

Given the current limitations of topical and systemic treatments on the long-term efficacy, safety, and compliance, novel methods for targeted drug delivery has been an area of ongoing investigation.[38] Administration of ADSC-conditioned media using a microneedle roller once per week, which creates microchannels in the scalp that facilitates drug penetration, resulted in significant increases in hair density and thickness after 12 weeks.[40] Similarly, low-frequency ultrasound devices that enhance skin permeability at specific locations of the scalp may also improve treatment efficacy; however, the regulatory status needs to be determined. In a study of 30 AA patients, applications of methylprednisolone or cyclosporine with ultrasound resulted in marked hair regrowth after 3 months.[41] It remains to be seen if clinically significant delivery of exosomes to the dermis and subcutis could occur with the use of low-frequency ultrasound devices. This may change the cosmetic designation of the therapy.

In addition, delivery systems that enhance the pharmacokinetics of exosomes may further improve the utility of topical formulations. Application of a microneedle patch loaded with MSC-Exo led to improved hair coverage compared to the subcutaneous injection method.[23] Similar findings were also reported using ADSC-Exo.[11] This higher rate of regrowth could be attributed to the improved drug penetration, duration as well as rate of release; the addition of chitosan lactate may also decrease the risk of bacterial infections.[11,23]

As the large-scale production of exosomes is currently limited due to its low yield in cell culture (<1 μg/mL); strategies that enhance exosome production as reported previously, such as the addition of plant extracts or phototherapy, as well as protruding cells using serial porous membranes (i.e., engineered nanovesicles [eNVs]), warrants further validation.[5,8,16,42] In a study applying low-level laser irradiation (LLLI), endothelial exosome production increased by 1.64-fold following LLLI treatment through modulations of the Wnt signaling

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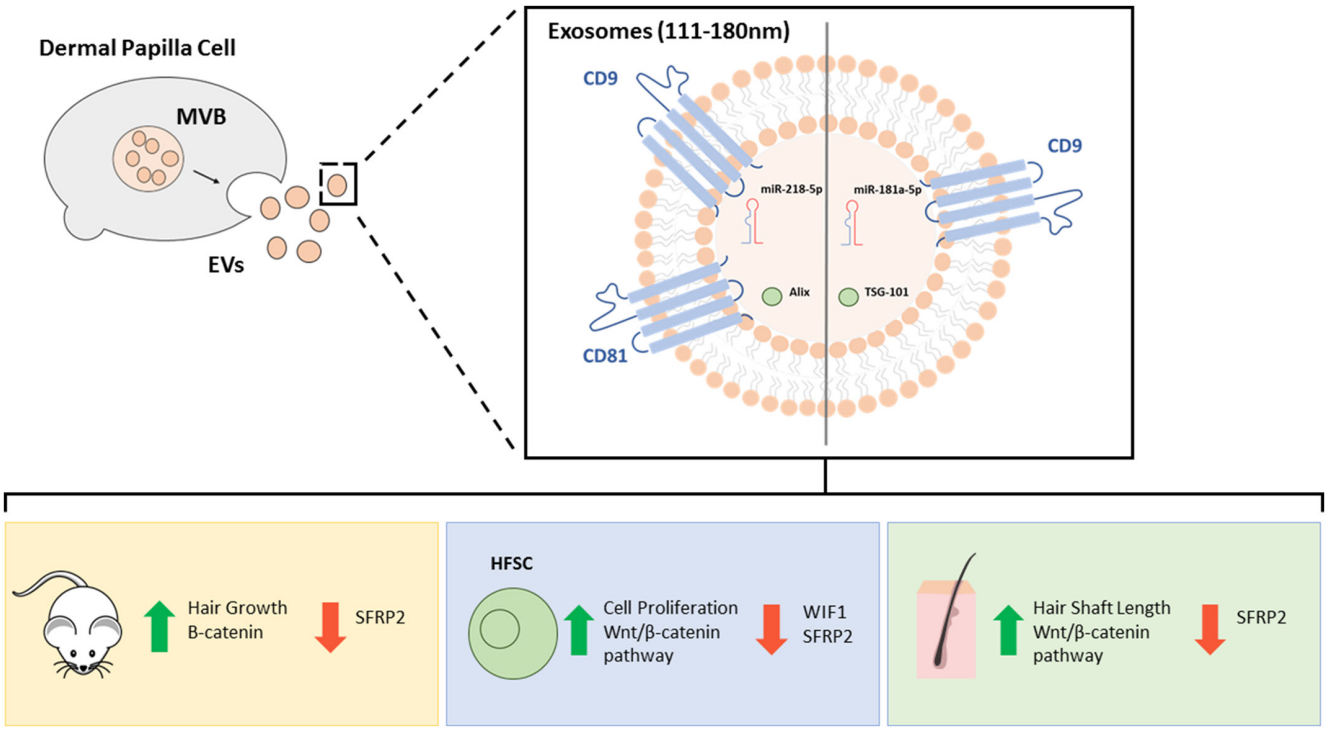

FIGURE 2 microRNA (miRNA) mediated effects through the transfer of dermal papilla cell-derived exosomes (DPC-Exo). Exosomes are secreted following the transport and fusion of multivesicular bodies to the cell membrane. Previous studies have identified two subsets of DPC-Exo containing miRNA with modulatory effects on hair growth.[14,20] $CD9^+$ $CD81^+$ DPC-Exo containing miR-218-5p demonstrated favorable effects in a mice model study.[20] While $CD9^+$ DPC-Exo containing miR-181a-5p demonstrated favorable effects in hair follicle stem cells and in organ culture of rabbit whisker follicles.[14] EV, extracellular vesicle; MVB: multivesicular body; SFRP2, secreted frizzled-related protein 2; WIF1, WNT inhibitory factor 1.

pathway.[43] Another study demonstrated a 250-fold increase in production yield for eNVs compared with the traditional exosome production method; however, although eNVs and exosomes share similar molecular characteristics, eNVs in comparison are packaged with non-selective cargos.[44]

Lastly, exosomes derived from alternative sources, such as bovine colostrum or plants, may be considered to increase production yield while adhering to GMP.[18,45] Bovine colostrum-derived exosomes were shown to enhance DPC proliferation in vitro, and improve hair coverage in vivo (Table 1).[18] Similarly, exosome-like nanovesicles derived from Ashwagandha seeds were also shown to enhance DPC proliferation in vitro.[45] This may allow for a clearer path to commercialization.

In summary, there has been exciting advances in the field exosome research over the past decade, despite significant roadblocks in its clinical translation. There are important safety concerns yet to be addressed. For alopecia patients, off-label exosome treatment has mainly been restricted to topical use under a cosmetic designation, and may be considered as a part of shared decision-making when conventional treatments fail. We anticipate that results from ongoing and future studies including clinical trials will only strengthen the therapeutic potential of exosome treatment.

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CONFLICT OF INTEREST STATEMENT

AKG, TW, and JAR have no competing interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Authors declare human ethics approval was not needed for this study.

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