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Plastic and Aesthetic Research

Sun et al. Plast Aesthet Res. 2026;13:28 DOI:10.20517/2347-9264.2026.70

Beyond lipofilling: adipose-derived stem cells in plastic surgery

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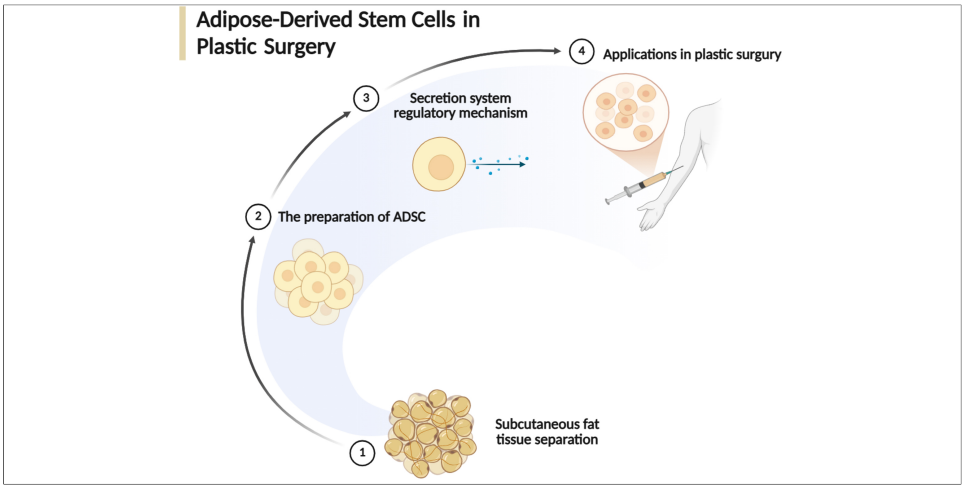
Keywords:
Adipose-derived stem cells, regenerative medicine, cell-assisted lipotransfer, exosomes, wound healing

Citation: Sun C, Jin M, An Y. Beyond lipofilling: adipose-derived stem cells in plastic surgery. *Plast Aesthet Res.* 2026;13:28. https://dx.doi.org/10.20517/2347-9264.2026.70

Received: 8 Jun 2026
First Decision: 21 Aug 2026
Revised: 4 Sep 2026
Accepted: 22 Sep 2026
Published: 28 Sep 2026

Academic Editor:
Pietro Gentile
Copy Editor:
Ting-Ting Hu
Production Editor:
Ting-Ting Hu



Abstract

Adipose-derived stem cells (ADSCs) have emerged as a pivotal tool in the paradigm shift of plastic and reconstructive surgery from traditional tissue transposition toward regenerative medicine, owing to their abundance, minimally invasive harvesting, and potent regenerative capabilities. Beyond their multilineage differentiation potential, the therapeutic efficacy of ADSCs is increasingly attributed to their sophisticated paracrine activity and exosome-mediated signaling. This review provides a comprehensive synthesis of the biological characteristics of ADSCs, their underlying molecular mechanisms, and their diverse clinical applications in plastic surgery. We discuss the orchestrated roles of the ADSC secretome in promoting neoangiogenesis, modulating the immune microenvironment, and regulating extracellular matrix remodeling. Clinically, we highlight the latest evidence for cell-assisted lipotransfer (CAL) in fat grafting, the acceleration of chronic wound healing, anti-fibrotic strategies for scar management, and the emerging role of ADSCs in facial rejuvenation and anti-aging. While issues regarding standardization and long-term oncological safety remain, the integration of ADSCs with biofabrication and cell-free therapies represents a promising frontier. Ultimately, ADSCs hold the potential to achieve functional and scarless tissue regeneration and may redefine the future of plastic and reconstructive surgery.

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INTRODUCTION

Plastic and aesthetic surgery has traditionally relied on the transposition of autologous tissues, such as skin grafts and vascularized flaps, to repair defects and restore function. However, the limitations of these conventional approaches include donor-site morbidity, limited tissue availability, and unpredictable long-term outcomes, which have catalyzed a shift toward regenerative medicine. At the forefront of this evolution are adipose-derived stem cells (ADSCs), a subset of mesenchymal stem cells (MSCs) that have redefined the landscape of tissue engineering and aesthetic surgery[1].

First characterized in the early 2000s, ADSCs are typically isolated from the stromal vascular fraction (SVF) of adipose tissue[2]. Compared to bone marrow-derived MSCs, ADSCs offer several distinct clinical advantages: they are more abundant, can be harvested through minimally invasive liposuction with lower donor-site morbidity, and exhibit a higher proliferative capacity *in vitro*[3-5]. Beyond their multi-lineage differentiation potential into adipogenic, osteogenic, and chondrogenic lineages, the therapeutic efficacy of ADSCs is increasingly attributed to their potent paracrine activity. By secreting a diverse array of growth factors, cytokines, and extracellular vesicles like exosomes[6], ADSCs effectively modulate the inflammatory microenvironment, promote neoangiogenesis, and accelerate tissue remodeling[7-9].

Despite the proliferation of preclinical studies demonstrating the regenerative potential of ADSCs in fat grafting, wound healing, and scar management, the transition from "bench to bedside" remains complex[10]. Challenges such as the standardization of isolation protocols, the long-term oncological safety of cell-assisted lipotransfer (CAL), and the regulatory hurdles for clinical translation continue to be subjects of intense debate.

Therefore, this review aims to provide a comprehensive overview of the biological characteristics and underlying regenerative mechanisms of ADSCs. Furthermore, we summarize the latest clinical advancements in plastic surgery, aiming to offer insights into future research directions and the potential for personalized regenerative treatments.

BIOLOGY AND CHARACTERIZATION OF ADSCs

The clinical ascendancy of ADSCs is traditionally predicated on their surgical accessibility and expansive potential[5,10-12]. However, contemporary regenerative medicine has moved beyond these logistical advantages, unveiling a biological landscape defined by intrinsic heterogeneity and context-dependent plasticity. Understanding ADSC biology now requires a shift from viewing them as a monolithic cell population to recognizing them as a dynamic, responsive therapeutic system[13] [Figure 1].

Phenotypic baseline and functional heterogeneity

While the International Society for Cell & Gene Therapy (ISCT) provides a necessary phenotypic baseline ($CD73^+/90^+/105^+$ and $CD34^-/45^-$)[11,12], these minimal criteria fail to capture the functional diversity inherent in ADSCs. Recent single-cell RNA and assay for transposase-accessible chromatin sequencing (scRNA-seq/ATAC-seq) studies have unmasked this biological noise, revealing that cultured ADSCs are a mosaic of proliferative, functional, and senescent subsets[13]. The identification of specific clusters like Cluster 6 and biomarkers like basonuclin 2 (BNC2) and high mobility group AT-hook 2 (HMGA2) suggests that future clinical success will depend less on bulk cell quantity and more on the enrichment of high-potency, non-senescent sub-lineages. However, the intrinsic molecular traits governing heightened regenerative capacity often overlap with oncogenic hallmarks. Specifically, the core transcription factors BNC2 and HMGA2, while essential for maintaining the undifferentiated state and proliferative vigor of ADSCs, are frequently implicated in malignant transformation and epithelial-mesenchymal transition. HMGA2, for instance, can

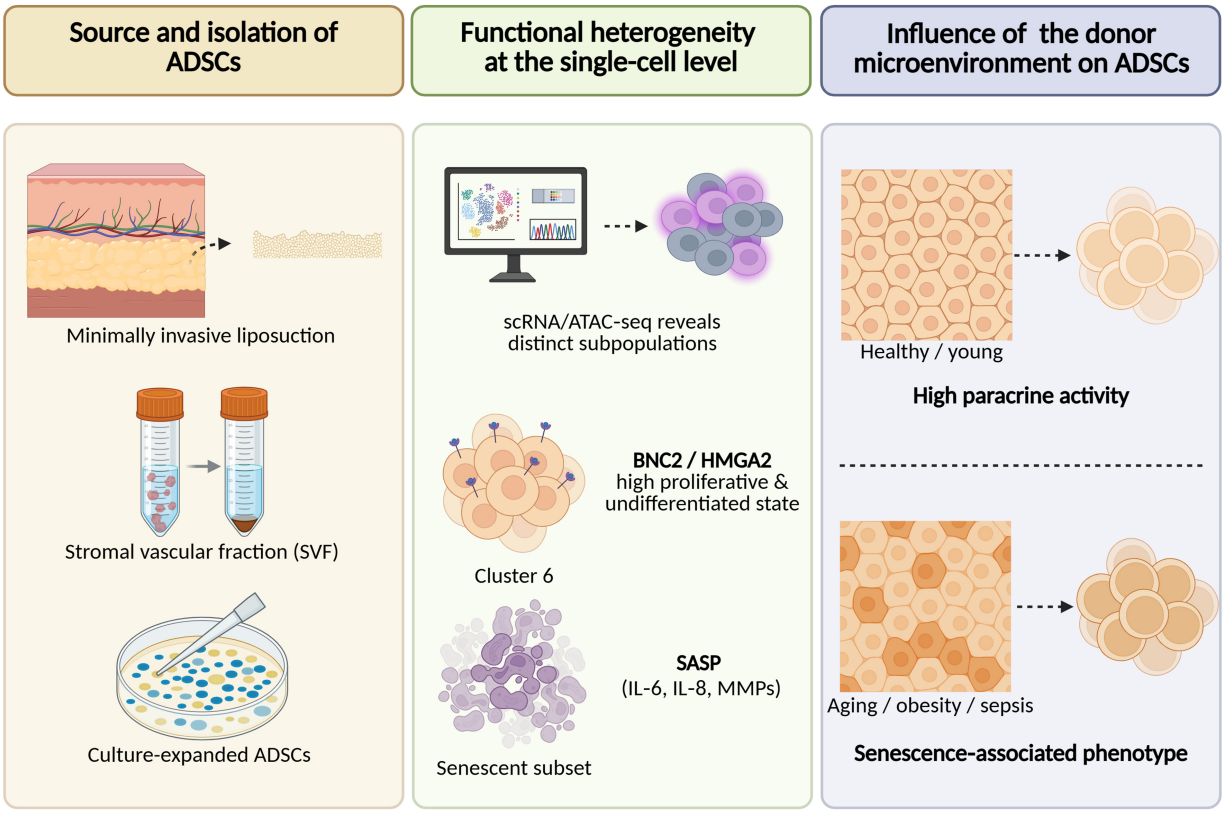

Figure 1. Biological characteristics and functional heterogeneity of ADSCs. ADSCs are isolated from adipose tissue via minimally invasive liposuction, followed by enzymatic digestion and culture expansion (Left). scRNA/ATAC-seq reveals functional subpopulations within cultured ADSCs, including a highly proliferative cluster (Cluster 6) marked by BNC2 and HMGA2, and a senescent subset exhibiting SASP (Middle). The regenerative capacity of ADSCs is heavily influenced by donor-specific factors; young/healthy donors yield cells with potent paracrine activity, whereas aging, obesity, or sepsis drive ADSCs toward a pro-inflammatory SASP, compromising their therapeutic potential (Right). Created in BioRender. (2026) https://BioRender.com/ru1r8t8. ADSCs: Adipose-derived stem cells; BNC2: basonuclin 2; HMGA2: high mobility group AT-hook 2; IL-6: interleukin-6; IL-8: interleukin-8; MMPs: matrix metalloproteinases; SASP: senescence-associated secretory phenotype; scRNA-seq/ATAC-seq: single-cell RNA and assay for transposase-accessible chromatin sequencing; SVF: stromal vascular fraction.

promote cancer cells to acquire stem cell-like characteristics by regulating chromatin structure, and enhance their invasive and migratory abilities[14]. Therefore, aggressive selection for these super-subpopulations warrants rigorous scrutiny to ensure that therapeutic potency does not come at the cost of genomic stability or an increased risk of long-term oncogenicity.

Secretome-mediated therapeutic framework

While traditional research emphasized the multi-lineage differentiation potential of ADSCs[15], contemporary focus has pivoted toward a paracrine-driven model. In this framework, the secretome serves as the primary vehicle for therapeutic delivery[16,17]. This paracrine dominance is particularly pronounced within wound microenvironments; here, ADSCs modulate the M1-to-M2 macrophage phenotypic transition and facilitate neoangiogenesis through the regulated secretion of vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and interleukin-6 (IL-6)[18,19]. Furthermore, ADSC-derived exosomes (ADSC-exos) - specifically those harboring bioactive cargo such as miR-378 - provide a robust cell-free mechanism to attenuate oxidative stress and enhance keratinocyte viability[20]. Such advancements underscore a significant transition toward standardized, off-the-shelf precision regenerative medicine.

Environmental modulation and bioengineering of ADSC function

Notably, the functional efficacy of ADSCs is not an inherent constitutive attribute but a context-dependent state dictated by the host microenvironment. This phenomenon, characterized by Wang *et al.* as "reciprocal regulation", entails the induction of an immunosuppressive phenotypic shift in response to inflammatory cues [e.g., interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α)] via indoleamine 2,3-dioxygenase (IDO) or inducible nitric oxide synthase (iNOS) pathways[21]. Conversely, deleterious environments - including donor senescence, obesity, or systemic sepsis - can "de-license" these cells, precipitating a transition toward a pro-inflammatory senescence-associated secretory phenotype (SASP)[22-25]. To circumvent these environmental constraints, emerging bioengineering strategies, such as mitochondrial transplantation for metabolic reprogramming[26] and the development of smart chimeric antigen receptor (CAR)-modified immunosuppression platforms[27], aim to transition ADSCs from inert cellular grafts into autonomous, responsive modulators of tissue regeneration.

MECHANISMS OF ACTION

Extracellular vesicles as functional mediators of paracrine signaling

The clinical application of ADSCs has undergone a strategic shift, moving from direct cellular replacement toward a paracrine-centered model[9] [Figure 2]. Within this framework, extracellular vesicles (EVs), particularly exosomes, serve as bioactive nanovesicles that mirror the regenerative potential of their parental cells while offering enhanced safety profiles and superior scalability[28-32]. Distinct from passive biological carriers, ADSC-EVs function as dynamic regulatory units, delivering functional non-coding RNAs (ncRNAs) and proteomic payloads that reprogram the recipient microenvironment through the sophisticated modulation of autophagy. Specifically, ADSC-EVs exhibit context-specific pleiotropy: they can either attenuate myofibroblast transformation by inhibiting TGF-β/Smad2-mediated autophagic flux[33] or mitigate fibrotic pathology by activating phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR)-dependent mitophagy[34], with the functional outcome being contingent upon the specific pathological cues of the wound environment.

The competitive endogenous RNA (ceRNA) regulatory axis and networks

The functional versatility of ADSC-EVs is sustained by a complex repertoire of ncRNAs operating via ceRNA networks. Long non-coding RNAs (lncRNAs), such as H19 and Neat1, function as molecular sponges that sequester microRNAs (miRNAs) to derepress regenerative pathways, including the Wnt/β-catenin and Ulk1-mediated autophagic axes[35,36]. Consistently, the miRNA profile of ADSC-EVs - further optimized by hypoxic preconditioning - functions as a coordinated toolkit for reversing ischemic stagnation. Upregulated miR-21, miR-126, and miR-31 facilitate high-quality healing by activating the PI3K/AKT signaling cascade, thereby promoting targeted vascularization and keratinocyte migration[37-39]. Recent identification of circular RNAs adds an additional layer of epigenetic control, modulating the miR-144/signal transducer and activator of transcription 3 (STAT3) axis to resolve chronic inflammation[29].

Inflammatory priming and macrophage plasticity

Inflammatory priming represents a key mechanism through which the context-dependent properties of ADSCs translate into immunomodulatory effects[21,29,31,32]. ADSC-EVs further reinforce this response by delivering miRNAs and lncRNAs that attenuate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. Moreover, unbiased omics analyses have elucidated pivotal molecular checkpoints, such as epiregulin (EREG) and cystatin A (CSTA). The targeted modulation of these factors by ADSCs correlates with enhanced M2 macrophage infiltration and accelerated re-epithelialization in diabetic foot ulcers (DFUs)[40].

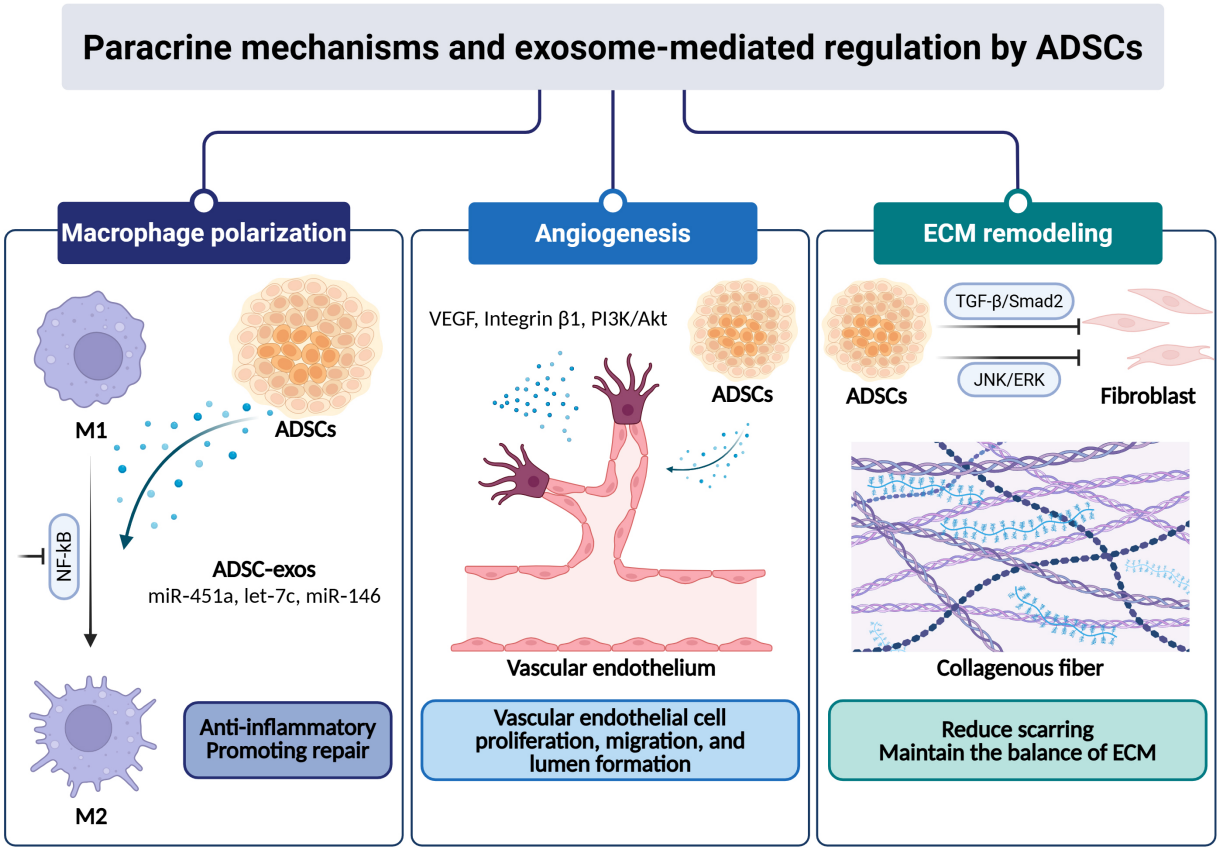

Figure 2. Paracrine mechanisms and exosome-mediated regulation by ADSCs. ADSCs secrete a diverse array of EVs/exosomes, miRNAs, and long non-coding RNAs. These bioactive factors orchestrate three key processes in tissue repair: (1) Macrophage polarization: ADSC-exos deliver miR-451a, let-7c, and miR-146 to suppress NF-κB signaling, driving the transition from pro-inflammatory M1 to reparative M2 macrophages; (2) Angiogenesis: ADSCs promote neovascularization via direct endothelial differentiation and paracrine activation of the integrin β1/PI3K/AKT pathway, supported by VEGF and other growth factors; (3) ECM remodeling and anti-fibrosis: ADSC-derived factors exert anti-fibrotic effects through distinct signaling mechanisms, including inhibition of the JNK/ERK pathway and modulation of TGF-β/Smad2 signaling, thereby suppressing myofibroblast activation and pathological scar formation. Created in BioRender. (2026) https://BioRender.com/1teq1ae. ADSC-exos: Adipose-derived stem cell-derived exosomes; ADSCs: adipose-derived stem cells; AKT: protein kinase B; ECM: extracellular matrix; ERK: extracellular signal-regulated kinase; EVs: extracellular vesicles; JNK: c-Jun N-terminal kinase; miRNAs: microRNAs; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: phosphoinositide 3-kinase; TGF-β: transforming growth factor-β; VEGF: vascular endothelial growth factor.

Spatiotemporal coordination of angiogenesis and extracellular matrix homeostasis

Optimal tissue restoration necessitates the precise integration of chemotaxis, revascularization, and extracellular matrix (ECM) reorganization. The recruitment of ADSCs is primarily mediated via the stromal cell-derived factor-1α (SDF-1α)/C-X-C motif chemokine receptor 4 (CXCR4)/CXCR7 signaling axis, a pathway amenable to targeted manipulation for enhanced site-specific homing[41]. Following recruitment, integrin β1/PI3K/AKT signaling contributes to the angiogenic response[39,42]. Concurrently, ADSC-EVs modulate fibroproliferative dynamics by fine-tuning collagen deposition and regulating matrix metalloproteinases (MMPs)[28,43]. Specifically, miR-141-3p-mediated suppression of c-Jun N-terminal kinase (JNK)/extracellular signal-regulated kinase (ERK) signaling inhibits myofibroblast differentiation, thereby favoring functional tissue regeneration over hypertrophic scar formation[44]. This multifaceted regulatory network is further reinforced by the broader ADSC secretome, which preserves ECM structural integrity and attenuates environmental senescence[43,45].

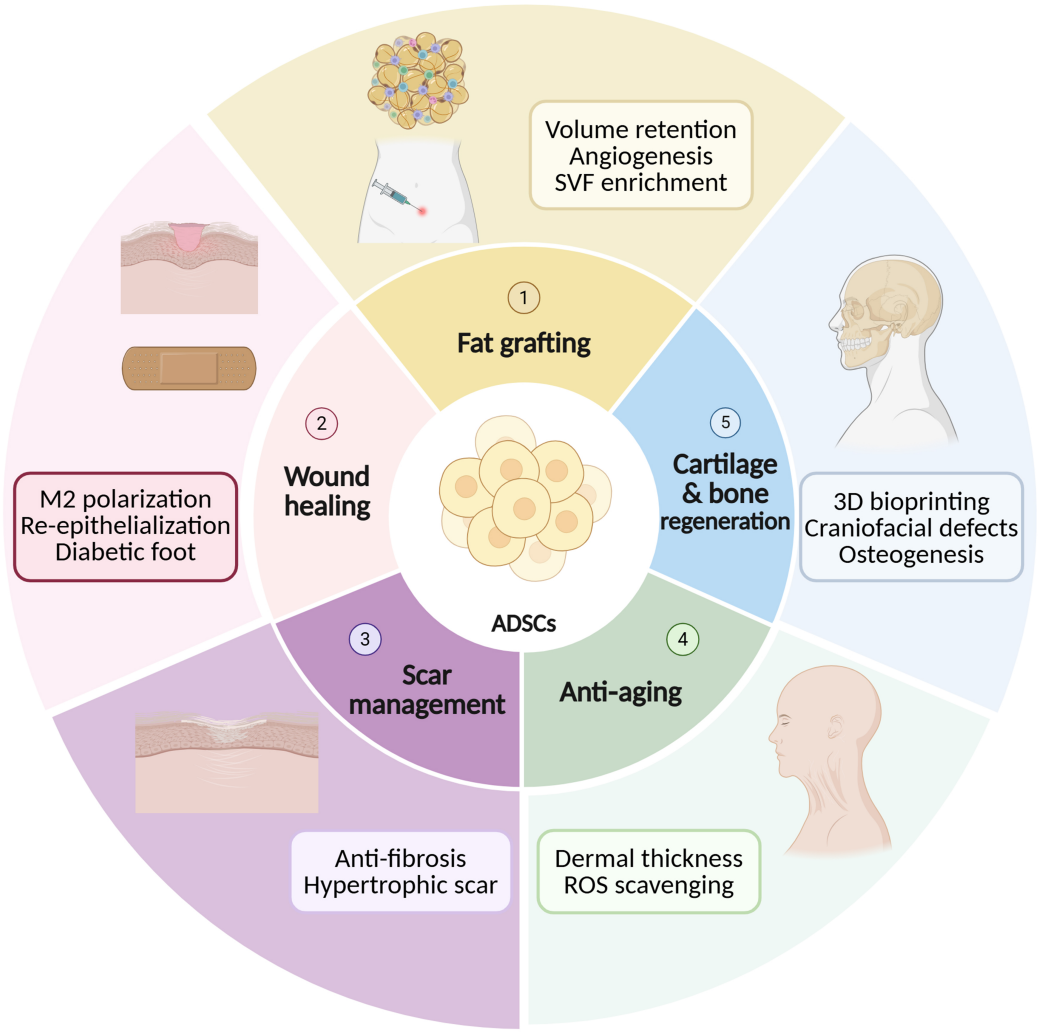

Figure 3. Major clinical applications of ADSCs in plastic and reconstructive surgery. Surrounding sectors illustrate five key areas where ADSCs have demonstrated therapeutic potential: (1) CAL for fat grafting; (2) chronic wound healing (e.g., diabetic foot ulcers); (3) scar management and anti-fibrosis; (4) facial rejuvenation and anti-aging; and (5) cartilage and bone regeneration for craniofacial reconstruction. Each sector highlights representative mechanisms or key molecules involved in ADSC-mediated tissue repair. Created in BioRender. (2026) https://BioRender.com/mdkvzrj. ADSCs: Adipose-derived stem cells; CAL: cell-assisted lipotransfer; M2: type 2 (alternatively activated) macrophage; ROS: reactive oxygen species; SVF: stromal vascular fraction.

CLINICAL APPLICATIONS IN PLASTIC SURGERY

The translation of ADSC biology into clinical practice has found its most fertile ground in plastic and reconstructive surgery. The mechanistic pillars detailed previously provide the biological scaffolding for a wide clinical spectrum, ranging from enhancing the fidelity of autologous fat grafting to the management of recalcitrant wounds and pathological scars[16,46,47] [Figure 3].

Fat grafting and CAL

Autologous fat grafting (AFG) remains the standard for soft tissue restoration, yet it is plagued by a volumetric lottery, with unpredictable resorption rates that range from 10% to 90%[48]. This phenomenon is primarily driven by delayed neovascularization, which subjects the central graft to lethal ischemic stress[49].

The identification of ADSCs within the SVF offered a transformative solution[50]. This catalyzed the advent of CAL, a strategy where lipoaspirates are enriched with either freshly isolated SVF or *ex vivo* culture-expanded ADSCs[51]. In this context, ADSCs function as "biologic factories", secreting a potent cocktail of pro-angiogenic and immunomodulatory factors that mitigate early inflammatory insult and facilitate host-graft integration[52]. The clinical applications of CAL have been increasingly explored. A landmark randomized controlled trial by Kølle *et al*. reported a remarkable 80.9% volume retention on day 121 with ADSC enrichment, compared to a mere 16.3% in controls [an absolute difference of 64.6 percentage points (pp)][53,54]. Although promising results have been reported, the clinical superiority of CAL over conventional fat grafting has not been consistently reproduced across all studies[51]. Differences in cell preparation methods, enrichment strategies, and outcome assessment criteria may contribute to the observed variability. This distinction underscores the importance of cell potency and dosage, though the ADSCs still face stringent regulatory and logistical hurdles[4,55-57].

Beyond volume, ADSCs are being instructed through innovative co-culture or functional enhancement strategies. For instance, co-culturing ADSCs with vascular regenerative cells (RE-01 cells) has been shown to achieve superior graft retention even with a tenfold reduction in cell dosage, signaling a shift toward precision cell therapy[58]. Furthermore, the field is pivoting toward a cell-free protocol, utilizing ADSC-exos. These nanovesicles recapitulate the parent cell's benefits while offering a superior safety profile, easier storage, and reduced risks of immunogenicity or unwanted differentiation[59-61].

Wound healing and chronic ulcers

Managing recalcitrant wounds, such as DFUs and major burns, remains a formidable challenge where ADSCs offer significant therapeutic leverage[62]. The pathophysiology of chronic wounds - often characterized by a stalled M1 inflammatory phase - is directly countered by the ADSCs' ability to drive M2 macrophage polarization, thereby re-initiating the regenerative cascade[47,63]. The key mechanism by which ADSCs promote the healing of DFUs is closely related to their powerful paracrine effect. Studies have shown that ADSC-exos are rich in various functional miRNAs, such as miR-451a, let-7c, miR-146, *etc.*[63,64]. These miRNAs target key molecules such as macrophage migration inhibitory factor (MIF), interferon regulatory factor 1 (IRF1), and CCAAT/enhancer-binding protein delta (C/EBP-δ), and jointly regulate the polarization of macrophages to the M2 anti-inflammatory phenotype, thereby breaking the pathological state of the chronic wound where the M1 inflammatory phase is stagnant. This creates a favorable immune microenvironment for tissue regeneration. Additionally, the growth factors secreted by ADSCs activate signaling pathways, promoting the proliferation and migration of vascular endothelial cells, protecting fibroblasts from apoptosis and accelerating re-epithelialization and collagen deposition. Based on these mechanisms, to enhance the therapeutic efficacy of ADSC-exos, researchers have adopted various engineering strategies. Among them, hypoxic preconditioning has been proven to effectively enrich the functional miRNAs in exosomes, which target inflammatory-related genes and activate signaling pathways such as PI3K/AKT, jointly regulating the polarization of macrophages to the M2 type, promoting the proliferation and migration of fibroblasts, and enhancing the function of vascular endothelial cells, thereby accelerating wound healing through multiple targets[46,47,61]. For deep-tissue defects, 3D-bioprinted hydrogel scaffolds co-delivering ADSCs and nitric oxide (NO) donors have demonstrated synergistic effects, promoting rapid re-epithelialization and organized collagen deposition[52,65,66]. Despite these encouraging findings, the clinical evidence for ADSC-based treatment of chronic wounds remains less mature than the preclinical evidence. Most available studies are experimental or translational, with substantial variation in cell source, delivery strategy, wound models, and outcome assessment. Therefore, the reproducibility and clinical relevance of these findings remain to be established in adequately powered controlled clinical trials.

Scar management and anti-fibrosis

ADSCs are equally pivotal in modulating the late stages of tissue repair to prevent pathological scarring. Their anti-fibrotic efficacy is primarily mediated through the inhibition of TGF-β1/Smad signaling, which prevents the transition of fibroblasts into hyperactive myofibroblasts[47]. Additionally, ADSCs help restore the ECM balance by upregulating MMPs while suppressing their inhibitors [tissue inhibitors of metalloproteinases (TIMPs)][67]. Clinical evidence, including a systematic review of 665 patients, suggests potential benefits of ADSCs or SVF in improving both the functional and aesthetic outcomes of scars[68]. Emerging data highlight the role of ADSC-exos in alleviating the progression of various fibrotic diseases via mitochondrial restoration and targeted miRNA delivery[47,60,63,68]. In aesthetic practice, the efficacy of local ADSC-exos or direct ADSC injection for acne scars has been confirmed to be comparable to that of fractional CO_2 laser treatment, indicating their potential as independent regenerative therapies. A randomized controlled study by Abou Eitta *et al.* demonstrated that a single ADSC injection was as effective as three sessions of fractional CO_2 laser in improving acne scars[69]. Additionally, ADSC-exos can serve as an adjunct to fractional CO_2 laser treatment, significantly enhancing efficacy, reducing erythema, and shortening recovery time[59]. These findings collectively support ADSCs and their exosomes as effective strategies for acne scar treatment, with their non-invasive and repeatable nature offering unique application value in aesthetic practice.

However, the strength of this evidence remains limited by heterogeneity in scar type, cell preparation, treatment protocols, comparator interventions, and outcome measures. Although some controlled studies suggest efficacy comparable to established treatments, the available evidence does not yet establish ADSC-based therapy as a standardized or superior treatment for scar management.

Facial rejuvenation and anti-aging

In the realm of aesthetic medicine, ADSCs have garnered attention for their ability to combat both intrinsic and extrinsic aging[70,71]. By neutralizing reactive oxygen species (ROS) and stimulating resident dermal fibroblasts, ADSCs can increase dermal thickness and restore elastic fiber architecture[72,73]. While clinical data suggest improvements in skin elasticity and hydration, meta-analyses have highlighted substantial heterogeneity in aesthetic outcomes, with some studies reporting limited or non-significant effects on wrinkle reduction[70]. This variability may reflect differences in administration routes, treatment protocols, and patient characteristics. Nevertheless, high-dose intradermal ADSC injections have demonstrated sustained facial rejuvenation for over a year, potentially through the activation of underlying facial musculature via exosomal signaling[73]. The use of ADSC-conditioned medium (ADSC-CM) also represents a growing trend, offering a potent, non-invasive secretome cocktail that protects against ultraviolet (UV)-induced senescence[28].

Cartilage and bone regeneration

The chondrogenic and osteogenic potential of ADSCs is being harnessed for complex craniofacial reconstruction[74]. Most clinical applications involve combining ADSCs with osteoconductive scaffolds like β-tricalcium phosphate (β-TCP) for mandibular or cranial defects[61]. In rhinoplasty, the convergence of ADSC biology and 3D bioprinting allows for the creation of patient-specific, stable cartilage constructs using bio-inks like gelatin methacryloyl (GelMA)[75]. Innovative injectable systems using ADSC-incorporated microspheres now offer a minimally invasive alternative for minor nasal contouring, bypassing the morbidity associated with traditional rib cartilage harvesting[76]. The evidence for craniofacial cartilage and bone regeneration remains predominantly preclinical or early translational. Outcomes are highly dependent on scaffold composition, cell source, differentiation conditions, and defect characteristics, which limits direct comparison between studies. Further long-term clinical studies are needed to determine the durability, safety, and functional relevance of these approaches.

A summary of key clinical studies on ADSCs in plastic surgery is provided in Table 1.

CHALLENGES AND SAFETY CONSIDERATIONS

Standardization and regulatory hurdles

Despite the promising clinical outcomes, the lack of standardized protocols for ADSC isolation, expansion, and administration remains a primary bottleneck[79]. The biological properties of ADSCs are significantly influenced by donor characteristics [e.g., body mass index (BMI), age, and anatomical harvest site] and processing techniques (enzymatic vs. mechanical)[12,22]. To move toward large-scale clinical application, it is imperative to establish Good Manufacturing Practice (GMP) standards and universal characterization criteria[80]. Furthermore, varying international regulatory classifications - ranging from minimally manipulated tissue to advanced therapy medicinal products - pose significant hurdles for global clinical translation and multicenter trials[11,32]. At present, the lack of standardized separation protocols and the significant impact of donor characteristics on cell quality make it extremely difficult to establish a unified risk monitoring system. Therefore, future research should not be limited to the observation of short-term complications, but should focus on building an early warning model based on single-cell omics, to achieve a leap from empirical application to precise regenerative medicine.

Oncological safety and long-term monitoring

A critical concern in plastic surgery, particularly in breast reconstruction following malignancy, is the potential for ADSCs to promote tumor recurrence or metastasis via their pro-angiogenic and anti-apoptotic signaling[81]. While available clinical evidence has not demonstrated a clear increase in oncological risk associated with CAL, the pro-angiogenic secretome of ADSCs, including VEGF and hepatocyte growth factor (HGF), warrants continued vigilance in post-oncologic reconstruction, particularly given the potential for interactions with residual or dormant tumor cells[82-84]. The powerful paracrine effect of ADSCs, through the secretion of VEGF, HGF and various cytokines, promotes the vascularization of transplanted fat but may also influence the local tumor microenvironment, highlighting the need for continued oncologic surveillance. In addition, the transcriptional heterogeneity of ADSCs further complicates risk assessment. Studies have shown that the drift of cell subpopulations during *in vitro* culture may increase the risk of embolism in the host[79]. Rigorous, large-scale prospective randomized controlled trials with extended follow-up periods are essential to definitively establish the safety profile of ADSC-based therapies. Clinically, these potential risks support careful patient selection and individualized timing of CAL rather than a universal waiting period. CAL should preferably be considered after completion of oncological treatment and confirmation of no active disease, with the timing determined according to tumor characteristics and recurrence risk; an interval of approximately 6-12 months may be considered in selected post-radiotherapy patients[85].

Future directions: biofabrication and cell-free therapies

The future of ADSCs in plastic surgery lies at the intersection of bioengineering and molecular medicine. 3D Bioprinting technology enables the creation of customized, ADSC-laden scaffolds that mimic the complex architecture of craniofacial bones or soft tissue defects, offering a path toward precision reconstructive surgery[86]. Simultaneously, the shift toward cell-free therapies using ADSC-derived exosomes represents a transformative trend[87]. Exosome-based products may retain some of the regenerative properties associated with ADSCs while offering potential advantages in terms of stability, immunogenicity, and translational feasibility, potentially serving as biological agents for wound repair and aesthetic enhancements[88]. Beyond these emerging strategies, further investigation is also warranted to clarify and optimize the potential applications of ADSCs in breast remodeling and reconstruction, facial soft-tissue restoration, and protection against UV-related skin damage and photoaging[89]. Future studies should focus on improving the consistency, safety, and long-term efficacy of these approaches and on translating promising preclinical findings into well-controlled clinical applications.

Table 1. Summary of key clinical studies on ADSCs in plastic surgery

Study (Year)	Design	*n*	Cell type/Dose	Follow-up	Primary outcome	Key findings	Evidence level/limitations
CAL and fat grafting							
Kølle *et al.*, 2013[54] (*Lancet*)	RCT (Triple-blind, placebo-controlled)	10	*Ex vivo*-expanded autologous ASCs 20 × 10^6 cells/mL fat 30 mL fat graft enriched *vs.* 30 mL control (contralateral arm)	121 days	Residual graft volume by MRI	ASC-enriched grafts: 80.9% retention *vs.* 16.3% control ($P < 0.0001$); Absolute difference = 64.6 pp. No serious AEs	High-level clinical evidence; small sample size and short follow-up
Li and Chen, 2021[51] (*Aesthetic Plast Surg*)	Meta-analysis	353 (6 studies)	CAL (*ex vivo* ADSC or SVF enrichment); dose heterogeneous across studies	Variable	Fat survival rate; Complication rate	CAL superior to conventional lipotransfer for fat survival ($P = 0.02$). No significant difference in complications (OR = 1.34, $P = 0.43$)	Moderate-to-high level evidence; limited by heterogeneity of included studies, cell preparations, and outcome measures
Hasiba-Pappas *et al.*, 2025[77] (*Aesthetic Surg J*)	Systematic review (12 clinical studies, 15 animal studies)	12 clinical studies (case numbers variable)	SVF and/or ADSC enrichment; also PRP, Vitamin D_3, botulinum toxin A, *etc.*	Variable	Graft survival; enhancement strategies	SVF/ADSC and PRP most promising for graft enhancement; marked protocol heterogeneity limits comparability. No gold standard established	Moderate-level evidence; substantial protocol heterogeneity and no established gold standard
Gao *et al.*, 2022[57] (*J Cosmet Dermatol*)	*In vivo* preclinical (nude mouse model; clinical ADSC harvest)	15 PHA patients *vs.* 15 healthy donors (fat grafts in nude mice)	ADSC-assisted fat graft; exosome-assisted fat graft; non-cell-assisted (control)	2, 4, 8, 12 weeks	Volume & weight retention; Histology (HE, CD31, CD68, perilipin)	PHA-ADSC group: lower retention than NORM-ADSC but superior to non-cell group. Exosome-assisted also improved fat survival. Supports CAL for hemifacial atrophy	Preclinical evidence; limited direct clinical generalizability
Wound healing & chronic ulcers							
Cao *et al.*, 2025[40] (*J Inflammation Res*)	Translational (Bioinformatics + ML + *in vivo/in vitro* validation)	GEO datasets: GSE134431, GSE80178; *in vivo*: DFU mouse model	ADSCs applied to DFU wound model	Not specified (wound closure endpoint)	AUC of 2-gene prognostic model; M2 macrophage polarization; wound healing rate	EREG & CSTA identified as key MA-DEGs. AUC > 0.944 in training and validation. ADSCs downregulate EREG/CSTA → promote M2 polarization → accelerate DFU healing	Translational/preclinical evidence; supported by bioinformatics and experimental validation but lacks direct human clinical evidence
Kohlhauser *et al.*, 2024[67] (*Cell Mol Biol Lett*)	Systematic Review (21 *in vivo* studies; rodent + 1 porcine model)	21 studies (all preclinical; no human RCTs included)	Heterogeneous across studies	Variable	Immunomodulation; neovascularization; granulation tissue; re-epithelialization; remodeling	ADSCs promoted wound healing in all 21 *in vivo* studies via immunomodulation, neovascularization, granulation tissue formation, re-epithelialization, and remodeling. The majority of studies reported positive outcomes across multiple healing phases. Clinical translation remains at an early experimental stage	Preclinical evidence; systematic review of animal studies without human RCTs, limiting clinical translation
Skin rejuvenation & anti-aging							
Ichihashi *et al.*, 2023[73] (*J Pers Med*)	Case Series (single-arm, open-label)	8 patients	1 × 10^8 autologous ADSCs (cultured from abdominal subcutaneous fat) Single intradermal injection to face	12 months (1, 3, 6, 12 months)	Photographic assessment of wrinkles (glabella, crow's feet, nasolabial), pore size, double eyelid	All 8 cases: wrinkle shallowing/disappearance from 1-several months, lasting > 1 year. Double eyelid sharpening and pore reduction. No adverse events reported	Moderate-level clinical evidence; single-arm case series with only 8 patients and no control group
Chon *et al.*, 2025[70] (*Aesthetic Surg J Open Forum*)	Systematic review (17 studies; SVF, ADSC, AD-MSC)	17 studies (sample sizes per included study)	SVF, ADSCs, or conditioned medium; heterogeneous protocols	Variable; heterogeneity limits pooling	Rhytid severity; skin elasticity; pigmentation (melanin index); texture	SVF and ADSC-CM reduced rhytid severity, especially periorbital and nasolabial. Meta-analysis of 2 studies: rhytid reduction non-significant ($P = 0.12$). Combination therapy (SVF+laser/PRP) outperformed SVF alone	Moderate-level evidence; substantial heterogeneity and limited statistical power for pooled clinical outcomes
Surowiecka and Strużyna, 2022[78] (*J Pers Med*)	Narrative review	Multiple clinical studies summarized	ADSCs or SVF injected intradermally; no standard dose	Variable	Skin density; appearance; hydration; capillary density	ADSC intradermal injection improved skin density, overall appearance, hydration, and capillary vessel number. Graft survival main limitation. No standardized protocol; longer follow-up needed	Moderate quality evidence; heterogeneous interventions and outcome measures
Scar treatment							
Stachura *et al.*, 2021[68] (*J Clin Med*)	Systematic review (19 clinical studies)	665 total patients (19 included studies)	ADSCs or SVF (enzymatic/mechanical/nanofat); heterogeneous across studies	Variable	Microscopic, functional, and aesthetic scar outcomes; Comparison to PRP/CO_2 laser	Low-to-average quality evidence for beneficial effects. Some studies: ADSC interventions non-inferior to PRP or fractional CO_2 laser. No gold standard established	Moderate quality evidence; heterogeneous interventions and outcome measures, with no established gold-standard treatment

Vascular & other applications							
Shikanai *et al.*, 2025[58] (*Regen Ther*)	Translational (*in vitro* co-culture + *in vivo* nude mouse fat graft model)	*In vitro*: human PBMC donors; *in vivo*: nude mice	ADSCs co-cultured with RE-01 cells (*ex vivo* peripheral blood MNCs); reduced ADSC number *vs.* ADSC-alone	Fat graft engraftment endpoint	Fat engraftment rate; blood vessel density; adipose tissue quality	ADSC+RE-01 combination significantly improved fat engraftment rate, blood vessel number, and fat quality *vs.* ADSC alone *in vivo*. RE-01 reduces ADSC requirement for breast reconstruction fat grafting	Translational/preclinical evidence; promising *in vitro* and animal findings but limited direct evidence of clinical efficacy

ADSCs: Adipose-derived stem cells; ADSC-CM: adipose-derived stem cell-conditioned medium; AEs: adverse events; AUC: area under the curve; CAL: cell-assisted lipotransfer; CD: cluster of differentiation; CM: conditioned medium; CSTA: cystatin A; DFU: diabetic foot ulcer; EREG: epiregulin; GEO: Gene Expression Omnibus; HE: hematoxylin and eosin; MA-DEGs: macrophage polarization-associated differentially expressed genes; ML: machine learning; MNCs: mononuclear cells; MRI: magnetic resonance imaging; NORM: normal (healthy donor); OR: odds ratio; PBMC: peripheral blood mononuclear cell; PHA: progressive hemifacial atrophy; PRP: platelet-rich plasma; RCT: randomized controlled trial; RE-01: vascular regenerative cells (*ex vivo* peripheral blood mononuclear cells); SVF: stromal vascular fraction.

CONCLUSION

In conclusion, ADSCs represent a transformative pillar in the field of plastic and reconstructive surgery, bridging the gap between traditional surgical techniques and advanced regenerative medicine. Their abundance, ease of isolation, and multifaceted mechanisms - ranging from direct differentiation to potent paracrine and exosome-mediated signaling - have redefined our approach to tissue repair and aesthetic enhancement. While CAL and chronic wound therapies have already shown encouraging preclinical efficacy, the emergence of cell-free strategies and biofabrication technologies marks the next frontier. Despite the remaining challenges in standardization and long-term regulatory oversight, ADSCs hold the potential to realize the goal of personalized, scarless, and functional tissue regeneration. As research continues to unravel the molecular intricacies of these cells, ADSCs will undoubtedly remain at the heart of the next generation of plastic surgery.

DECLARATIONS

Acknowledgments

The Graphical Abstract and figures were created using BioRender. Publication licenses were obtained for the BioRender content used in this manuscript. (2026) https://BioRender.com/smn4uzm.

Authors' contributions

Made substantial contributions to the conception and design of the review, and performed literature search and analysis: Sun C

Provided critical feedback on the structure and intellectual content, and revised the manuscript: Jin M

Supervised the study, acquired funding, and revised the manuscript for important intellectual content: An Y

All authors read and approved the final manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (GPT-5.6 Luna, released 2026-07-09) was used solely for language polishing and proofreading to improve readability and grammatical clarity. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

Financial support and sponsorship

This work was supported by the Grant Beijing Natural Science Foundation (Nos. L244086 and 7264349).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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