Review

Adipose-derived preparations for wound regeneration: From hierarchical classification to clinical translation

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Abstract

Adipose-derived preparations have increasingly become a focal point in wound regeneration research due to their abundant availability, relatively facile acquisition, and combined potential for structural support, bioactive regulation, and engineering applications. Based on compositional characteristics and processing methods, these preparations can be classified into five major categories: tissue-level, particulate-level, cellular-level, secretome-level, and extracellular matrix-level preparations. Preparations at different hierarchical levels exert distinct yet synergistic effects across key wound

repair processes, including correction of inflammatory imbalance, alleviation of oxidative stress, angiogenesis and microcirculatory reconstruction, re-epithelialization and barrier restoration, and extracellular matrix remodeling and scar modulation. Framing the discussion around the "regenerative cascade" of wound repair, this review systematically summarizes the functional scope, mechanistic features, indication stratification, and current limitations of various adipose-derived preparations, and further highlights their application potential in different wound types. Meanwhile, recent advances in integrating adipose-derived preparations with engineering strategies are discussed, alongside major challenges in standardized preparation, identification of critical quality attributes, process scale-up, and clinical translation. Future research on adipose-derived preparations should move beyond repeated verification of "whether they are effective," and instead focus on precise matching to dominant pathological barriers, the establishment of quantifiable potency evaluation systems, and the development of translational frameworks tightly integrated with engineered delivery strategies and regulatory pathways, thereby facilitating the transition from empirical application to standardized, precise, and broadly translatable clinical regenerative therapeutic strategies.

Keywords: Adipose-derived preparations, wound healing, regenerative microenvironment, tissue engineering

INTRODUCTION

Wound healing remains a central priority and a major challenge in regenerative medicine and clinical practice[1]. The therapeutic challenge extends beyond achieving wound closure to restoring tissue structural integrity, physiological function, and aesthetic outcomes[2]. Adipose-derived preparations, owing to their integrated characteristics of cellular components, bioactive molecules, and extracellular matrix support[3], exhibit unique advantages in modulating inflammatory responses[4], promoting angiogenesis[5], facilitating matrix remodeling[6], and improving the wound

microenvironment[7], and are increasingly recognized as a promising regenerative strategy for wound healing.

The understanding of adipose-derived preparations originated from the clinical application of autologous fat grafting (AFG)[8]. Initially, AFG was primarily used for soft-tissue volume reconstruction[9]. However, with the accumulation of clinical follow-up data and experimental evidence, it has become increasingly recognized that recipient sites following fat grafting often exhibit “regenerative changes” beyond simple volumetric effects, including scar softening, improved pigmentation and texture, and pain relief[10]. These findings suggest that adipose tissue has the capacity to remodel the local microenvironment and promote tissue regeneration. In recent years, accumulating evidence indicates that adipose tissue and its derived bioactive preparations are not merely passive soft-tissue fillers, but actively participate in multiple key stages of wound repair through intercellular communication[11], paracrine signaling[5], matrix support, and related mechanisms, thereby driving the transition from conventional repair toward regenerative healing[3]. Accordingly, adipose-derived preparations are evolving from simple tissue-filling materials into an important biological intervention platform for wound repair and regenerative medicine.

Centered on the concept of the “regenerative cascade,” this review systematically summarizes the biological effects, key signaling pathways, and clinical indications of multilevel adipose-derived preparations in wound healing, further discusses synergistic strategies enabled by engineering approaches, and explores their future directions for clinical translation.

ADIPOSE-DERIVED PREPARATIONS

Adipose tissue is abundant, readily accessible, and rich in stromal vascular fraction (SVF), adipose-derived mesenchymal cells, and diverse paracrine bioactive factors; therefore, it can be regarded as an “accessible living biomaterial reservoir.”[12,13] Based

on their intrinsic characteristics and processing methods, adipose-derived preparations can be broadly classified into five categories: tissue-level, particulate-level, cellular-level, secretome-level, and extracellular matrix-level preparations[8,12,14]. Collectively, spanning from whole tissue to extracellular matrix and from structural support to bioactive regulation, adipose-derived preparations at different levels constitute a regenerative intervention system for wound healing that is both functionally diverse and mechanistically complementary [Figure 1].

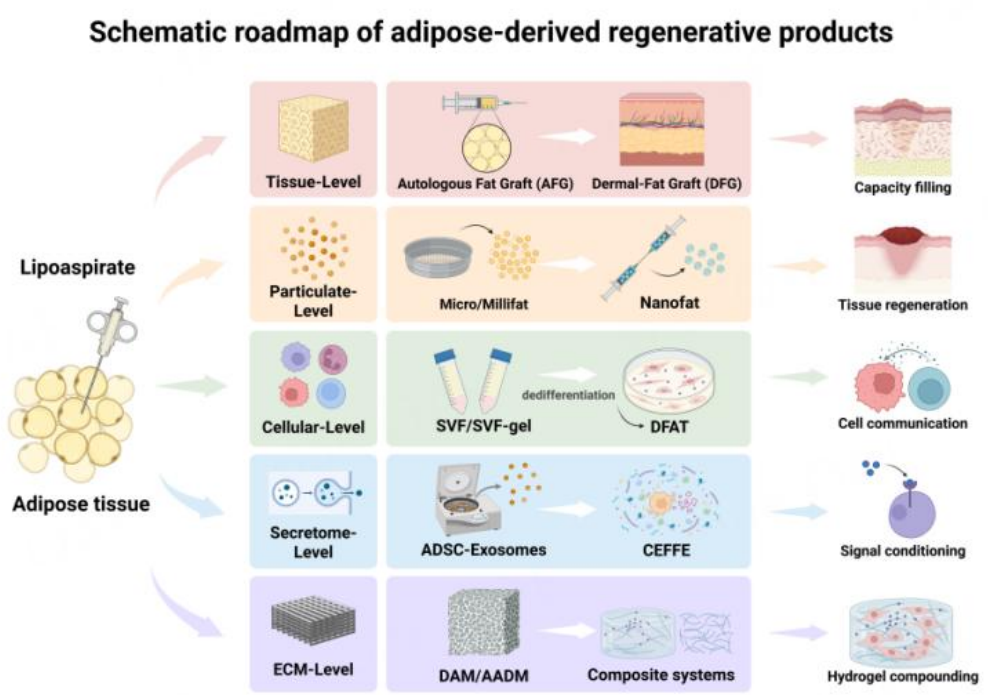

Figure 1. Acquisition routes and principal functions of adipose-derived preparations. This schematic summarizes the major adipose-derived preparations obtained from lipoaspirate or adipose tissue and their principal regenerative functions. AFG: autologous fat graft; DFG: dermal-fat graft; SVF: stromal vascular fraction; SVF-gel: stromal vascular fraction gel; DFAT: dedifferentiated fat cells; ADSC-Exosomes: adipose-derived stem cell exosomes; CEFFE: cell-free fat extract; ECM: extracellular matrix; DAM: decellularized adipose matrix; AADM: acellular adipose-derived matrix.

Tissue-level preparations

Tissue-level preparations mainly include AFG and dermal fat grafting (DFG). Their principal advantage lies in preserving, to the greatest extent possible, the native macroscopic architecture, cellular composition, and extracellular matrix microenvironment of adipose tissue[8,15]. AFG is typically applied for recipient-site repair following low-negative-pressure liposuction, purification, and layered injection, and can immediately provide volume restoration, mechanical cushioning, and a certain degree of trophic support[8,10]. DFG, by retaining dermal components, exhibits greater mechanical stability and is therefore more suitable for applications requiring deep support, contour maintenance, or correction of depressed scars[15]. From a regenerative perspective, the value of tissue-level preparations lies not only in "replacing missing tissue", but also in providing the recipient site with a composite biological unit capable of maintaining viability for a defined period.

However, it should be emphasized that the regenerative potential of tissue-level preparations is critically dependent on early vascular reconstruction and perfusion within the recipient site[16]. Their survival and integration are fundamentally constrained by diffusion distance, graft particle size, and the risk of central ischemia[17]. These constraints result in a relatively restricted range of indications, rendering tissue-level preparations suitable primarily for wounds with adequate vascular supply and concomitant structural collapse or soft-tissue volume deficiency, rather than for all wound types. Consequently, their current therapeutic orientation is largely confined to structural reconstruction rather than microenvironmental modulation.

Particulate-level preparations

Particulate-level preparations mainly include microfat, millifat, and nanofat. These preparations are typically generated through mechanical shearing, emulsification, filtration, or graded sieving, resulting in reduced adipose lobule size and improved injection uniformity[18]. Compared with tissue-level preparations, these preparations exhibit significantly enhanced injectability, distribution uniformity, and tissue

integration while retaining a certain degree of biological activity[8]. Nanofat, in particular, has largely lost its conventional volume-filling capacity but remains rich in SVF-related cells, matrix fragments, and paracrine signals; it is therefore often applied in superficial scars, photoaged skin, wound-edge activation, and repair scenarios requiring broad distribution[19].

However, the preparation process is highly influenced by emulsification intensity, filtration pore size, and separation methods[17]. Currently, no unified standard exists across medical centers, and most procedures rely heavily on operator experience, which may result in substantial variability in cellular activity and cargo profiles among preparations generated at different centers[20]. In addition, due to the involvement of mechanical manipulation, suboptimal processing may result in substantial structural debris and oil residues in the final product, thereby exacerbating postoperative inflammatory reactions and increasing the risk of adverse events[21]. Particulate-level preparations also contain heterogeneous cell populations. Although their therapeutic scope is broader, their capacity for microenvironmental modulation remains limited compared with cellular-level preparations[22]. Therefore, they are generally regarded as a functional transitional level between structural support and microenvironmental regulation.

Cellular-level preparations

Cellular-level preparations mainly include stromal vascular fraction (SVF) and dedifferentiated fat cells (DFAT), with their core therapeutic unit comprising biologically active cell populations[23]. SVF can be isolated via enzymatic or mechanical methods and comprises heterogeneous components, including adipose-derived stromal cells, adipose-derived mesenchymal stem cells, endothelial-related cells, pericytes, and immune cells. In contrast, DFAT are generated through in vitro dedifferentiation of mature adipocytes and exhibit a relatively homogeneous cellular phenotype. Compared with tissue-level and particulate-level preparations, cellular-level preparations more

closely resemble standardized regenerative cell therapies. Their primary advantage lies not in volume restoration, but in actively remodeling the wound microenvironment through viable cell integration, immunoregulation, and paracrine signaling[3].

However, cellular-level preparations face the highest translational barriers[14]. On the one hand, donor age, metabolic status, harvest site, and isolation procedures can significantly affect cell composition, activity, and potency. On the other hand, cell-based preparations are subject to substantially stricter requirements regarding preparation, storage and transport, release testing, and regulatory compliance[24,25]. Therefore, cellular-level preparations are not inherently superior to other levels; rather, their advantages are more pronounced in contexts characterized by chronic inflammation, insufficient angiogenesis, and marked depletion of regenerative cell populations. Nevertheless, current evidence for cellular-level preparations remains predominantly preclinical, and extrapolation to clinical efficacy should be approached with caution.

Secretome-level preparations

Secretome-level preparations mainly include adipose-derived stem cell exosomes (ADSC-Exos) and cell-free fat extract (CEFFE)[12]. A defining feature of secretome-level preparations is the removal of viable cellular carriers, while bioactive signals—including exosomes, proteins, growth factors, lipid mediators, and other components—are retained or enriched[5,26]. Compared with cell-based therapies, secretome-level preparations offer advantages such as lower immunogenicity, greater convenience in storage and transport, enhanced potential for scalable production, and a relatively clearer regulatory pathway[27]. Accordingly, in recent years, secretome-level preparations have emerged as one of the most promising directions among adipose-derived preparations for achieving early large-scale clinical translation[28].

However, secretome-level preparations are not necessarily safer or uniformly effective[29]. Their principal challenge lies in the insufficiently defined relationship

between quality attributes and functional potency[30]. Variations in isolation methods can markedly affect particle purity, protein impurity levels, and the profile of key bioactive cargoes[31]. Variations in dosing regimens, administration frequency, and delivery routes can directly influence local retention and pharmacokinetics[32,33]. Thus, "adipose-derived" is not a sufficient quality descriptor. Without standardized particle characterization, cargo profiling, and potency testing, secretome-level preparations remain poorly comparable, poorly reproducible, and difficult to translate.

ECM-level preparations

ECM-level preparations mainly include decellularized adipose matrix (DAM) and its derived composite systems[6]. Through physical, chemical, or enzymatic decellularization and delipidation, ECM-level preparations preserve the adipose tissue-specific ECM composition, microscopic porous architecture, and a subset of matrix-bound signaling cues, therefore offering broad potential for engineering applications[34,35]. DAM offers low immunogenicity, good biocompatibility, and strong potential for re-engineering, making it particularly suitable for integration with exosomes, cells, or growth factors to develop composite regenerative systems[36,37].

However, ECM-level preparations also have clear limitations. When applied alone to complex wound beds characterized by high inflammation, elevated protease activity, severe ischemia, or pronounced infection, their passive support is often insufficient to restore microenvironmental balance[34,38]. Therefore, standalone application of ECM-level preparations is relatively uncommon, with greater emphasis placed on their coupling efficiency, degradation kinetics, and spatial delivery performance when combined with cellular-level or secretome-level preparations[35,37].

ROLES OF ADIPOSE-DERIVED PREPARATIONS IN THE REGENERATIVE CASCADE OF WOUND HEALING

The classical model of wound healing divides the repair process into four sequential

stages: hemostasis, inflammation, proliferation, and remodeling. While this framework is useful for depicting the temporal sequence, it is limited in capturing the complexity of chronic wounds, where multiple pathological barriers coexist and mutually exacerbate one another[39]. The therapeutic value of adipose-derived preparations does not reside in acting at a single phase, but rather in their ability to simultaneously target multiple rate-limiting nodes within wound repair. Based on current evidence, we adopt the concept of the regenerative cascade in wound healing, highlighting five major rate-limiting nodes[40]: inflammatory and immune imbalance, antioxidation and cytoprotection[41], angiogenesis and microcirculatory reconstruction, re-epithelialization and barrier restoration, and ECM remodeling and functional recovery. Notably, these five modules are not isolated, but exhibit continuous coupling and interdependence[11]. The therapeutic advantage of adipose-derived preparations lies in their ability to exert coordinated effects across this network, rather than targeting a single node [Figure 2].

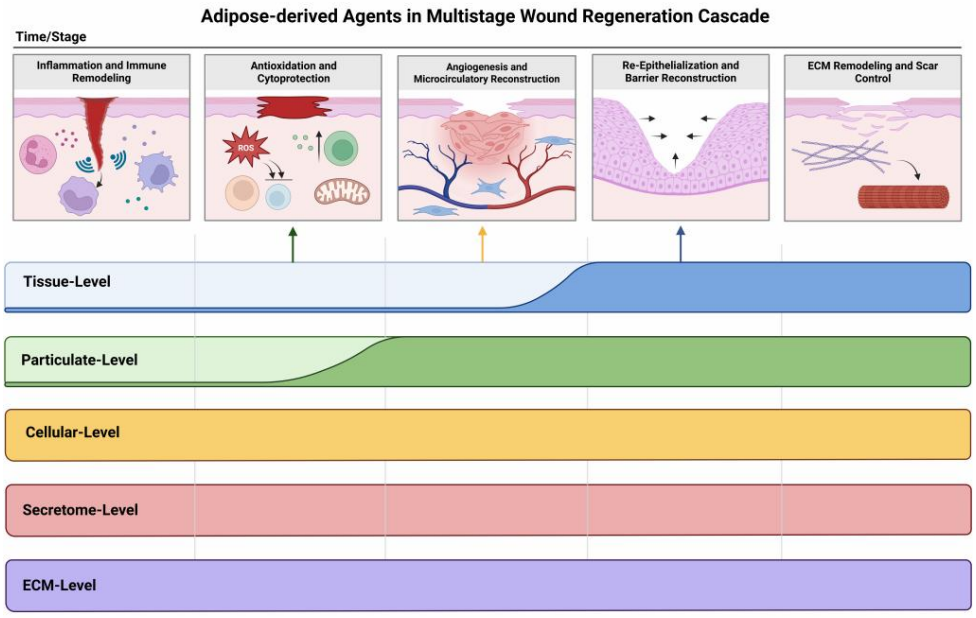

Figure 2. Roles of adipose-derived preparations in the wound regenerative cascade. This schematic illustrates the involvement of different adipose-derived preparations in key stages of wound regeneration. ECM: extracellular matrix.

Inflammation and immune remodeling

During wound repair, inflammation is essential not only for the initial injury response and debris clearance, but also as a key determinant of subsequent healing progression[40]. In complex wounds, persistent ischemia, hyperglycemia, infection, and mechanical or metabolic stress often induce chronic inflammatory imbalance, which suppresses cell proliferation, angiogenesis, and matrix remodeling, ultimately leading to delayed healing[39,42]. At this stage, the therapeutic value of adipose-derived preparations extends beyond mere anti-inflammatory activity, encompassing mitigation of chronic inflammation drivers through immunomodulation and microenvironmental remodeling. Among the various levels, cellular- and secretome-level preparations serve as the primary direct regulators of inflammation. SVF exerts anti-inflammatory effects by regulating inflammatory cytokines and immune-cell behavior, accompanied by macrophage phenotypic conversion toward a reparative phenotype, thereby promoting wound resolution and reducing post-healing fibrosis[43]. DFAT also appears to contribute to tissue repair, although its precise role remains insufficiently defined[44]. Secretome-level preparations, such as ADSC-Exos[5] and CEFFE[45], can further modulate the inflammatory microenvironment by reducing pro-inflammatory signaling and promoting repair-associated immune responses. In contrast, tissue-, particulate-, and ECM-level preparations mainly provide indirect support by improving the local mechanical environment, alleviating ischemia and hypoxia, and supplying structural matrix support[6,9,44]. Collectively, these different levels act synergistically to facilitate the transition from persistent inflammation to organized wound repair.

Antioxidation and cytoprotection

In complex wounds, oxidative stress imbalance is a critical mechanism contributing to impaired wound repair. Physiological ROS levels are essential for cellular signaling and host defense, but sustained ROS overproduction can disrupt the reparative microenvironment and delay wound healing[46,47]. At this stage, adipose-derived preparations confer therapeutic benefit not merely through ROS scavenging, but by mitigating oxidative damage via cytoprotection and microenvironmental regulation.

Secretome- and cellular-level preparations constitute the primary direct mediators of antioxidant interventions. Secretome-level preparations, such as ADSC-Exos, can enhance macrophage autophagy and alleviate oxidative stress-induced mitochondrial injury, thereby promoting diabetic wound healing[48]. Cellular-level preparations, including SVF and adipose-derived stromal cells, reduce oxidative injury and apoptosis via paracrine cytoprotective mechanisms[49,50]. By contrast, particulate-level preparations may provide indirect antioxidant support by improving the local reparative microenvironment rather than by acting as primary ROS-scavenging agents[19,51], whereas tissue- and ECM-level preparations confer relatively limited direct antioxidant effects. Overall, these levels work synergistically to promote the transition from oxidative injury to stabilized wound repair.

Angiogenesis and microcirculatory reconstruction

During wound repair, angiogenesis and microcirculatory reconstruction are essential for the transition from inflammatory imbalance to organized healing[52,53]. At this stage, the therapeutic value of adipose-derived preparations extends beyond merely increasing vessel number, encompassing promotion of angiogenesis, enhancement of vascular maturation and stability, and restoration of functional perfusion.

Particulate-, cellular-, secretome-, and ECM-level preparations collectively constitute the principal framework for vascular reconstruction. Particulate-level preparations, such as microfat, millifat, and nanofat, facilitate early nutrient diffusion and vascular ingrowth, with nanofat additionally supporting lymphangiogenesis and tissue integration[54,55]. Cellular-level preparations, especially SVF, provide vascular progenitor cells and paracrine pro-angiogenic factors, thereby promoting vessel sprouting and stabilization[56]. Secretome-level preparations exert potent cell-free pro-angiogenic effects by transferring angiogenic bioactive cargoes that activate endothelial repair responses and promote neovascularization during wound healing[5].

ECM-level preparations mainly provide matrix architecture and adhesion templates to support vascular ingrowth, and can further improve local retention of active components when integrated with cells or secretome-level preparations[57]. Overall, these levels act synergistically to promote the transition of the wound from hypoperfusion to effective repair.

Re-epithelialization and barrier reconstruction

During wound repair, re-epithelialization and barrier reconstruction are essential for achieving wound closure and restoring functional integrity[58]. This process requires the proper migration, proliferation, and differentiation of keratinocytes, as well as restoration of the structural connections among the epidermis, basement membrane, and dermis[59]. At this stage, adipose-derived preparations exert therapeutic benefit not only by modulating keratinocyte behavior but also by optimizing the wound bed, and supporting reconstruction of adhesion interfaces, thereby accelerating restoration of epidermal continuity and barrier function.

Preparations across multiple levels participate in this process. Tissue-level preparations mainly alleviate local ischemia, buffer mechanical tension, and release bioactive factors to improve wound-bed quality[9,10]. Particulate-level preparations, including microfat and nanofat, favor local integration and bioactive factor release, with nanofat additionally supporting keratinocyte migration via retained progenitor cells, microvascular fragments, and ECM components[55]. Cellular-level preparations, especially SVF[56], promote re-epithelialization by improving chronic inflammation, enhancing wound-bed activity, and secreting pro-repair bioactive factors. Secretome-level preparations exhibit potent pro-epithelial effects by attenuating inflammatory and oxidative injury, while directly promoting keratinocyte migration and proliferation[5]. ECM-level preparations primarily provide favorable adhesion interfaces and structural support to facilitate reconstruction of a basement membrane-like microenvironment[35,38]. Overall, these levels act synergistically to promote the

transition from an open wound surface to complete barrier restoration.

ECM remodeling and scar control

In the late stage of wound repair, ECM remodeling and scar modulation are critical determinants of final repair quality[40]. This process is modulated by balanced collagen metabolism, mechanical microenvironment, fibroblast function and fibrogenic signaling[60,61]. Adipose-derived preparations exert therapeutic benefit at this stage not only by improving scar appearance, but also by attenuating excessive fibrosis, promoting orderly collagen remodeling, and supporting a regenerative microenvironment conducive to functional recovery.

Preparations across multiple levels contribute to this process. Tissue-level preparations, such as autologous fat grafting, reduce local tension and improve scar quality through their compliant mechanical properties[9,10]. Particulate-level preparations, especially nanofat, further modulate collagen organization and facilitate scar maturation[19,62]. Cellular-level preparations, including SVF, suppress chronic inflammation and aberrant fibrosis via multicellular interactions and paracrine mechanisms. Secretome-level preparations show potent antifibrotic effects by inhibiting myofibroblast transdifferentiation and enhancing collagen organization. ECM-level preparations provide near-native three-dimensional scaffolds and tissue-guiding cues that support orderly collagen deposition and preserve a regenerative microenvironment[6,38]. Overall, these levels act synergistically to limit fibrosis and promote the transition from scar-mediated repair to higher-quality regeneration.

APPLICATIONS OF ADIPOSE-DERIVED PREPARATIONS IN DIFFERENT TYPES OF WOUNDS

Based on etiology and tissue injury characteristics, wounds can be broadly categorized as superficial skin injuries, acute defect wounds, chronic refractory wounds, diabetic wounds, and special types, including radiation-induced wounds[63,64]. Due to their

multilevel forms and multidimensional regenerative capacities, adipose-derived preparations are applicable across diverse wound-repair scenarios, offering targeted interventions against dominant pathological barriers. The indication-based applications of adipose-derived preparations are summarized in Table 1.

Superficial skin injuries

Superficial skin injuries are among the most common cutaneous lesions and are usually limited to the epidermis and superficial dermis, as observed in photoaging, post-acne atrophic scars, and inadequately repaired superficial scars[65,66]. Unlike deep wounds, their primary challenge is not extensive tissue loss, but persistent low-grade inflammation, oxidative stress, superficial matrix damage, and disruption of skin microarchitecture. Consequently, therapeutic strategies should prioritize the remodeling of the microenvironment and the repair of the superficial matrix over merely filling defects. Various preparations demonstrate specific applicability: nanofat, microfat, and adipose-derived exosomes are particularly effective for addressing photoaging[67], whereas microfat, nanofat, and SVF/ECM-SVF gel show greater efficacy in treating atrophic scars[19,68]. For hypertrophic scars, preparations at the particulate and secretome levels may enhance scar quality by modulating fibrosis-related signaling pathways and the local mechanical environment[69,70]. Overall, adipose-derived preparations facilitate superficial skin repair primarily through microenvironmental remodeling and superficial matrix reconstruction, although comprehensive comparative clinical evidence remains limited.

Acute wounds

Acute wounds are frequently encountered lesions that may involve partial- or full-thickness loss of skin and underlying soft tissue, including traumatic lacerations, surgical defects, and burn injuries[71]. Unlike chronic wounds, the main challenge in acute wounds is rapid restoration of tissue integrity while mitigating inflammation, oxidative stress, and disruption of the extracellular matrix[40,41,72]. Therefore, therapeutic

strategies should prioritize rapid tissue repair and microenvironmental optimization over mere defect filling. In this context, adipose-derived preparations confer therapeutic benefit by exerting anti-inflammatory, antioxidant, and pro-remodeling effects while improving the local microenvironment. Different preparations exhibit distinct applicability depending on wound type and depth. Tissue- and particulate-level preparations, such as nanofat and microfat, facilitate defect coverage and early matrix stabilization[9,10,73]. Cellular- and secretome-level preparations, including SVF and ADSC-Exos, actively modulate inflammation, oxidative stress, and fibroblast activity to optimize healing outcomes[74]. Particulate- and secretome-level preparations may further improve scar quality by modulating profibrotic signaling pathways and local mechanical cues[69,75]. Overall, adipose-derived preparations promote acute wound repair by combining structural support, microenvironmental modulation, and matrix reconstruction, although robust comparative clinical evidence remains limited.

Chronic ulcers

In this review, chronic ulcers primarily encompass venous leg ulcers, pressure injuries, and arterial ischemic ulcers[76]. The defining challenge of these wounds is not simply persistent tissue loss, but a chronically dysregulated wound microenvironment characterized by sustained inflammation, excessive protease activity, growth factor degradation, impaired cellular responsiveness, and recurrent biofilm formation[39]. In this context, adipose-derived preparations serve not merely as tissue fillers, but as regenerative modalities capable of modulating inflammation, oxidative stress, angiogenesis, matrix stability, and bioactive signaling.

The suitability of different adipose-derived preparations varies according to ulcer type[77,78]. In venous leg ulcers, characterized by microcirculatory dysfunction and MMP-mediated extracellular matrix degradation, secretome-level and cell/matrix composite preparations appear particularly appropriate[79]. In pressure injuries, secretome-level preparations, such as ADSC-Exos, may more effectively mitigate

oxidative stress and ischemia-reperfusion injury. In arterial ischemic ulcers, cellular- and secretome-level preparations show greater therapeutic potential by promoting angiogenesis, supporting endothelial repair, and alleviating ischemia-induced injury. ECM-level preparations primarily function as scaffold platforms providing sustained support[35], whereas tissue- and particulate-level preparations mainly play adjunctive roles. Overall, adipose-derived preparations facilitate healing of chronic ulcers mainly by restoring regenerative responsiveness within a chronically impaired wound bed, although robust comparative clinical evidence remains limited.

Table 1. Indication-based application of adipose-derived preparations in wound repair

Wound type	Key barriers	Preferred preparations	Major roles
Superficial wounds	Mild inflammation, oxidative stress, superficial matrix damage[46,47,66,67]	Nanofat, microfat, SVF/ECM-SVF gel, ADSC-Exos[5,19,67,68]	Microenvironmental improvement and matrix repair[67-70]
Acute wounds	Inflammation, oxidative injury, ECM disruption[40,41,63,72]	Nanofat, microfat, SVF, ADSC-Exos[5,9,10,73]	Structural support and early repair[9,10,63,72,73]
Chronic ulcers	Persistent inflammation, protease overactivity, poor perfusion[27,39]	Secretome-based preparations, cell/matrix composites, ADSC-Exos, ECM-based preparations[27,35,77,78]	Reparative microenvironment reconstruction and angiogenesis[27,35,39,77,79]
Diabetic wounds	Metabolic dysfunction,	SVF, ADSC-Exos, ECM-based	Anti-inflammatory modulation,

	microvascular impairment, immune dysregulation[53,80-82]	preparations[35,49,57,78,83]	angiogenesis, and regenerative activation[49,53,57,78]
Radiation ulcers	Endothelial injury, hypoxia, fibrosis[64,84,85]	Nanofat, SVF, ADSC-Exos, DAM scaffolds[5,64,86,87]	Vascular restoration, antifibrotic regulation, and structural support[64,84-87]

Abbreviations: SVF: stromal vascular fraction; ECM: extracellular matrix; ADSC-Exos: adipose-derived stem cell exosomes; DAM: decellularized adipose matrix.

Diabetic wounds

Diabetic wounds, while categorized as chronic wounds, are often considered separately because of their high prevalence, complex pathophysiology, and comparatively poorer clinical outcomes[80,81]. Unlike typical acute or chronic wounds, impaired healing in diabetic wounds is primarily driven not by local tissue loss but by systemic abnormalities associated with chronic hyperglycemia[82,88]. Therefore, therapeutic strategies should aim not only at achieving wound closure, but also at restoring the chronically dysregulated wound microenvironment and re-establishing a reparative foundation with adequate perfusion, immune homeostasis, and regenerative capacity.

Among adipose-derived preparations, cellular-, secretome-, and ECM-level preparations demonstrate particular therapeutic promise in diabetic wounds[35,77]. Cellular-level preparations, including SVF and adipose-derived stromal cells, can suppress inflammation, promote macrophage polarization toward the M2 phenotype, enhance angiogenesis, and reactivate reparative processes within the wound bed[78]. Secretome-level preparations, especially ADSC-Exos, offer distinct cell-free advantages by delivering bioactive signals that improve endothelial repair, support fibroblast and

keratinocyte migration, and regulate inflammatory and oxidative stress pathways[83,89]. ECM-level preparations mainly provide sustained structural and biochemical support by prolonging local factor retention and optimizing the extracellular matrix microenvironment. By contrast, tissue- and particulate-level preparations generally serve adjunctive roles[77]. Overall, adipose-derived preparations exert their effects mainly by concurrently targeting inflammation, ischemia, oxidative injury, and impaired regenerative capacity[79], although robust comparative clinical evidence remains limited.

Radiation ulcers

Radiation-induced wounds differ from conventional wounds in that their impaired healing is driven not mainly by tissue loss, but by radiation-induced DNA damage, persistent endothelial injury, microvascular occlusion, chronic hypoxia, and progressive fibrosis[84]. Accordingly, therapeutic strategies should focus on restoring perfusion, limiting fibrosis, and reconstructing the local regenerative microenvironment[85]. In this context, adipose-derived preparations demonstrate considerable applicability[64]. Nanofat and SVF facilitate vascular reconstruction[86], whereas ADSC-Exos are particularly effective for delivering antifibrotic signals. When combined with ECM scaffolds, such as DAM, these bioactive components may further provide structural support and sustained regenerative activity[87].

SYNERGISTIC STRATEGIES ENABLED BY ENGINEERING: IMPROVING RETENTION, STABILITY, AND SPATIAL PRECISION

Despite their intrinsic regenerative potential, adipose-derived preparations are limited by poor retention, unstable bioactivity, insufficient spatial control, and weak adaptability to hostile wound microenvironments[57,90]. Engineering strategies address these bottlenecks by stabilizing bioactive components, prolonging local activity, and enabling spatiotemporally controlled delivery[35], thereby transforming adipose-derived preparations into more precise, durable, and clinically translatable regenerative systems[91] [Figure 3].

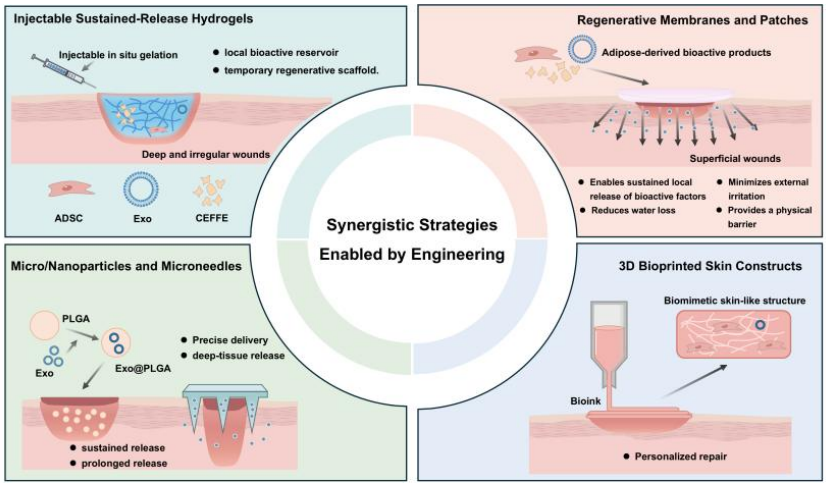

Figure 3. Engineering strategies for adipose-derived preparations. This schematic summarizes representative engineering strategies for improving the retention, stability, and spatial delivery of adipose-derived preparations. ADSC: adipose-derived stem cell; Exo: exosome; CEFFE: cell-free fat extract; PLGA: poly(lactic-co-glycolic acid); PEI: polyethyleneimine; 3D: three-dimensional.

Injectable sustained-release hydrogels

Injectable *in situ*-gelling hydrogels represent one of the most widely used and translationally promising engineering strategies for adipose-derived preparations[57,90]. Zhang *et al.* constructed a GelMA-based three-dimensional network that markedly enhanced the sustained release of ADSC-Exos, thereby producing a synergistic effect on wound healing[92]. Ru *et al.* further used adipose acellular matrix as a carrier for adipose-derived growth factors. This injectable engineered system not only served as a local delivery platform, but also significantly promoted re-epithelialization, angiogenesis, and skin appendage regeneration[91].

Regenerative membranes and patches

Regenerative membrane and patch systems constitute an engineering approach characterized by sheet-like structures that combine wound coverage with localized bioactive delivery[93,94]. Wang *et al.* developed a scaffold composed of collagen and

platelet-rich plasma, incorporating exosomes derived from adipose mesenchymal stem cells. This scaffold provided a supportive matrix for keratinocytes and fibroblasts, facilitating wound repair through anti-inflammatory and pro-angiogenic properties[95]. In a separate study, Jiang *et al.* employed small intestinal submucosa as an extracellular matrix-based membranous scaffold for the delivery of adipose-derived stem cells, highlighting its efficacy as a bioactive dressing for diabetic wounds[93]. These systems function as physical barriers, mitigate water loss and external irritation, and enhance the wound-bed microenvironment before definitive reconstruction[96]. Nonetheless, compared with injectable or cavity-filling platforms, membrane and patch systems are generally more suitable for superficial to mid-depth defects and wound-bed pretreatment. Their capacity to conform to complex three-dimensional wound geometries or to support deep volumetric defects remains relatively constrained.

Micro/nanoparticles and microneedles

Micro/nanoparticles and microneedles represent important engineering strategies for the precise delivery of adipose-derived bioactive components. Peng *et al.* developed adipose-derived stem cell membrane-coated PLGA-PEI nanoparticles, which efficiently promoted epithelialization, dermal reconstruction, and neovascularization, thereby accelerating wound repair[97]. Lv *et al.* further engineered adipose-derived mesenchymal stem cell exosomes for diabetic wound modulation, showing their potential to enhance angiogenesis and collagen remodeling[98]. In parallel, microneedle-assisted delivery can overcome the stratum corneum barrier and improve the dermal delivery efficiency of adipose-derived extracellular vesicles or exosome-based preparations. This strategy is particularly relevant for localized interventions, including small refractory wounds, photoaged skin, and superficial scars, where precise dermal administration is required[99,100]. Nevertheless, clinical translation of these systems still depends on the standardization of extracellular vesicle sources, scalable manufacturing processes, batch-to-batch consistency, long-term preservation of bioactive cargoes, and a clearer regulatory framework for biomaterial-biologic combination preparations.

3D bioprinted skin constructs

Three-dimensional bioprinting further promotes the evolution of adipose-related preparations from active delivery systems into structured regenerative constructs[101,102]. By incorporating adipose-derived stem cells, exosomes, and/or decellularized matrix microparticles into bioinks, biomimetic skin-like constructs with hierarchical epidermal and dermal architecture can be fabricated layer by layer, enabling a single construct to simultaneously provide structural support, cellular delivery, and bioactive signal release[103,104]. Compared with conventional planar dressings or single-carrier systems, 3D bioprinting is more capable of achieving individualized repair tailored to wound geometry and of promoting the transformation of skin substitutes from passive coverage to active regenerative platforms. Nevertheless, substantial challenges remain regarding printing resolution, cell viability maintenance, mechanical stability of the constructs, standardized production, and regulatory compliance, and the field remains largely preclinical[105] [Figure 4].

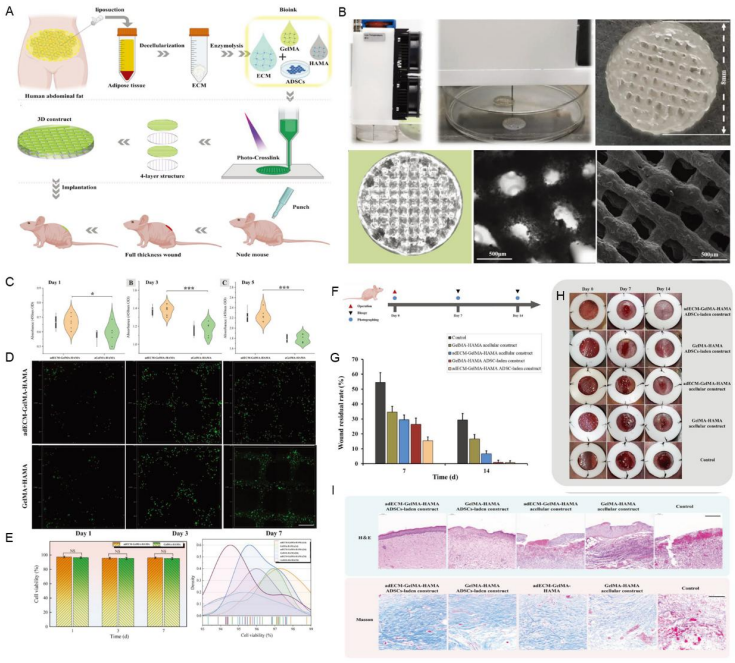

Figure 4. Therapeutic evaluation of ADSC-laden ECM-GelMA-HAMA constructs for

wound repair. A: Schematic illustration of construct fabrication and implantation; B: 3D printing of the constructs; C-E: In vitro biocompatibility evaluation; F: *In vivo* study design; G-H: Wound healing evaluation. I: Histological assessment of wound repair. Reproduced with permission from ACC Science. ADSC: adipose-derived stem cell; ECM: extracellular matrix; GelMA: gelatin methacryloyl; HAMA: hyaluronic acid methacrylate; 3D: three-dimensional.

LIMITATIONS AND OUTLOOK

Adipose-derived preparations exhibit significant promise in the fields of wound repair and regenerative medicine[14]. Nevertheless, their clinical application is hindered by a lack of standardization, ambiguous product definitions, and incomplete quality control frameworks. In contrast to single-molecule pharmaceuticals, these preparations comprise diverse cell populations, bioactive factors, and extracellular matrix components, and their therapeutic efficacy often relies on intricate, multilevel mechanisms[24,106]. Consequently, their potency cannot be adequately evaluated using simple metrics such as cell count, total protein content, or morphological characteristics alone. Currently, donor-related factors, including age, sex, metabolic status, adipose tissue harvest site, and prior treatment history, may affect product composition and biological activity[107]. Moreover, variations in harvesting techniques, processing workflows, storage and transportation conditions, and final dosage forms further exacerbate batch-to-batch variability. Therefore, future research should advance beyond simply demonstrating therapeutic efficacy and instead prioritize the establishment of a quantifiable, controllable, and verifiable product development framework[29]. Within this framework, critical quality attributes and critical process parameters should be defined in alignment with the target product profile[108]. This approach will facilitate the creation of an integrated validation chain encompassing raw material selection, preparation procedures, release criteria, and potency evaluation[30].

Optimization priorities should vary across different product levels. At the tissue level,

improvements in graft survival and long-term stability are essential[16,17]. For particulate-level preparations, it is necessary to clarify the relationship between particle size, processing methods, and clinical indications[18,22]. Cellular-level preparations should focus on addressing cellular heterogeneity and establishing potency-linked quality control measures[14,24]. Secretome-level preparations require further refinement in large-scale production, purification, and delivery strategies[29-31]. Preparations at the extracellular matrix (ECM) level should prioritize decellularization quality, mechanical tunability, and active regulatory functions[6,34,38]. In summary, the advancement of adipose-derived preparations should not depend on a single product type to address all wound scenarios. Instead, stratified and precise application models should be developed according to wound type, predominant pathological barriers, and repair stage. Only by transforming their complex biological advantages into stable, traceable, and regulatory-compliant product forms can adipose-derived preparations transition from empirical exploration to standardized, scalable, and widely applicable clinical therapies.

CONCLUSION

Overall, adipose-derived preparations should be regarded not as a single product, but as a multilevel regenerative platform designed to address the pathological heterogeneity of complex wounds. Their primary value lies in coordinated interventions across structural support, microenvironmental remodeling, and regenerative regulation, tailored to wound stage and dominant pathological barriers. In the future, only with substantial advances in indication stratification, potency quantification, standardized preparation, and clinical translation can adipose-derived preparations progress from empirical use to precise, reproducible, and broadly applicable regenerative therapies.

DECLARATIONS

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Authors' contributions

Conception and design of the study and critical revision of the manuscript: W.S, S.X;

Acquisition of data: JS.Z;

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During the preparation of this manuscript, the artificial intelligence tool ChatGPT (OpenAI) was used solely for language editing. The tool did not participate in the study design, data collection, data analysis, interpretation of results, or the development of the scientific content of the manuscript. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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