Review

Hierarchical approaches and regenerative applications of adipose tissue derivatives

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Received: 27 April 2026 | Approved: 11 May 2026 | Online: 11 May 2026

Abstract

Autologous fat grafting is widely used in reconstructive and aesthetic surgery due to its abundance, biocompatibility, and low immunogenicity. With a history spanning more than a century, it remains a popular option for soft tissue augmentation. Recent advances in understanding the composition and regenerative mechanisms of adipose tissue have led to the development of a range of adipose tissue derivatives with distinct structural and biological functions. Through techniques including physical fragmentation, centrifugation, decellularization, and morphological engineering, a lineage has been established, ranging from cell-composite materials to functional scaffolds. This review systematically examines the preparation principles, structural characteristics, and regenerative applications of diverse adipose tissue derivatives, ranging from cellular and micro-fragmented preparations to matrix-enriched, decellularized scaffolds, and membrane or film-like constructs. It highlights their applications in volume augmentation, wound healing, scar treatment, skin expansion, and tissue engineering, while also discussing challenges related to standardization, mechanistic studies, and regulatory pathways for clinical translation. This review aims to provide a comprehensive reference for the precise application of adipose tissue derivatives and future research directions in this field.

Keywords: Adipose tissue derivatives, decellularized extracellular matrix, adipose matrix complex, membrane, film, tissue engineering, regenerative medicine

INTRODUCTION

Autologous adipose tissue has been widely recognized as a valuable material for soft-tissue augmentation owing to its abundant availability, relatively simple harvesting procedure, and minimal risk of immunologic rejection. Since its first documented use by Neuber in 1893, autologous fat grafting (AFG) has become a cornerstone procedure in aesthetic and reconstructive surgery, with widespread applications in facial rejuvenation, breast augmentation, hemifacial atrophy, and scar revision[1]. However, traditional fat grafting remains constrained by two major clinical bottlenecks: unpredictable retention and complications such as cyst formation, calcification, and unpredictable resorption[2,3]. These limitations largely arise from the view of adipose tissue as merely an inert volumetric filler,

which has overlooked its intrinsic complexity as a dynamic and bioactive material[4].

Over the past two decades, a paradigm shift has emerged alongside a deepening understanding of adipose tissue composition and its inherent regenerative mechanisms. Adipose tissue is now recognized not simply as a reservoir of mature adipocytes, but as a sophisticated regenerative niche enriched with adipose-derived stem cells (ADSCs), the heterogeneous stromal vascular fraction (SVF), and a complex extracellular matrix (ECM) composed of collagen, elastin, and glycosaminoglycans[2,5]. Together, these components create a microenvironment capable of self-renewal, paracrine signaling, and immunomodulation. Building on this knowledge, researchers have developed a spectrum of adipose tissue derivatives through techniques such as physical emulsification, centrifugal purification, decellularization, and morphological engineering, thereby establishing a technological lineage that extends from cell-composite materials to functional scaffolds[6].

This review aims to systematically delineate the evolution of adipose-derived products, focusing on the preparation principles, structural characteristics, and regenerative applications of three major categories: (1) cellular and micro-fragmented derivatives, represented by SVF, ADSCs, nanofat, stromal vascular fraction gel (SVF-gel) and cell-free fat extract (CEFFE); (2) matrix-enriched and decellularized derivatives, represented by adipose matrix complex (AMC), adipose collagen fragment (ACF), and decellularized adipose extracellular matrix (adECM); and (3) membrane and film-like constructs, represented by adipose-derived matrix film (ADF) and acellular adipose matrix-derived film (AAF)[7,8]. Furthermore, this review summarizes their emerging applications in regenerative medicine, including volume augmentation, wound healing, scar treatment, skin expansion, and tissue engineering[8,9]. It also discusses future directions, aiming to provide a reference for precise clinical application and to guide further research in this field[10].

CONCEPTUAL FRAMEWORK AND DEVELPOMENT OF ADIPOSE TISSUE DERIVATIES

AFG has undergone substantial evolution since its initial application as a simple volumizing material. Although it offers advantages such as biocompatibility and availability,

traditional approaches continue to face significant limitations, including unpredictable graft survival, resorption, and inconsistent clinical outcomes[11,12]. These challenges largely stem from the historical perception of adipose tissue as merely a passive filler, which overlooked its inherent biological complexity as a dynamic regenerative microenvironment.

With advances in regenerative medicine, adipose tissue is now recognized as a rich reservoir of ADSCs, a heterogeneous SVF, and a complex ECM network[13]. This deeper understanding has fundamentally transformed the conceptual framework of fat grafting, shifting it from a purely structural intervention to a biologically active regenerative strategy. Adipose tissue is no longer viewed as an inert filler but rather as a multifunctional biomaterial capable of self-renewal, paracrine signaling, angiogenesis, and immunomodulation[14,15].

Driven by this paradigm shift, research has increasingly focused on isolating, enhancing, and engineering the functional components of adipose tissue. Through physical processing, enzymatic digestion, and decellularization techniques, a broad spectrum of adipose-derived products has been developed[16]. These derivatives extend beyond traditional fat grafts to include more sophisticated and functionally tailored biomaterials designed to maximize regenerative potential[17]. Based on their cellular content, matrix preservation, and morphological characteristics, adipose tissue derivatives can be broadly categorized into several interconnected classes [Figure 1,Table 1][18].

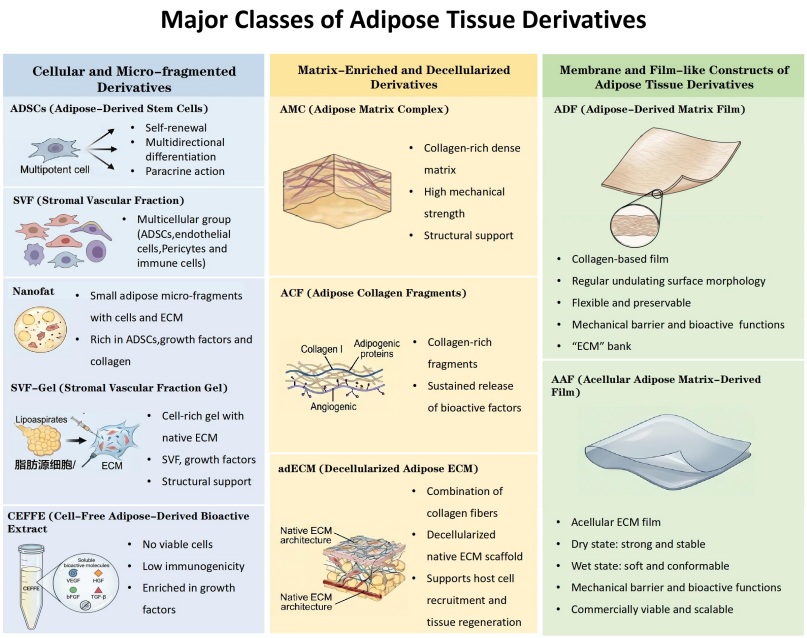

Figure 1. Overview of the major classes of adipose tissue derivatives.

Cellular and micro-fragmented derivatives

Adipose-derived stem cells (ADSCs) and stromal vascular fraction (SVF)

ADSCs are a multipotent cell population residing within the SVF of adipose tissue. They possess the capacity for self-renewal and multilineage differentiation, including adipogenic, osteogenic, chondrogenic, and myogenic lineages[19]. ADSCs also exert potent paracrine effects by secreting a wide array of growth factors, cytokines, and extracellular vesicles, which collectively promote angiogenesis, modulate immune responses, and support tissue repair[20,21]. These properties have positioned ADSCs as a key cellular component in regenerative medicine[22]. SVF is a foundational cellular derivative that is typically isolated from adipose tissue by enzymatic digestion. It comprises a heterogeneous cell population that includes ADSCs, endothelial cells, pericytes, and immune cells. However, the composition and therapeutic potential of SVF are highly sensitive to processing methods. Procedures such as tissue washing can markedly alter the proportion of blood-derived cells, thereby affecting subsequent cellular activity and culture outcomes[23,24]. In addition to enzymatically isolated SVF, mechanical processing techniques have gained increasing attention for the isolation of tissue stromal vascular fraction (tSVF), which preserves the native ECM together with cellular components. Mechanical approaches, including filtration

and centrifugation, can effectively disrupt adipocytes and enrich regenerative tSVF, which has shown particular promise in pro-inflammatory conditions such as osteoarthritis[25,26].

Nanofat: Emulsified cell suspension

Nanofat is a mechanically processed adipose tissue derivative generated through purely physical emulsification and filtration, resulting in a liquid suspension containing extremely small tissue fragments devoid of intact adipocytes. The typical preparation protocol involves harvesting fat via standard liposuction, followed by mechanical emulsification through repeated passage between two syringes connected by a small-bore connector, and finally filtration to remove coarse fibrous components[27,28]. This process selectively disrupts mature adipocytes while theoretically preserving the SVF, including ADSCs, endothelial cells, and pericytes, along with some ECM components[29].

Unlike conventional fat, nanofat is too liquid to serve as a volumetric filler. Instead, its therapeutic value lies in its paracrine activity and cellular components. Studies have demonstrated that nanofat retains viable ADSCs and other progenitor cells capable of proliferation and differentiation[30]. Moreover, nanofat secretes a rich cocktail of growth factors, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and basic fibroblast growth factor (bFGF), which collectively promote angiogenesis, modulate inflammation, and stimulate dermal remodeling[31]. These properties make nanofat particularly suitable for indications requiring biological regeneration rather than volume augmentation, such as skin rejuvenation, scar treatment, and periorbital hyperpigmentation[32].

SVF-gel: Concentrated cell-matrix gel

SVF-gel, also known as stromal vascular fraction gel, is an advanced adipose tissue derivative that combines the cellular components of the stromal vascular fraction with the native extracellular matrix[21]. Its injectable, gel-like consistency, represents a transitional product between cell-rich suspensions (such as SVF and nanofat) and matrix scaffolds, offering both biological activity and minimal structural support for soft tissue regeneration[33]. SVF-gel is typically prepared through mechanical processing of

lipoaspirates without the addition of exogenous enzymes[34]. The most established protocol involves emulsification of harvested adipose tissue by repeated passage between two syringes, followed by centrifugation at a specific speed. This process disrupts mature adipocytes, releases their lipid content, and concurrently concentrates the cellular and ECM components into a viscous gel phase[35]. The injectable gel is enriched with ADSCs, endothelial cells, pericytes, and a preserved ECM framework, while largely devoid of the lipid content[36]. SVF-gel possesses several distinctive structural and biological properties: its gel-like consistency allows for injection through fine needles (as small as 25-27 gauge), enabling precise delivery and minimally invasive application; the preservation of native ECM provides a supportive microenvironment for the embedded cells, enhancing their survival, retention, and paracrine function following transplantation; and the removal of most lipid components reduces the inflammatory burden associated with necrotic adipocytes, thereby minimizing complications such as cyst formation and calcification[37, 38]. Studies have shown that SVF-gel retains viable ADSCs that maintain their differentiation capacity and secrete a range of pro-angiogenic and immunomodulatory factors, including VEGF, HGF, and transforming growth factor-beta (TGF-β)[39].

CEFFE(cell-free fat extract): Cell-free adipose-derived bioactive extract

CEFFE is an acellular, bioactive extract obtained from adipose tissue through a process that removes adipocytes, stromal cells, and large structural components while preserving soluble growth factors and cytokines[40,41]. The preparation typically involves harvesting lipoaspirates, followed by sequential centrifugation to eliminate lipids and cellular debris and concentration using ultrafiltration to yield a liquid extract enriched in bioactive factors[42,43]. CEFFE contains no viable cells, a feature that minimizes immunogenicity and lowers the risks associated with transplantation, while also allowing for potential allogeneic application and off-the-shelf storage[44]. The extract retains a complex mixture of growth factors, including VEGF, HGF, bFGF and TGF-β, which collectively promote angiogenesis, immunomodulation, and tissue repair[45]. As a liquid product, CEFFE can be administered via injection or topical application, making it particularly suitable for regenerative interventions such as skin rejuvenation, wound healing, and anti-inflammatory therapy[46]. Its regenerative potential is mediated primarily through paracrine mechanisms, enhancing

collagen synthesis, cell migration, and tissue remodeling without relying on the proliferation or differentiation of viable cells[40]. CEFFE thus represents a cell-free adipose tissue derivative that emphasizes the role of soluble bioactive factors in tissue regeneration, complementing other adipose-derived products such as SVF, Nanofat, and SVF-gel in the context of regenerative medicine[47,48].

Matrix-enriched and decellularized adipose derivatives

Adipose matrix complex (AMC): High-rigidity, collagen-enriched matrix for structural support

AMC is a high-rigidity, collagen-rich adipose-derived material prepared through a purely mechanical filtration and dehydration process, representing a specialized derivative designed for structural support and volume augmentation in soft tissue reconstruction[49]. The preparation protocol begins with harvesting lipoaspirates, followed by centrifugation to obtain Coleman fat or high-density fat (HDF), which is then passed through a filtering device consisting of a sleeve and three internal sieves with 1.5 mm filter screen spacing[50]. The tissue retained on the sieves is collected and subsequently dehydrated in a 100-mesh filter bag surrounded by gauze until no obvious liquid droplets fall upon forceps pickup, yielding the final AMC product[51].

AMC possesses several distinctive structural and mechanical properties that differentiate it from conventional fat grafts. Histological analysis (hematoxylin/eosin and Masson's trichrome staining) has demonstrated that AMC contains significantly higher levels of ECM and collagen fibers compared to Coleman fat, with electron microscopy confirming the presence of dense fibrous connective tissue[17]. Quantitatively, the collagen content of AMC is 45% ± 3.2%, which is markedly higher than the 15% ± 3.5% found in Coleman fat ($P < 0.01$). Correspondingly, the stiffness of AMC, measured at 6.1 ± 0.83 kPa, is substantially greater than that of Coleman fat at 1.9 ± 0.22 kPa ($P < 0.01$). Notably, AMC contains fewer viable cells than Coleman fat, indicating that its regenerative and volume-retention effects are mediated primarily through matrix-dependent mechanisms rather than cellular activity[17,51].

The regenerative efficacy of AMC has been evaluated in preclinical models. In nude mouse transplantation studies, AMC demonstrated a volume retention rate of 75% ± 7.5% at 90 days post-grafting, which was significantly higher than the 42% ± 13.5% retention rate observed for Coleman fat ($P < 0.05$)[9]. Moreover, AMC maintained a stable higher stiffness throughout the observation period, whereas Coleman fat exhibited progressive loss of mechanical integrity [52]. These findings suggest that AMC is particularly suitable for clinical applications requiring rigid structural support, such as facial contouring, nasal augmentation, chin enhancement, and deep soft tissue filling, where traditional fat grafts often fail to provide adequate projection and long-term volume stability. As a mechanically processed derivative without enzymatic treatment, AMC offers the advantages of simplified regulatory pathways and point-of-care availability, positioning it as a promising biomaterial for precision fat grafting in structural reconstruction[53].

Adipose collagen fragment (ACF): Acellular collagen scaffold for sustained-release bioactive delivery

ACF is a novel adipose-derived ECM concentrate prepared through a purely mechanical processing technique involving pulverization, filtration, and centrifugation[54]. It represents a collagen-based scaffold that retains native matrix components while eliminating viable cells[55]. The typical preparation protocol begins with harvesting lipoaspirates, followed by centrifugation to generate Coleman fat, which is then washed, homogenized, sequentially filtered through mesh screens of decreasing pore sizes (e.g., 0.25 mm or 0.15 mm), and finally centrifuged at higher speed to collect the solid portion as ACF[55]. ACF is characterized as an adipokine-enriched, sustained-release collagen scaffold that retains high levels of collagen I, collagen IV, and laminin, while containing nonviable cells[55]. Proteomic analysis has revealed that ACF contains diverse adipogenic and angiogenic proteins, including components involved in lipid metabolism, angiogenesis, antioxidant defense, and cell proliferation[56]. Unlike viable cell-containing derivatives such as SVF or nanofat, ACF exerts its regenerative effects primarily through matrix-mediated mechanisms, providing structural support and sustained release of bioactive factors that promote host cell recruitment, adipogenesis, and neovascularization. Preclinical studies have demonstrated that ACF promotes soft tissue regeneration, wound healing, and volume retention. It offers

advantages for off-the-shelf availability, reduced regulatory complexity, and improved storage stability, making it a promising platform for translational applications in regenerative medicine.

Decellularized adipose extracellular matrix (adECM): Native three-dimensional scaffold for host-guided regeneration

adECM, also known as decellularized adipose tissue (DAT) , decellularized adipose matrix (DAM) and acellular adipose matrix (AAM), is an acellular scaffold produced by removing cellular and lipid components from adipose tissue while preserving the native extracellular matrix architecture and bioactive cues[57]. The decellularization process typically involves a combination of physical, chemical, and enzymatic treatments, including repeated freeze-thaw cycles, mechanical agitation, treatment with detergents, and nuclease digestion to remove cellular debris and nuclear material[58]. The resulting product is a three-dimensional, porous scaffold composed primarily of collagen, elastin, glycosaminoglycans, and various growth factors bound to the matrix, such as VEGF, basic fibroblast growth factor (bFGF), and TGF-β[59,60].

adECM possesses several critical properties that make it an ideal scaffold for tissue engineering. First, it retains the native three-dimensional biomechanical characteristics of adipose tissue, providing a physiologically relevant microenvironment for cell attachment, migration, and differentiation[61]. Second, the preserved bioactive components, including matricellular proteins and growth factors, actively direct host cell behavior by promoting adipogenesis, angiogenesis, and immunomodulation[62]. Third, as an acellular product, adECM eliminates concerns related to immunogenicity and disease transmission associated with allogeneic or xenogeneic cellular components, while also offering the advantages of off-the-shelf availability and prolonged storage stability[63].

The regenerative potential of adECM is attributed to its retained proteomic profile, which includes proteins involved in lipid metabolism, extracellular matrix organization, and tissue remodeling. Studies have demonstrated that adECM can recruit host ADSCs and direct their differentiation toward the adipogenic lineage, as indicated by the upregulation of key

regulators such as peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα)[64]. *In vivo* implantation studies have shown that adECM promotes vascularized adipose tissue regeneration, with newly formed adipocytes appearing within the scaffold as early as two weeks post-implantation. The scaffold gradually degrades over time, being replaced by host-derived, functional adipose tissue that integrates with the surrounding native tissue.

Membrane and film-like constructs of adipose tissue derivatives

Adipose-derived matrix film (ADF)

ADF is an innovative autologous ECM-based bio-membrane fabricated through a simple physical compression process inspired by traditional papermaking technology[65]. It transforms clinically discarded adipose tissue into a ready-to-use, cell-free membrane that preserves native ECM bioactivity while providing favorable mechanical properties and storage stability[66]. The preparation protocol involves harvesting autologous adipose tissue via liposuction or abdominal surgery, followed by sequential crushing and washing to remove lipids, blood components, and cellular debris while preserving native ECM architecture. Finally, mechanical pressing forms a cohesive, thin, pliable film. Histological analysis confirmed effective removal of nuclei and lipids, while ADF retains key ECM components including collagen (types I, III, and IV), elastin, and glycosaminoglycans, as well as bound growth factors[67].

ADF exhibits several advantageous properties for tissue regeneration. Its flexibility allows for easy handling, cutting, and application to wound beds or defect sites. Mechanical testing demonstrates that ADF exhibits a typical J-shaped stress-strain curve and maintains structural integrity during handling[68]. Its dense collagenous structure provides a physical barrier against bacterial invasion and fluid loss while permitting gas exchange[69]. Importantly, ADF can be cryopreserved at -80 °C without functional compromise (frozen ADF, F-ADF), with proteomic analysis confirming remarkable stability of proteins after 12 months of storage[70]. Moreover, ADF acts as a bioactive substrate that supports the adhesion, proliferation, and migration of various cell types and promotes adipogenic differentiation[71]. *In vivo* studies have demonstrated that ADF promotes wound healing and

soft tissue regeneration, partly through angiogenesis-related mechanisms involving the recruitment of monocytes that differentiate into macrophages, which serve as central regulators of angiogenesis[72]. As an autologous, cell-free product, ADF offers the advantages of low immunogenicity, reduced regulatory burden, and off-the-shelf potential for manufacturing, while its capacity for long-term cryopreservation enables the establishment of personalized "ECM banks" for future regenerative applications[73].

Acellular adipose matrix-derived film (AAF)

AAF is an adECM-based bio-membrane, which transforms human adipose tissue into a ready-to-use, cell-free film. It exhibits dry-state toughness and wet-state plasticity, allowing close adaptation to tissue expanders and irregular wound surfaces[74]. The preparation protocol involves decellularization of human adipose tissue aspirates to remove cellular components, followed by freeze-drying and mechanical grinding to convert the material into powder form. The powder is digested in hydrochloric acid and pepsin solution to form a pre-gel solution, which then transform into a hydrogel state[75,76]. Finally, the hydrogel is cast into a mold and dried at low temperature to form the AAF membrane. Mechanical property tests demonstrate that AAF does not fracture when repeatedly folded and curled in the dry state, indicating high strength and toughness under moisture-free conditions[77]. However, upon contact with tissue fluid, the material rapidly absorbs fluid and becomes soft enough to tightly fit and adhere to the dilation capsule, exhibiting excellent swelling capacity and deformation adaptability in wet environments[78].

AAF exhibits several advantageous properties for tissue regeneration. Its dry-state toughness enables easy handling, sterilization, and storage, while its wet-state plasticity allows conformable adaptation to underlying structures[79]. In vitro studies have demonstrated that AAF significantly promotes the proliferation and migration of skin cells, vascular endothelial cells, and ADSCs. Moreover, AAF enhances the adipogenic differentiation of ADSCs[77]. In a rat skin expansion model, AAF significantly improved skin expansion efficiency while reducing skin retraction. Histological analysis revealed that AAF increased skin thickness and dermal collagen content, facilitating skin renewal and enhancing expansion efficiency. Furthermore, AAF significantly enhanced local blood flow

and promoted neovascularization. Notably, AAF was also found to promote subcutaneous adipose tissue regeneration[80]. As a decellularized, cell-free product, AAF offers the advantages of reduced immunogenicity, sustained release of ECM-derived bioactive factors, and the ability to provide both mechanical support and biological stimulation for skin and soft tissue regeneration, making it a promising biomaterial for tissue expansion and reconstructive surgery.

Table 1. Classification and Characteristics of Adipose Tissue Derivatives

Category	Product	Main Composition	Preparation Method
Cellular and Micro-fragmented	SVF	ADSCs, endothelial cells, pericytes, immune cells, ECM fragments	Enzymatic digestion and/or mechanical isolation
	ADSCs	Multipotent stem cells	Isolation from SVF, culture expansion
	Nanofat	Mechanically emulsified adipose tissue fragments, SVF, partial ECM	Mechanical emulsification, filtration
	SVF-gel	SVF and preserved ECM	Mechanical processing of lipoaspirate
	CEFFE	Soluble bioactive factors	Centrifugation, ultrafiltration
Matrix-enriched and Decellularized	AMC	ECM, collagen, SVF	Mechanical filtration, dehydration
	ACF	ECM, collagen, adipokines	Mechanical pulverization, filtration, centrifugation

	adECM	ECM, collagen, elastin, glycosaminoglycans, bound growth factors	Decellularization (physical, chemical, enzymatic)
Membrane and Film-like	ADF	ECM,collagen, elastin, bound growth factors	Mechanical compression
	AAF	ECM,collagen, elastin, bound growth factors	Decellularization, freeze-drying, pepsin digestion, casting

RESEARCH ADVANCES IN THE APPLICATIONS OF KEY DERIVATIVES

Adipose tissue has evolved from a conventional volumetric filler into a versatile source of cellular, matrix-based, and cell-free regenerative products. These products can be broadly divided into: cellular and micro-fragmented derivatives, including SVF, ADSCs, nanofat, SVF-gel and CEFFE; matrix-enriched and decellularized derivatives, including AMC, ACF and adECM; and membrane and film-like constructs, including ADF and AAF. Although these products share overlapping regenerative properties, their functional emphasis differs according to their cellular content, extracellular matrix architecture, mechanical stiffness, soluble factor profile, and mode of delivery [Table 2].

Cutaneous wound repair and chronic wound healing

In wound healing, adipose-derived products mainly function through angiogenesis, inflammation regulation, fibroblast activation, epithelialization, extracellular matrix remodeling, and restoration of tissue perfusion[81].

SVF is one of the most frequently studied adipose-derived products for wound repair. It is a heterogeneous cell population derived from adipose tissue and the cellular heterogeneity allows SVF to participate in wound repair through several coordinated mechanisms: secretion of proangiogenic factors, modulation of inflammatory cells, support of endothelial network formation, recruitment of host repair cells, and enhancement of granulation tissue formation[82]. SVF is an autologous, multifunctional strategy for wound healing, especially because it combines cellular trophic activity with vascular and immunomodulatory

functions. ADSCs contribute to wound repair mainly through paracrine effects rather than direct tissue replacement. They secrete growth factors, cytokines, extracellular vesicles, and matrix-remodeling mediators. These signals can promote endothelial cell migration, keratinocyte proliferation, fibroblast activity, collagen deposition, and macrophage polarization toward a pro-repair phenotype. ADSCs are therefore often regarded as a central biological component underlying the regenerative effects of SVF, nanofat, and other adipose-derived products[83].

Nanofat is suitable for cutaneous repair because it is mechanically emulsified into adipose fragments that can be injected into superficial dermal or subdermal planes. It has limited volumizing capacity but retains stromal cells, vascular-associated cells, and extracellular matrix microfragments[84]. Nanofat has been investigated for wound healing and skin rejuvenation. Its main functions in wound repair are to enhance angiogenesis, improve dermal matrix remodeling[85].

SVF-gel is particularly relevant to chronic wounds because it combines stromal vascular components with concentrated adipose extracellular matrix[86]. Compared with isolated SVF cell suspension, SVF-gel may provide better local retention, a more favorable microenvironment for stromal cells, and longer-lasting paracrine activity. Clinical and mechanistic studies have reported that SVF-gel can promote chronic wound healing[87], restore more normal cutaneous structures, enhance collagen deposition, reduce inflammation and fibrosis, promote angiogenesis, and support peripheral nerve recovery[88]. CEFFE represents a different wound-healing strategy. Unlike SVF and ADSCs, CEFFE is cell-free; unlike adECM or ADF, it is not primarily a structural scaffold. Instead, it is a soluble adipose-derived extract enriched in bioactive factors. In wound repair, CEFFE acts as a paracrine mimetic product that promotes cell proliferation, endothelial activity, angiogenesis, and matrix remodeling. As an adipose-derived cell-free therapy, CEFFE can accelerate angiogenesis, epithelial ingrowth, and wound closure in experimental models[89]. adECM, ADF, and AAF are more scaffold-oriented wound-healing products. adECM retains adipose-tissue specific extracellular matrix cues after decellularization and can support host-cell infiltration, angiogenesis, and soft-tissue remodeling. ADF and AAF

extend this concept into film-like materials that can be applied as wound covering membranes or regenerative interfaces. ADF has been described as an adipose-derived matrix membrane with mechanical strength and biological activity, while AAF has been developed as a flexible acellular adipose-derived film for skin soft-tissue regeneration[90].

Skin rejuvenation, photoaging, fine wrinkles, and dermal regeneration

In aesthetic dermatology, adipose-derived products are used for dermal thickening, collagen remodeling, vascular regeneration, improvement of skin texture, correction of fine wrinkles, and reversal of photoaging associated matrix degeneration.

Nanofat is one of the most representative adipose-derived products for skin rejuvenation. Because it is injectable through small gauge needles and contains stromal cells and matrix microfragments, nanofat is often used for fine wrinkles, acne scars, periorbital skin thinning, and general skin-quality improvement. Its effect is not primarily based on long term fat survival, but rather on regenerative signaling, dermal remodeling, neovascularization, and stimulation of local repair pathways. Nanofat is a minimally invasive regenerative tool in aesthetic and reconstructive surgery, although the need for standardized preparation protocols and stronger long term clinical evidence[91].

ACF is especially relevant to dermal filling and rejuvenation. It is prepared from adipose tissue by mechanical processing and is enriched in collagen extracellular matrix components. ACF contains high levels of collagen I, collagen IV, and laminin, with low or absent viable cellular content. Functionally, ACF acts as a collagen rich, adipose-derived matrix scaffold that can improve dermal thickness, stimulate collagen synthesis, and serve as an autologous filler for fine wrinkles, particularly in superficial areas such as infraorbital rhytides[92].

CEFFE can also be classified under skin rejuvenation because it provides soluble regenerative signals without live cells or structural matrix. In experimental models, CEFFE increased dermal thickness, capillary density, proliferating cells, and collagen I/III expression[46]. This suggests that CEFFE may improve aging skin by promoting

angiogenesis, keratinocyte or fibroblast proliferation, and dermal extracellular matrix production[93].

SVF-gel occupies an intermediate position between regenerative skin therapy and soft-tissue filling. It contains concentrated stromal vascular components and adipose extracellular matrix, so it can provide mild volumetric correction while also improving dermal trophic support[86]. It is therefore suitable for facial soft tissue atrophy, periorbital hollowing, nasolabial folds, post traumatic contour defects, and areas where both regeneration and limited filling are desired[36].

Scar remodeling, fibrosis reduction, and radiation-damaged tissue repair

Scarred and fibrotic tissues are characterized by abnormal collagen deposition, reduced vascularity, chronic inflammation, stiffness, and impaired extracellular matrix organization. In this field, adipose-derived products function mainly through anti-inflammatory, proangiogenic, antifibrotic, and matrix-remodeling mechanisms[91].

Nanofat is widely used for scar remodeling because it can be injected into superficial fibrotic tissue and contains stromal cells and extracellular matrix fragments. Systematic reviews indicate that nanofat has been primarily investigated in the context of skin scar repair, including improvement of scar quality, texture, pliability, and dermal structure[95]. Experiment also supports the concept that nanofat can enhance tissue vascularization and improve healing in radiation-injured skin[95,96].

SVF and ADSCs contribute to scar remodeling by regulating inflammation, suppressing excessive fibroblast activation, and altering collagen remodeling. ADSC-derived paracrine factors may reduce profibrotic signaling, enhance local vascularity, and promote a more regenerative immune microenvironment[39]. SVF may provide a broader stromal and vascular cell mixture than isolated ADSCs, which may be advantageous in scarred tissue where vascular deficiency and chronic inflammation coexist[91].

SVF-gel is useful for scars that combine tissue depression, fibrosis, and poor vascularity. It can provide both a regenerative extracellular matrix niche and stromal vascular components[97]. Studies of SVF-gel in chronic wounds reported reduced fibrosis and inflammation, improved collagen deposition, angiogenesis, and peripheral nerve recovery, suggesting that its functions extend beyond volume correction to active scar remodeling[98]. ACF can be used for superficial scars and fine scar-like wrinkles because it provides a collagen-rich autologous matrix. Its main contribution is dermal extracellular matrix support and collagen remodeling rather than cellular immunomodulation. This makes ACF conceptually useful for atrophic scars, fine rhytides, and dermal thinning, especially when a more matrix dominant product is preferred[99].

Soft-tissue reconstruction, facial contouring, and fat graft survival

In soft tissue reconstruction, adipose-derived products are used to restore volume, improve graft survival, enhance vascular ingrowth, reduce resorption, and reconstruct adipose-like tissue. The most relevant products are SVF, ADSCs, SVF-gel, AMC, ACF, adECM, ADF, and AAF, but their roles differ substantially[100].

SVF- and ADSC-assisted fat grafting aim to improve fat graft survival by accelerating early revascularization and reducing ischemic injury after transplantation. SVF and ADSCs provide endothelial support, perivascular cells, trophic factors, and immunomodulatory signals. SVF- and ADSC-enriched fat grafting is a good strategy used in reconstructive and aesthetic plastic surgery to improve graft retention and regenerative outcomes, although long-term efficacy, mechanistic clarity, and standardization remain variable[2,101].

SVF-gel is useful when conventional fat grafting is limited by oil cyst formation, unpredictable retention, or poor contour control. Because it contains concentrated extracellular matrix and stromal vascular components with less free lipid, SVF-gel can act as a regenerative filler for facial atrophy, contour depression, scar-related soft-tissue defects, and potentially breast or reconstructive applications[53].

AMC is better suited to structurally demanding regions. Because AMC contains a higher proportion of type I collagen and has greater stiffness than Coleman fat, it can be used for clinical filling of areas requiring rigid support, such as the nasal base and chin. In functional terms, AMC should be classified as a high-rigidity, collagen-rich adipose matrix filler rather than primarily as a cellular regenerative product[17].

adECM are important for scaffold-based soft tissue reconstruction. These materials remove immunogenic cellular components while preserving adipose-specific extracellular matrix cues. They can support host-cell infiltration, vascularization, adipogenesis, and long-term tissue remodeling. adECM have undergone preclinical characterization and pilot clinical testing, and human decellularized adipose matrix is a promising off-the-shelf scaffold for soft-tissue regeneration[11].

ADF may expand soft-tissue reconstruction from injectable grafting toward sheet-like regenerative interfaces. ADF has been proposed as an adipose-derived extracellular matrix film with mechanical strength, biological activity, and potential for personalized matrix storage ("ECM" bank)[11].

Tissue expansion, flap ischemia, and expanded-skin regeneration

Tissue expansion requires adequate vascularity, dermal thickness, epidermal proliferation, extracellular matrix remodeling, and resistance to ischemia. Similarly, flap survival and ischemic tissue repair depend on effective neovascularization and tissue remodeling. Adipose-derived products such as CEFFE, SVF, ADSCs, and AAF play key regenerative roles.

CEFFE is a cell-free, soluble adipose-derived product that improves expanded skin quality by promoting angiogenesis and keratinocyte proliferation. In rat tissue expansion models, CEFFE increased the expression of VEGFR, EGFR, collagen type I and III, and enhanced keratinocyte proliferation in vitro. Its proangiogenic and proliferative activity also makes it suitable for ischemic soft tissue, chronic wounds, and biomaterial-assisted vascularization, providing regenerative support without cell transplantation[102].

AAF is a film-like acellular adipose matrix designed as a flexible bioactive interface for skin soft tissue expansion. It can enhance keratinocyte, fibroblast, and endothelial cell activity, promote angiogenesis, increase expanded skin thickness, and induce subcutaneous adipose regeneration. AAF may also provides a structural template that supports vascular ingrowth in ischemic tissues[14].

SVF contains endothelial progenitor-like cells, pericytes, ADSCs, and vascular-supporting stromal cells, contributing directly to vascular regeneration. Transplanted SVF can form mature vascular networks, including arteries, capillaries, veins, and lymphatics. In human-in-mouse models, SVF-derived endothelial cells form hybrid vessels stabilized by perivascular cells, supporting both tissue expansion and flap perfusion[103]. ADSCs promote vascular regeneration primarily through paracrine signaling. They secrete VEGF, HGF, angiopoietin-related signals, extracellular vesicles, and anti-apoptotic factors, which enhance endothelial survival, capillary sprouting, and tissue perfusion. ADSCs are a major source of trophic and proangiogenic factors, addressing vascular insufficiency and impaired tissue remodeling in expanded or ischemic skin[104].

Orthopedics, osteoarthritis, cartilage repair, and tendon regeneration

In musculoskeletal applications, adipose-derived products are used mainly for anti-inflammatory regulation, pain reduction, joint microenvironment modulation, chondroprotection, matrix protection, and tendon repair[105].

SVF and ADSCs are widely studied for knee osteoarthritis. Their expected benefit is not simply direct cartilage replacement, but modulation of synovial inflammation, suppression of catabolic mediators, secretion of trophic factors, and improvement of joint homeostasis. Clinical studies with more than two years of follow-up reported that most studies found pain relief and joint function improvement after SVF treatment, with minimal adverse reactions, although protocols and outcome measures remain heterogeneous. However, the clinical evidence remains mixed and that robust standardization is still lacking. SVF preparations differ according to enzymatic or mechanical processing, cell composition,

dose, donor variability, and injection protocols. Therefore, SVF and ADSCs should be described as promising but not yet fully standardized therapies for osteoarthritis[106].

CEFFE has emerging relevance in musculoskeletal regeneration as a cell-free alternative to adipose-derived cell therapy. CEFFE is a non-cellular adipose-derived therapies alongside extracellular vesicles. Because CEFFE contains soluble trophic factors, it may theoretically regulate inflammation, oxidative stress, and matrix metabolism, but its orthopedic evidence base is still less mature than that of SVF or ADSCs. CEFFE loaded biomaterials may be especially useful in tendon repair. A long-acting microneedle patch loaded with adipose-derived bioactive components has been developed for tendinopathy, suggesting that cell-free adipose extracts may be delivered through sustained release platforms to reduce inflammation, protect matrix integrity, and support tissue recovery[107].

adECM functions as a versatile and bioactive scaffold, preserving native matrix components and three-dimensional architecture that support cell adhesion, migration, and differentiation. In volumetric muscle loss (VML) models, perfusable adECM scaffolds co-recellularized with ADSCs and L6 myoblasts enable uniform cell distribution, enhance myogenesis and angiogenesis, and improve functional muscle recovery, while revealing ADSCs subpopulations with enhanced regenerative potential. Complementarily, adECM combined with STIM1-overexpressing ADSCs and sustained IGF-2 delivery directs myogenic differentiation, suppresses fibrosis, and promotes M2 macrophage polarization, optimizing the immune microenvironment for muscle repair. Together, these studies demonstrate that adECM serves as a multifunctional platform that synergizes with therapeutic cells and growth factors to promote oriented muscle fiber formation, vascularization, immune modulation, and functional restoration after severe muscle injury, highlighting its translational potential in regenerative medicine[10,63].

Table 2. Indication-specific and Modular Strategy of Adipose Tissue Derivatives.

Product	Dominant Function	Recommended Applications	Notes

Product	Dominant Function	Recommended Applications	Notes
SVF	Angiogenesis, immune modulation	Chronic wounds, osteoarthritis, soft tissue reconstruction	High cellular activity; requires optimized dosing and delivery
ADSCs	Paracrine signaling, multilineage differentiation	Wound healing, soft tissue repair, skin rejuvenation	Supports angiogenesis and ECM remodeling
Nanofat	Regenerative filling, scar remodeling	Skin rejuvenation, superficial soft tissue	Emphasizes regenerative repair rather than volume filling
SVF-gel	Combined cellular + ECM support	Chronic wounds, soft tissue filling	Prolonged retention, favorable stromal microenvironment
CEFFE	Soluble factor delivery, paracrine signaling	Wound healing, tissue expansion	Requires engineered carrier for sustained local activity
AMC	Structural support, high rigidity	Facial contouring, deep tissue filling	Collagen-rich, matrix-dominant; mechanical support
ACF	Collagen-rich, sustained release	Superficial scars, fine wrinkles	Matrix-dominant; low cellular content
adECM	ECM scaffold, host-cell guidance	Soft tissue reconstruction, tissue engineering, volumetric muscle repair	Supports angiogenesis and tissue remodeling
ADF	ECM film	Wound healing,soft tissue reconstruction	Provides mechanical strength and regenerative interface

Product	Dominant Function	Recommended Applications	Notes
AAF	ECM film	Skin expansion	Conforms to tissue surfaces; promotes angiogenesis and tissue regeneration

CHALLENGES AND BOTTLENECKS IN CLINICAL TRANSLATION

Adipose-derived regenerative products have progressed from simple fat grafts to a diverse platform with varying cell content, matrix composition, mechanical properties, and bioactive factors[108]. They should be selected based on function: SVF and ADSCs for angiogenesis and immunomodulation; nanofat and SVF-gel for regenerative filling and tissue remodeling[41]; CEFFE for trophic-factor delivery[43]; AMC for structural support[109]; ACF for collagen remodeling[110]; and adECM, ADF, and AAF as scaffolds or bioactive films. Despite strong preclinical evidence, clinical translation is limited by heterogeneity, unclear mechanisms, lack of standardization, regulatory challenges, safety concerns, and scalability[114]. Future progress depends on standardized production, potency assays, mechanistic studies, engineered delivery, clinical validation, and modular, indication-specific strategies[111,112][Table 3].

Product heterogeneity and standardized characterization

A major translational challenge of adipose-derived products is their intrinsic heterogeneity, influenced by donor characteristics, tissue harvest site, mechanical processing, and operator variability[108]. This affects cellular composition, extracellular matrix integrity, cytokine profiles, and mechanical properties. SVF is particularly variable due to its mixture of ADSCs, endothelial cells, pericytes, immune cells, fibroblasts, and stromal components[113]. Nanofat, SVF-gel, AMC, and ACF are subject to processing-dependent variability, such as differences in shearing, emulsification, centrifugation, and filtration, which can alter cell retention, ECM content, viscosity, injectability, and regenerative potency[112]. CEFFE requires standardized evaluation of proteomic, cytokine, growth-factor, and extracellular

vesicle composition[41]. adECM, ADF, and AAF must be characterized for residual DNA, lipid removal, protein preservation, ultrastructure, stiffness, porosity, degradation rate, sterility, and batch-to-batch consistency. Establishing quantitative potency assays, such as angiogenic activity for SVF/CEFFE, immunomodulatory capacity for ADSCs, collagen remodeling for ACF, mechanical stiffness and retention for AMC, and host-cell infiltration or vascularization potential for adECM/ADF/AAF, is critical for reproducibility[10].

Mechanism elucidation and multi-omics approaches

The precise mechanisms underlying adipose-derived products are incompletely understood, limiting rational clinical application[114]. SVF and ADSCs act mainly via paracrine signaling, extracellular vesicles, and immune modulation rather than direct differentiation[97]. Nanofat and SVF-gel combine cellular and matrix effects to provide mechanical support and local trophic signals, enhancing angiogenesis and tissue remodeling[87]. CEFFE delivers soluble factors that stimulate proliferation, angiogenesis, and immunomodulation, but the specific active components remain unclear. adECM, ADF, and AAF provide structural guidance for host-cell infiltration and sustained factor delivery, with bioactivity influenced by preparation and tissue context[115]. Future studies should leverage multi-omics, single-cell sequencing, proteomics, spatial transcriptomics, and advanced imaging to dissect these mechanisms and establish indication-specific therapeutic rationales[116].

Delivery systems and sustained bioactivity

Many adipose-derived products fail clinically due to insufficient retention or rapid diffusion rather than lack of biological activity[117]. Engineered delivery platforms (hydrogels, microneedles, injectable ECM carriers, 3D-printed scaffolds, and bioactive films) can improve local retention, controlled release, and sustained regenerative signaling. CEFFE benefits from incorporation into hydrogels, microneedles, or ECM scaffolds. ACF can be delivered via microneedle patches to reduce repeated injections while maintaining dermal regenerative effects[118]. adECM, ADF, and AAF serve as injectable, implantable, or film-like scaffolds supporting host-cell infiltration, ADSC delivery, growth-factor retention,

tissue expansion, and soft-tissue interface applications. Optimized delivery systems are essential to translate inherent biological activity into reproducible clinical outcomes[72].

Clinical validation and safety

Successful translation requires rigorous evaluation of safety, efficacy, and regulatory compliance. Key concerns include immunogenicity, infection, fibrosis, ectopic tissue formation, mechanical failure, and cellular stability, particularly for culture-expanded, allogeneic, or combination products[119,120]. Regulatory classification varies by product type, preparation method, and jurisdiction, determining whether a product is considered human cells/tissues, biologics, drugs, devices, or combination products. GMP-compliant manufacturing, standardized quality control, preclinical validation, and clinical trials with long-term follow-up and standardized outcome measures are essential to ensure safety and efficacy[121].

Indication selection and modular strategies

A translational bottleneck is overgeneralizing product use across unrelated indications[122]. Products must be matched to dominant biological and material functions: cellular fractions for immunomodulation and paracrine signaling, gels for local retention and regenerative filling, collagen-rich fragments for structural support, soluble extracts for trophic-factor delivery, and ECM films/scaffolds for guided tissue remodeling[17,123]. For example, AMC is suitable for structural contouring, ACF for superficial dermal support, CEFFE for angiogenesis and tissue expansion, and adECM/ADF/AAF for matrix-guided regeneration dependent on host-cell infiltration and vascularization[17]. Modular, indication-specific strategies allow combination of different products for precise applications, avoiding functional mismatches and enhancing therapeutic outcomes in wounds, scar remodeling, soft-tissue reconstruction, tissue expansion, osteoarthritis, ischemic diseases, and peripheral nerve repair[123].

Delivery, retention, and storage considerations

Clinical efficacy is often limited by suboptimal delivery, retention, and storage rather than lack of bioactivity. Cells may die, be cleared, or fail to engraft; soluble factors like CEFFE can diffuse or degrade quickly; ECM scaffolds may fail if mechanically inadequate or if vascular ingrowth is insufficient[124]. Optimal dosing, injection frequency, route, and carrier selection are crucial for SVF and ADSCs; nanofat and SVF-gel require attention to injectability, viscosity, tissue-plane selection, and volume retention[20]; CEFFE needs sustained-release systems; adECM, ADF, and AAF depend on vascularization, degradation kinetics, mechanical matching, and host immune response[125]. Storage and transport add additional constraints: same-day autologous products reduce culture manipulation but limit standardization; off-the-shelf or stored products require cryopreservation, stabilization of proteins and extracellular vesicles, sterilization, lyophilization, hydration management, mechanical preservation, and bioactivity maintenance. Matrix films can facilitate handling and storage if their structure and activity are preserved[7].

Table 3. Delivery and Sustained Activity Strategies of Adipose Tissue Derivatives.

Product	Main Challenge	Delivery Strategy	Clinical Advantage
SVF	Cell retention, survival	Optimized injection, local ECM scaffolds	Enhances vascular regeneration, immunomodulation, wound healing
ADSCs	Retention and trophic support	Scaffold or co-injection with SVF	Promotes paracrine repair, soft tissue regeneration
Nanofat	Short-term persistence	Superficial injection	Stimulates dermal remodeling, scar repair without volumetric filling
SVF-gel	Sustained presence, mechanical support	Injectable gel	Combined cellular + ECM support; prolonged retention in chronic wounds

CEFFE	Rapid diffusion, short local retention	Hydrogels, microneedles, ECM scaffolds, films	Prolonged bioactivity, promotes angiogenesis, tissue expansion, wound repair
AMC	Short-term persistencet	Injectable scaffold	Structural support, volume augmentation
ACF	Maintaining local efficacy	Microneedle patches	Sustained release of collagen and bioactive factors; reduces repeated injections
adECM	Integration depends on vascularization and mechanical match	Injectable scaffold	Supports host-cell infiltration, ADSC delivery, tissue expansion, soft tissue interface applications
ADF	Coverage and structural support	Membrane application	Provides regenerative interface, localized delivery, mechanical protection
AAF	Adaptation to irregular surfaces, controlled release	Film application	Conforms to tissue surfaces, promotes angiogenesis and subcutaneous tissue regeneration

CONCLUSION AND FUTURE PERSPECTIVE

As a diversified regenerative platform, adipose-derived products include cellular products, cell matrix composites, soluble cell-free extracts, injectable matrix fragments, decellularized scaffolds, and film-like biomaterials. SVF and ADSCs form the cellular foundation; nanofat and SVF-gel preserve stromal cells and extracellular matrix components; CEFFE provides a cell-free, paracrine-factor-rich extract; AMC and ACF offer matrix-dominant injectable materials with distinct mechanical and biological properties; and adECM, ADF, and AAF serve as scaffolds and bioactive films. The field is shifting from volume replacement toward mechanism-driven tissue regeneration, and products should be selected according to their dominant functional properties: SVF and ADSCs for angiogenesis, immunomodulation, and paracrine repair; nanofat and SVF-gel for regenerative filling, scar remodeling, and dermal repair; CEFFE for trophic-factor delivery;

AMC for structural support; ACF for collagen-rich remodeling; and adECM, ADF, and AAF for scaffold-guided regeneration, wound coverage, tissue expansion, and sustained bioactive delivery.

Future development should focus on several directions: (1) standardized preparation and characterization to reduce variability and improve reproducibility; (2) quantitative potency assays for each product type, such as angiogenic activity for SVF/CEFFE, immunomodulatory capacity for ADSCs, collagen-remodeling ability for ACF, stiffness and retention for AMC, and host-cell infiltration or vascularization potential for adECM/ADF/AAF; (3) mechanistic studies using multi-omics, single-cell sequencing, proteomics, spatial transcriptomics, and advanced imaging; (4) engineered delivery systems (hydrogels, microneedles, injectable ECM carriers, 3D-printed scaffolds, and bioactive films) to improve retention, controlled release, and tissue-specific efficacy; and (5) rigorous randomized controlled trials, long-term follow-up, and standardized outcome measures to define safety and efficacy.

Looking ahead, adipose-derived products are likely to become indication-specific and modular, enabling combinations of cellular fractions for immune and vascular regulation, soluble extracts for trophic stimulation, collagen-rich matrices for dermal or mechanical support, and acellular scaffolds or films for guided tissue reconstruction. Such strategies may facilitate precise applications in chronic wounds, skin rejuvenation, scar remodeling, soft-tissue reconstruction, tissue expansion, osteoarthritis, ischemic diseases, and peripheral nerve repair. Adipose tissue is no longer merely a passive filler or energy storage, but a rich biological resource for regenerative medicine. The next stage will depend on transforming empirically prepared products into standardized, mechanism-defined, clinically validated, and regulation-compatible therapies. Advances in biomaterials engineering, cell-free therapy, extracellular matrix biology, and precision manufacturing will further support personalized and minimally invasive regenerative applications.

DECLARATIONS

Authors' contributions

Conceptualization, literature search, data synthesis, and drafting of the manuscript: TH.H;
Literature collection, analysis of relevant studies, and manuscript revision: YY.Y;
Data interpretation, figure and table preparation: HX.Y;
Critical review of the intellectual content and literature verification: Z.X;
Literature screening and extraction of key findings: T.Y,YX.Y;
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Supervision and validation of the review structure: J.Z, R.C;
Conceptualization, overall supervision, and final approval of the version to be published: CG.Y;
Project administration, funding acquisition, and final review: HC.L;
All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Not applicable. No new datasets, code, or physical materials were generated or analyzed during this review. All referenced data are available from the cited published articles.

Financial support and sponsorship

This work was supported by the National Natural Science Foundation of China (Grant No. 82402935), the National Key Laboratory of Oral & Craniomaxillofacial Reconstruction and Regeneration (Grant No. 2024QN05), the Fourth Military Medical University (Grant No. 2023JSYX36) and Airborne Army Hospital (Grant No. FY2024A04).

Conflict of interest

The authors declare no conflicts of interest.

Ethical approval and consent to participate

Not applicable. This article is a literature review and does not involve any new studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable. This review does not contain any individual person's data in any form.

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