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The Fibrin-Nanofat Membrane for Coverage of Raw Wound Surfaces: A Literature Review

REVIEW ARTICLE

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ABSTRACT

Chronic and complex wounds, including acute and extensive poor-healing injuries, present a significant challenge in reconstructive surgery. Conventional therapies—such as advanced dressings, negative pressure therapy, skin grafts, flaps, and recombinant growth factors-often fail to restore complete tissue architecture and function due to persistent inflammation, impaired angiogenesis, bacterial colonization, and deficient regenerative responses. To address these limitations, this review examines the regenerative rationale and clinical applications of fibrin-nanofat bioactive membranes as an innovative strategy for managing problematic and chronic wounds. Analysis of the literature on platelet concentrates and adipose tissue derivatives, with a focus on platelet-rich fibrin (PRF) and nanofat, demonstrates that PRF acts as a reservoir for the sustained release of growth factors that orchestrate tissue repair. Mechanically processed nanofat retains adipose-derived stem cells, stromal cells, exosomes, and bioactive mediators that stimulate proliferation, enhance neovascularization, and regulate fibrosis. Recent advances in tissue engineering have successfully integrated the scaffold properties of fibrin with the regenerative potential of nanofat into bioactive membranes. Experimental evidence indicates that these hybrid constructs yield uniform, flexible, and biologically active biomaterials that adapt to tissue defects, support cell adhesion, migration, and survival, and provide a sustained release of growth factors and progenitor cells. Fibrin-nanofat membranes therefore represent a promising regenerative tool in reconstructive surgery, with significant potential to advance chronic wound management by accelerating healing, improving tissue quality, and reducing reliance on complex procedures.

Keywords: Chronic wounds, regenerative medicine, platelet-rich fibrin, nanofat, bioactive membranes

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INTRODUCTION

Chronic wounds, including diabetic ulcers, pressure injuries, complex traumatic lesions, and poor-healing postoperative wounds, represent a major clinical challenge in reconstructive surgery. Persistent inflammation, impaired angiogenesis, bacterial colonization, and deficient tissue regeneration contribute to delayed healing and increased patient morbidity. Conventional treatments—such as advanced dressings, negative pressure therapy, skin grafts, flaps, and recombinant growth factors have demonstrated utility in many cases. Yet they often fail to fully restore the architecture and functionality of affected tissues (1–3). In light of these limitations, regenerative medicine has emerged as a promising alternative to optimize tissue repair. Among the most extensively studied strategies are platelet concentrates (4,5) and adipose tissue derivatives (6,7), owing to their capacity to modulate inflammation, stimulate angiogenesis, and promote cellular regeneration. Platelet-rich fibrin (PRF), a second-generation platelet concentrate, functions as a biological reservoir of growth factors—including transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF)—which are gradually released to orchestrate the cellular and molecular events underlying wound healing (8).

Nanofat, obtained through mechanical processing of adipose tissue, retains a high concentration of adipose-derived stem cells (ASCs), stromal cells, exosomes, and other bioactive mediators capable of stimulating cell proliferation, promoting neovascularization, and modulating fibrosis. In addition to its use as a filler material, nanofat has been established as an effective regenerative tool in the treatment of cutaneous alterations, scars, and complex tissue defects (9). Recent advances in tissue engineering have enabled the combination of fibrin's biological properties with nanofat's regenerative potential through the creation of bioactive membranes. This association leverages fibrin's role as a three-dimensional scaffold that supports cell adhesion, migration, and survival, while providing sustained release of growth factors. Nanofat contributes progenitor cells and bioactive molecules that enhance tissue repair and regeneration (10). Fakih Gomez et al. (11) demonstrated that incorporating nanofat into a fibrin membrane yields a uniform, flexible, and easily manipulable biomaterial capable of adapting to tissue defects and serving as a biologically active coverage for chronic wounds. Although this is an incipient methodological approach, the fibrin-nanofat membrane may represent an innovative strategy within regenerative and reconstructive surgery, with the potential to improve wound healing quality, accelerate tissue coverage, and reduce the need for more complex reconstructive procedures. This review aimed to highlight the regenerative rationale and clinical applications of this hybrid membrane in the management of chronic wounds.

MATERIALS AND METHODS

A comprehensive literature review was conducted using PubMed, Google Scholar, ResearchGate, and SciELO, including publications in both English and Spanish. The search strategy utilized combined descriptors combined with Boolean operators: "AND" was used to connect different terms, while "OR" linked similar concepts.

The main search strings were:

1. Regenerative therapy OR tissue engineering AND nanofat PRF membrane
2. Nanofat PRF membrane AND raw wound surfaces OR coverage defects OR reconstruction
3. Nanofat PRF membrane AND plastic surgery OR reconstructive surgery OR aesthetic surgery

From an initial set of 174 references, 36 articles were selected that met the inclusion criteria: full text availability, originality, bibliographic reviews, meta analyses, and clinical trials published over a 12-year period (2013 to 2025) in English or Spanish. The remaining 138 records were excluded because they consisted of short communications, conference abstracts, letters to the editor, or in press articles.

Development: Preparation and Mechanical Properties of the Nanofat-PRF Membrane

Tissue engineering has driven the development of autologous biomaterials that combine structural support with regenerative biological activity. The nanofat-PRF membrane integrates the cellular and paracrine components of adipose tissue with the biomechanical and bioactive properties of PRF, resulting in a biologically active construct with potential applications in soft tissue regeneration and the coverage of complex wounds (10).

Nanofat, first described by Tonnard et al. (12), is obtained through mechanical emulsification and subsequent filtration of aspirated adipose tissue. This process destroys most mature adipocytes but preserves a high concentration of ASCs, progenitor cells, stromal vascular fraction components, growth factors, cytokines, and extracellular vesicles, including exosomes with recognized regenerative activity. Multiple studies (13–16) have demonstrated nanofat's abundance of cells with angiogenic, immunomodulatory, and extracellular

matrix remodeling capacities, explaining its growing use in regenerative medicine and reconstructive surgery.

The PRF, the second component, is a platelet concentrate obtained by centrifugation of peripheral blood without anticoagulants. This process generates a three-dimensional fibrin matrix that entraps platelets, leukocytes, and plasma proteins. Unlike other platelet concentrates, PRF enables the progressive and sustained release of growth factors—including PDGF, TGF-β, VEGF, epidermal growth factor (EGF), and insulin-like growth factor-1 (IGF-1)—which are essential for angiogenesis, cell proliferation, extracellular matrix synthesis, and tissue repair (17–20).

The hybrid membrane is created by incorporating nanofat into PRF during the initial fibrin polymerization phase. This ensures the homogeneous distribution of progenitor cells, growth factors, and extracellular vesicles within the fibrin network, forming a biologically active and structurally stable biomaterial. Fibrin acts as a natural three-dimensional scaffold that facilitates cell adhesion, fibroblast migration, neovascularization, and the spatial organization of regenerative components. Thus, the membrane functions not only as a physical support but also as a dynamic reservoir of biochemical signals capable of modulating the wound microenvironment (10,21).

Biomechanically, the fibrin network provides viscoelastic properties that distribute mechanical loads and resist moderate tensile forces. The PRF membranes have demonstrated sufficient tensile strength for surgical manipulation, suturing, and fixation, while maintaining flexibility and adaptability to irregular anatomical defects (10,11,22). Incorporation of nanofat further enhances plasticity, improves adaptation to recipient beds, and maintains a moist environment conducive to healing. Residual extracellular matrix from adipose tissue may act as an additional biological reinforcement, promoting internal cohesion and prolonging local bioactive factor availability (13).

Although specific biomechanical characterization of nanofat-PRF membranes remains limited, available studies (10,11,21,22) suggest that combining both components simultaneously enhances structural stability and regenerative potential. Fibrin also functions as a controlled-release system for bioactive molecules. Its three-dimensional network retains proteins, cytokines, and growth factors, enabling their gradual release during physiological degradation. This prolongs local availability of regenerative signals and optimizes interactions between resident cells and progenitor cells derived from nanofat, thereby stimulating key biological processes such as cell proliferation, angiogenesis, collagen synthesis, extracellular matrix remodeling, and modulation of inflammation (11).

Adipose-derived stem cells and adipose-derived exosomes play a central role in tissue regeneration through paracrine mechanisms. These extracellular vesicles contain proteins, growth factors, mRNA, and microRNA that regulate cell proliferation, fibroblast migration, angiogenesis, and immune modulation. Their incorporation into the fibrin matrix provides a biological platform that enhances local persistence and therapeutic activity (15,23).

Although evidence on the impact of varying proportions of PRF and nanofat within the membrane remains limited, available data suggest that compositional differences directly influence biomechanical properties. A higher proportion of PRF yields a thicker, denser, and more mechanically resistant membrane, useful for areas requiring structural support, though potentially less permeable to immediate cell migration. Conversely, a higher proportion of nanofat produces a more fragile but highly bioactive construct. The optimal balance likely involves PRF acting as a biological "glue" that traps nanofat components, ensuring both surgical manageability and regenerative activity (10).

In summary, the nanofat-PRF membrane can be regarded as a bioactive autologous biomaterial that integrates the mechanical properties of fibrin with the regenerative potential of adipose-derived stem cells, growth factors, and exosomes.

Synergistic Mechanisms of the Nanofat-PRF Membrane

The regenerative potential of the nanofat-PRF membrane lies in the synergistic interaction between ASCs present in nanofat and the three-dimensional fibrin matrix provided by PRF (Figure 1). Rather than a mere physical association, the membrane constitutes a functional unit in which the cellular and molecular properties of each component mutually enhance regenerative activity (10,11).

Adipose-derived stem cells are multipotent cells with the ability to differentiate into fibroblasts, endothelial cells, adipocytes, osteoblasts, and chondrocytes. However, their therapeutic effect is now recognized to depend primarily on paracrine activity. Adipose-derived stem cells secrete a wide variety of growth factors, cytokines, chemokines, and extracellular vesicles that regulate tissue responses to injury. Key molecules include VEGF, hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), IGF-1, PDGF, TGF-β, and stromal cell-derived factor-1 (SDF-1), which drive angiogenesis,

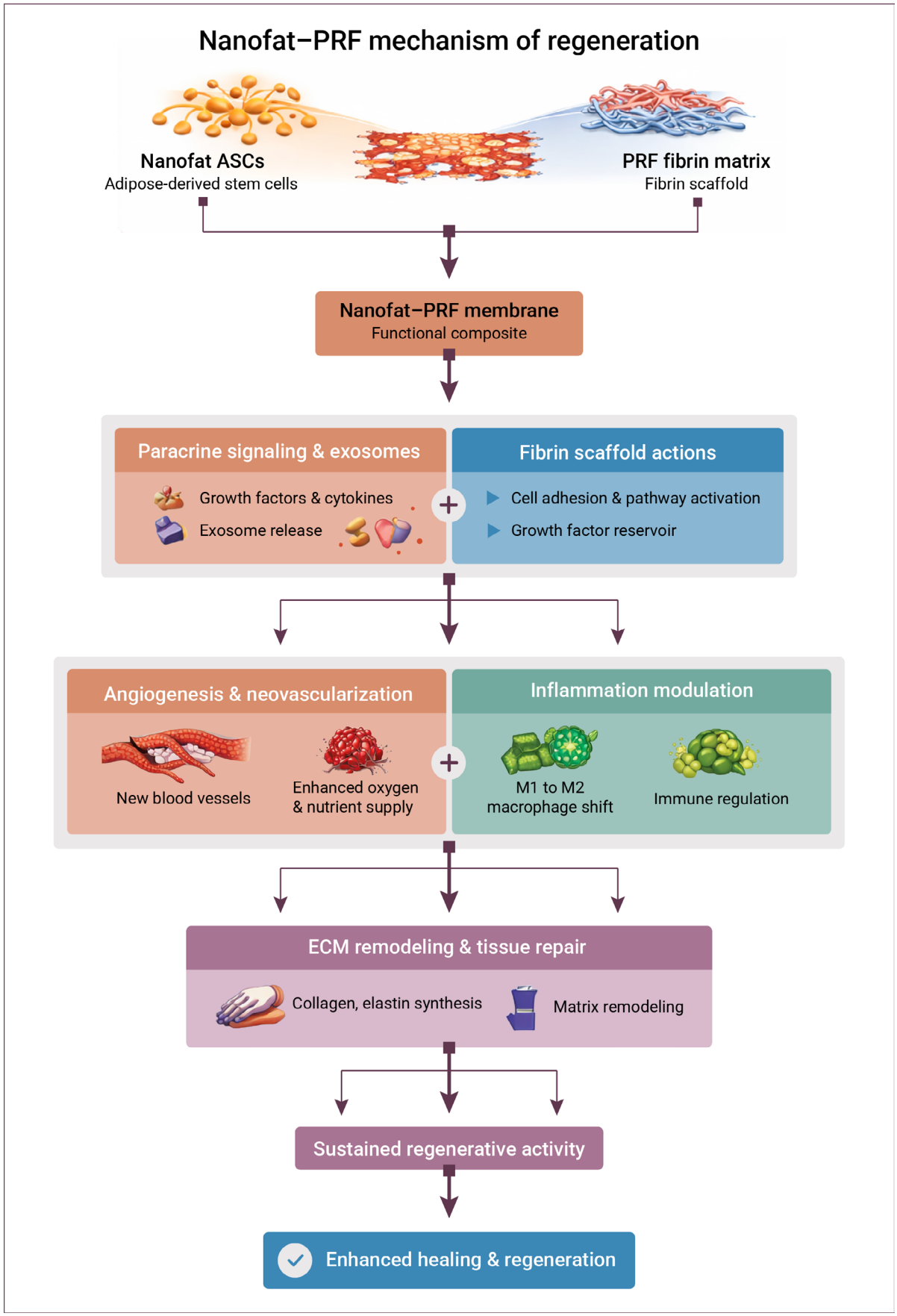

FIGURE 1. Regenerative synergy between nanofat-derived ASCs and PRF in wound healing.

fibroblast migration, and extracellular matrix synthesis. Exosomes released by ASCs are rich in microRNAs and signaling proteins that modulate gene expression in resident cells (24,25).

The fibrin matrix of PRF acts as a dynamic biological scaffold, mimicking early wound-healing events. Its porous architecture facilitates cell adhesion via integrins (α5β1, αvβ3), promoting ASC survival, proliferation, and migration. This cell-matrix interaction activates intracellular pathways such as focal adhesion kinase (FAK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), which regulate proliferation, survival, and synthesis of reparative proteins (26–28). Furthermore, fibrin serves as a molecular reservoir, retaining growth factors from both PRF platelets and ASCs. These molecules are trapped within the fibrillar network and gradually released during physiological degradation, maintaining high local concentrations of bioactive mediators for extended periods (10,11,29). Growth factors such as VEGF, angiopoietin-1 (Ang-1), HGF, and bFGF stimulate endothelial cell proliferation and migration, while fibrin provides a physical guide for capillary formation. This dual mechanism enhances neovascularization, improving oxygen and nutrient supply essential for tissue repair (24,30). Studies confirm that fibrin scaffolds enriched with mesenchymal stem cells exhibit superior angiogenic capacity compared to either component alone (10,11,21,22).

Inflammation modulation is another critical mechanism. Chronic wounds often exhibit persistent pro-inflammatory M1 macrophages producing TNF-α, interleukin-1β (IL-1β), and IL-6. Adipose-derived stem cells release IL-10, prostaglandin E2 (PGE2), tumor necrosis factor-stimulated gene-6 (TSG-6), and indoleamine 2,3-dioxygenase (IDO), promoting polarization toward anti-inflammatory M2 macrophages. Fibrin further supports ordered immune cell recruitment (13,31). Extracellular matrix remodeling is facilitated by ASC-induced fibroblast proliferation and synthesis of collagen I/III, elastin, fibronectin, and hyaluronic acid. Concurrent secretion of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) ensures balanced degradation and reconstruction. Fibrin acts as a provisional matrix, progressively replaced by mature functional tissue (32). Ultimately, exosomes derived from ASCs add another layer of regulation. These vesicles contain microRNAs that modulate signaling pathways including PI3K/Akt, Wnt/β-catenin, Notch, TGF-β/Smad, and MAPK/ERK. Fibrin protects exosomes from rapid degradation, enabling sustained release and prolonged local activity (33,34) Nanofat-derived adipose stem cells release paracrine signals and exosomes enriched in growth factors and cytokines, which are retained within the fibrin scaffold. The PRF matrix serves as both a reservoir and a structural support, enabling cell adhesion and pathway activation. Collectively, these processes initiate angiogenesis, enhancing oxygen and nutrient delivery to the healing tissue. Simultaneously, immune modulation occurs through a macrophage phenotype shift (M1 to M2), reducing inflammation and promoting a pro-regenerative environment. The composite membrane further drives extracellular matrix remodeling, stimulating collagen and elastin synthesis. These integrated mechanisms result in sustained regenerative activity, leading to accelerated tissue repair and enhanced healing outcomes.

Clinical Evidence of Efficacy and Safety

Recent clinical evidence is encouraging regarding the efficacy and safety of nanofat and PRF, whether used individually or in combination for reconstructive, aesthetic, and complex wound-healing applications. Systematic reviews published between 2023 and 2025 highlight consistent benefits of nanofat in improving skin quality, regenerating soft tissues, treating scars, and correcting volumetric defects (14,35,36). These effects are attributed to the high concentration of stromal cells, pericytes, growth factors, and extracellular vesicles that stimulate angiogenesis and matrix synthesis. However, most studies remain limited to case series or small prospective cohorts, reducing the overall level of evidence. Given the promising therapeutic effects of the nanofat-PRF combination, larger controlled studies are needed based on standardized preparation protocols. Meta-analyses and systematic reviews converge to indicate that PRF formulations (advanced platelet-rich fibrin [A-PRF], injectable platelet-rich fibrin [i-PRF]) significantly enhance tissue healing, angiogenesis, and soft-tissue regeneration through sustained growth-factor release (Table 1). Preliminary clinical improvements have been documented in oral surgery, periodontal regeneration, facial rejuvenation, and wound repair, with superior tissue quality, reduced inflammation, and accelerated healing compared with conventional treatments (10,17,19).

Although clinical studies specifically targeting hybrid nanofat-PRF membranes remain scarce, available data suggest improved tissue regeneration, vascularization, and aesthetic outcomes compared with either component alone (10,11,22). Hence, further studies are needed to provide more consistent and conclusive data on their safety and efficacy. Both nanofat and PRF are autologous, minimizing risks of immune reactions, disease transmission, or tissue rejection. Reported adverse events are mild and transient, including edema,

Table 1. Platelet-rich fibrin variants in wound healing.

Type	Preparation	Form	Growth factor release	Clinical use
Advanced platelet-rich fibrin (A-PRF)	Low speed centrifugation	Solid fibrin membrane	Sustained, prolonged release	Wound coverage, scaffolds, oral/maxillofacial surgery
Injectable platelet-rich fibrin (i-PRF)	Very low speed centrifugation	Liquid, later gels	Rapid, concentrated release	Injectable therapy, mixing with grafts, regenerative infiltration

ecchymosis, local pain, or self-limited inflammation. No major complications have been identified when standardized protocols are followed (10,12,14,19,21).

Nevertheless, methodological limitations persist, including heterogeneity in preparation protocols, differences in application techniques, small sample sizes, and short follow-up periods. The authors emphasize the need for multicenter randomized clinical trials with standardized methodologies to validate efficacy and establish optimal protocols (10,11,22). Overall, available evidence suggests that nanofat-PRF membranes represent a safe and promising regenerative strategy for complex wounds, soft-tissue defects, and skin rejuvenation (10).

Practical Considerations and Applications

Tailoring membrane composition to specific clinical requirements may improve outcomes. For example:

- Formulation for rigidity (coverage in tension zones): Increasing the PRF proportion yields a thicker, denser, and more resistant membrane, useful for mechanical protection, though potentially less permeable to immediate cell migration.
- Formulation for regeneration (ischemic ulcers): Prioritizing nanofat maintains high bioactivity and moisture, facilitating stem-cell release, though with reduced mechanical strength.

Currently, no standardized protocols define exact proportions for specific properties; adjustments remain empirical. A balanced ratio—nanofat emulsified with centrifuged PRF—appears most reliable, with modifications reserved for cases requiring additional mechanical support. Clinical applications reported include temporary coverage of exposed cartilage after nasal reconstruction, early re-epithelialization following rhinophyma surgery, facial fillers, management of chronic wounds resulting from aesthetic complications, and pressure ulcers, all with satisfactory outcomes and absence of major complications (Figure 2).

Limitations and Future Perspectives

Despite the growing interest in the nanofat-PRF membrane as a regenerative medicine tool, the currently available scientific evidence remains subject to significant limitations that must be acknowledged when interpreting reported clinical outcomes. As mentioned, a major constraint is the paucity of randomized, prospective, and controlled clinical trials specifically evaluating this hybrid membrane as a combined product. Most publications consist of case reports, small case series, or observational studies with limited sample sizes, thereby reducing the strength of the conclusions and hindering extrapolation to broader patient populations.

Another critical limitation lies in the lack of standardized protocols for membrane preparation. Considerable variability exists among studies regarding liposuction techniques, nanofat emulsification and filtration methods, centrifugation parameters for PRF isolation, and the strategies used to integrate both components into a single construct. Such methodological heterogeneity may influence the cellular yield, biological composition, and mechanical properties of the final product, complicating direct comparisons across investigations and limiting reproducibility.

Equally important is the incomplete biological characterization of the hybrid membrane. While it is known to combine stromal vascular fraction cells, growth factors, and a three-dimensional fibrin scaffold, data remain scarce on the precise concentration of viable cells, biomolecule release kinetics, long-term cell survival, and the mechanistic basis of the observed *in vivo* effects. This lack of uniformity hampers the establishment of quality control parameters necessary for routine clinical application.

Follow-up periods reported in the literature are generally short, focusing primarily on early wound closure and immediate outcomes (10,11). Consequently, evidence regarding the durability of regenerative effects, long-term stability of repaired tissues, and functional outcomes remains limited.

Table 2. Nanofat-PRF membrane main potential clinical indications, advantages, limitations, and future research directions.

Potential Indications
Chronic wounds (diabetic ulcers, pressure injuries)
Complex traumatic lesions
Poorly healing postoperative wounds
Soft-tissue defects and reconstructive surgery
Facial fillers and aesthetic corrections
Temporary coverage in nasal and **facial reconstruction or rhinophyma surgery**
Potential Advantages
Key regenerative and clinical benefits observed.
Accelerated epithelial closure and tissue repair
Enhanced angiogenesis and neovascularization
Modulation of inflammation (M1 to M2 macrophage shift)
Improved extracellular matrix remodeling (collagen, elastin)
Autologous origin minimizes immune rejection
Flexible, adaptable biomaterial for irregular defects
Current Limitations
Constraints in evidence and methodology that limit widespread adoption
Few randomized controlled trials; mostly case series
Lack of standardized preparation protocols (liposuction, centrifugation)
Short follow-up periods; limited long-term data
Heterogeneity in biological composition and mechanical properties
Technical complexity requiring specialized equipment and trained personnel
Patient-specific variability (age, comorbidities, and metabolic status)
Future Research Priorities
Conduct multicenter randomized clinical trials with larger cohorts
Standardize harvesting and processing protocols for reproducibility
Define optimal PRF-to-nanofat ratios for mechanical vs regenerative needs
Expand biological characterization (cell viability, release kinetics)
Explore integration with smart biomaterials and controlled-release systems
Investigate novel applications in tissue engineering and organ regeneration

Comparative studies assessing the superiority of nanofat-PRF membranes over other autologous biomaterials or dermal substitutes are also scarce.

From a technical standpoint, membrane preparation requires specialized equipment, trained personnel, and careful coordination between adipose tissue harvesting and blood processing. These factors may increase procedural complexity and restrict availability in certain centers. Furthermore, product quality may be influenced by patient-specific variables such as age, comorbidities, metabolic status, and the intrinsic quality of adipose and blood-derived tissues (10).

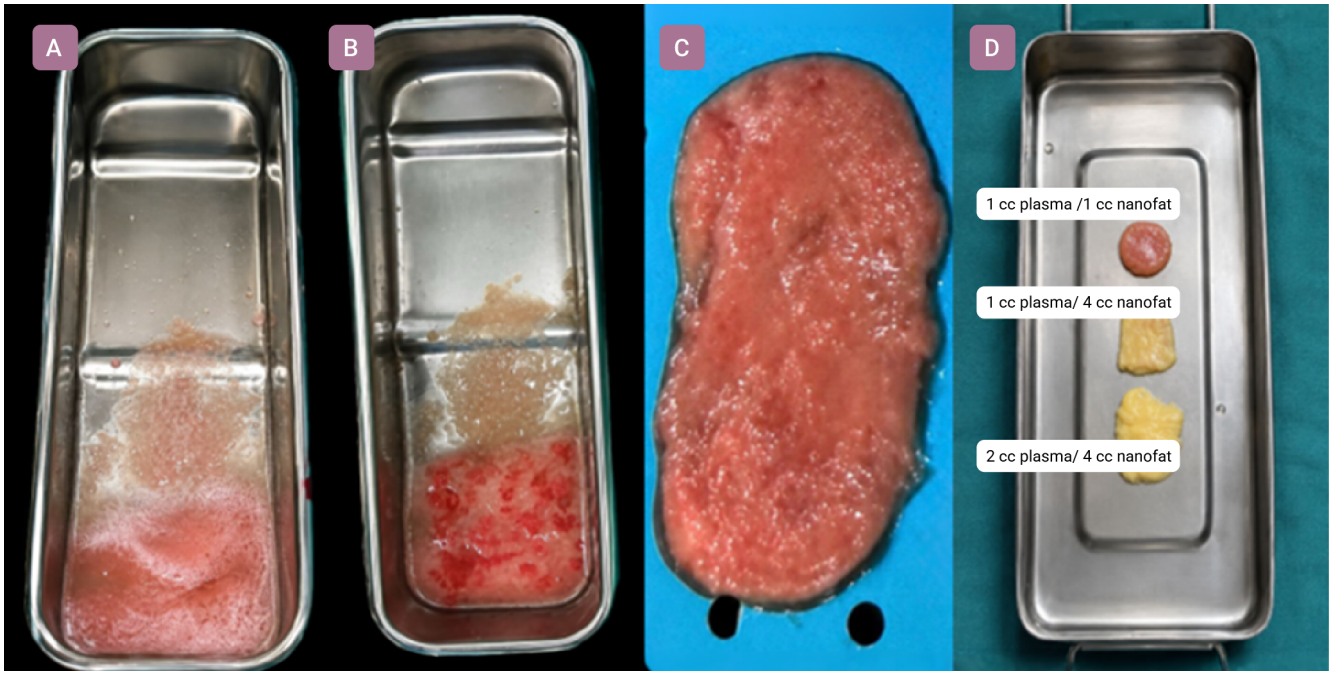

FIGURE 2. Stages of membrane formation.

Note: The content of this image reflects the major steps in the preparation of the membrane variants. **A. Fusion mixture:** Components being mixed. **B. Final result:** Membrane in its final form. **C. Final result**: Final outcome with consistency varying according to the proportions of the components. Picture taken by the lead author in a surgical setting. Plastic and Reconstructive Surgery Service, Hermanos Ameijeiras Hospital.

Although published studies to date suggest a favorable safety profile due to the autologous nature of the product, multicenter investigations with larger cohorts and standardized protocols are essential to more precisely define efficacy, safety, specific indications, and cost-effectiveness. High-level clinical evidence will be pivotal for consolidating the role of nanofat-PRF membranes within reconstructive surgery and regenerative medicine algorithms.

Future perspectives focus on the standardization of harvesting and processing protocols to ensure reproducible biological composition and consistent clinical outcomes. Advances in tissue engineering may further enhance the mechanical and biological properties of the membrane through integration with smart biomaterials, controlled-release systems for growth factors, and biofabrication technologies. Such innovations could expand therapeutic indications to include complex wounds, soft tissue defects, and cutaneous regeneration.

Collectively, the nanofat-PRF membrane represents a promising strategy whose clinical potential will continue to evolve as scientific evidence matures (Table 2).

CONCLUSION

The use of nanofat combined with PRF may represent a potentially effective and safe autologous strategy, particularly for the management of complex and chronic wounds, as multiple studies report accelerated epithelial closure without complications. Although the mechanism of action involves both the release of growth factors and a pro-angiogenic scaffold effect, the precise contribution of adipose-derived stem cells within the membrane remains to be fully characterized. Rigorous clinical trials are necessary to confirm its efficacy in cosmetic indications and to explore novel applications such as peripheral nerve regeneration.

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