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REVIEW ARTICLE

# CLINICAL APPLICATIONS AND REGENERATIVE POTENTIAL OF DECELLULARIZED HUMAN AMNIOTIC MEMBRANE IN WOUND HEALING: A:LITERATURE REVIEW

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## ABSTRACT

**Background:** Chronic and acute wounds continue to pose significant clinical and socioeconomic challenges, particularly when complicated by infection, ischemia, or delayed re-epithelialization. Decellularized human amniotic membrane (dHAM) has gained attention as a biological scaffold capable of supporting tissue regeneration due to its intrinsic biocompatibility, anti-inflammatory properties, and structural similarity to native extracellular matrix (ECM).

**Objective:**This literature review examines the clinical evidence on the safety and effectiveness of dHAM in skin and soft tissue wound healing, focusing on decellularization methods, scaffold properties, and patient outcomes.

**Methods:**A systematic search of PubMed, Scopus, and Web of Science was conducted using keywords such as "decellularized human amnion," "scaffold," and "wound healing." Only human clinical studies involving dHAM were included; preclinical, animal, and fresh or cryopreserved amnion studies were excluded. Thirteen studies out of 278 met the inclusion criteria for qualitative analysis.

**Results:** Decellularization via physical, chemical, and enzymatic methods effectively removed cells while preserving ECM structure and bioactivity. Clinically, dHAM promoted faster epithelialization and angiogenesis, reduced inflammation, and improved scar quality in various wound types. Most wounds achieved closure within two to four weeks, with less pain and exudate compared to conventional dressings. Furthermore, modified dHAM scaffolds containing bioactive agents or hydrogels showed enhanced tissue regeneration and vascularization.

**Conclusion:** dHAM is a safe, versatile biomaterial that combines structural support with biological activity to accelerate organized wound healing. With standardized processing and additional clinical trials, dHAM holds significant promise as a component of advanced regenerative wound care.

***Keywords****:* Decellularized human amniotic membrane, wound healing, scaffold, extracellular matrix, regenerative medicine, angiogenesis, epithelialization

## INTRODUCTION

Chronic and acute wounds pose a major global health challenge. Chronic, non-healing wounds are estimated to cost the U.S. healthcare system over US$25 billion per year, with individual severe ulcers sometimes costing in excess of US$50,000 per case.[1] Moreover, chronic wounds place strain on healthcare systems—consuming a significant proportion of resources and substantially impair patients' health-related quality of life, contributing to pain, reduced mobility, social isolation, anxiety, and depression.[2,3]

Despite numerous advances in wound care dressings, many limitations remain. Traditional dressings (gauze, cotton) fail to maintain the moist environment critical for optimal healing, and often adhere to the wound bed causing pain and additional tissue damage upon removal.[4] Advanced dressings attempt to address some of these issues but are not without drawbacks: many require frequent changes, are not adaptive to dynamic wound conditions (exudate fluActuation, pH shifts), struggle at motional sites (e.g. joints), or risk peri-wound skin damage from adhesive interfaces.[5,6]

In severely exuding wounds, dressing saturation and pooling become problematic; if dressings dry out, trauma occurs on removal, and mechanical disruption may spread bacteria via airborne dispersion.[6] Also, the evidence base for many advanced or antimicrobial dressings is weak: few high-quality randomized trials exist, and cost-effectiveness data are limited.[7]

These gaps underscore the need for innovative biomaterials and scaffold-based solutions (such as decellularized human amnion membrane) that can better

integrate with wound biology, minimize secondary trauma, and address the dynamic and pathological features of wound microenvironments.

Human amniotic membrane (HAM), the innermost layer of the placenta, exhibits several biologically active qualities that support its use in wound healing. It demonstrates anti-inflammatory behavior by expressing interleukin-1 receptor antagonist (IL-1Ra), interleukin-10 (IL-10), and tissue inhibitors of metalloproteinases (TIMPs), which modulate inflammation and matrix degradation.[8–10] It also demonstrates anti-fibrotic/anti-scarring effects: for example, HAM's hyaluronic acid content can modulate TGF-β signaling and reduce fibroblast activation and scar formation.[10]

HAM's pro-angiogenic capacity arises from its reservoir of growth factors (VEGF, bFGF, etc.) and extracellular matrix elements that support endothelial migration and vessel ingrowth. In addition, HAM exhibits antimicrobial effects—its membrane contains natural antimicrobial peptides, protease inhibitors (e.g. secretory leukocyte proteinase inhibitor, elafin), and inhibitory effects on bacterial growth have been documented.[10,11]

Crucially, HAM is known to have low immunogenicity: it is relatively non-vascular, expresses minimal classical HLA antigens, and has been shown in transplantation models to provoke only mild host immune responses.[12] Altogether, these integrated properties render HAM not just a passive physical scaffold, but an active biological modulator of the wound microenvironment—mitigating inflammation, suppressing fibrosis, encouraging new vessel formation, and defending against infection—making it a promising candidate in both acute and chronic wound care.

Decellularization is used to remove immunogenic cellular material (cells, DNA, antigens) from donor tissues to reduce host immune responses and graft rejection, while retaining the extracellular matrix (ECM) that provides structural and biochemical cues for healing.[13,14] Optimized protocols aim to preserve ECM architecture and matrix-bound bioactive factors (e.g., collagens, laminin, fibronectin, GAGs, and growth factors), because these govern cell adhesion, migration, angiogenesis, and constructive remodeling; overly harsh chemistries can remove cells but damage the scaffold's ultrastructure and function.[13,15] For human amniotic membrane (HAM) specifically, decellularization (e.g., SDS, Triton X-100, trypsin/EDTA, or combined/stepwise methods) has been shown to reduce immunogenicity and preserve the native ECM and bioactivity when properly tuned—supporting its use as an allogeneic, bioactive scaffold for wound healing.[16,17]

**Decellularization Strategies for HAM**

Physical strategies such as freeze–thaw cycles, agitation, and hyper/hypotonic rinses are often used up front to lyse cells while limiting chemical exposure. These steps can better preserve basement-membrane ECM and embedded cues than harsher detergents but rarely achieve complete nucleic-acid removal on their own, so they're typically followed by chemical/enzymatic steps. Recent reviews on decellularized amniotic membrane (dAM) highlight this sequencing and the rationale for combining physical with chemical methods to balance efficacy and ECM preservation.[18,19]

Among detergents, SDS is very effective for cell clearance but is the most disruptive to ECM proteins (e.g., laminin/fibronectin), whereas Triton X-100 is milder on matrix architecture but may leave residual DNA without enzymatic help; trypsin/DNase/RNase adjuncts are commonly added to finish nucleic-acid and cytoskeletal cleanup. Contemporary reviews and experimental papers on HAM/dHAM document these trade-offs and also show workable alternatives (e.g., thermolysin + brief NaOH to denude epithelium while preserving ultrastructure), reinforcing that protocol choice should be matched to the intended indication (e.g., wound vs ocular use).[18,19]

After decellularization, scaffolds require terminal sterilization—commonly gamma irradiation, ethylene oxide (EtO), or peracetic acid—each with known effects on mechanical and biochemical integrity. Gamma sterilization can increase stiffness and reduce tensile performance in some contexts, while EtO demands careful aeration to avoid residues; peracetic acid is broadly antimicrobial with relatively gentle ECM impact but repeated exposure can still alter mechanics. Clinical and translational studies using lyophilized/sterilized HAM show good feasibility in skin and head-and-neck applications, and ocular prep papers quantify how preservation + gamma can change key growth factors (e.g., TGF-β, bFGF)—underscoring why sterilization choice should be reported alongside outcomes.[20–22]

**Characterization of dHAM Scaffolds**

One of the key requirements for an effective dHAM scaffold is the preservation of extracellular matrix (ECM) components such as collagen types I and III, laminin, and fibronectin, along with the integrity of the basement membrane. Appropriate decellularization protocols are able to clear cellular debris while maintaining these structural proteins, which are essential for scaffold bioactivity. Histological and ultrastructural analyses consistently demonstrate that dHAM can retain collagen fibers and basement membrane architecture even after processing, ensuring that the characteristic trilaminar structure of the amnion is preserved. The maintenance of these ECM cues is fundamental in supporting cell adhesion, directing keratinocyte migration, and promoting re-epithelialization during wound healing.[23,24]

Beyond its structural framework, dHAM retains measurable levels of bioactive growth factors, including VEGF, TGF-β, EGF, FGF, and PDGF, all of which play central roles in angiogenesis, cell proliferation, and tissue remodeling. Analyses of decellularized preparations show that most of these molecules remain detectable after

processing, indicating that decellularization does not completely eliminate the scaffold's bioactivity. The presence of such factors, together with embedded cytokines, contributes to the regenerative potential of dHAM, allowing it to function not only as a physical support but also as a biologically active matrix that promotes vascular ingrowth and epithelial regeneration in wound environments.[23,24]

The biocompatibility of decellularized human amniotic membrane (dHAM) has been widely validated across multiple assays and experimental settings. dHAM consistently supports stem cell proliferation and attachment, preserving regenerative cues even after cellular removal.[25] Both in vitro and in vivo investigations confirm its non-cytotoxic behavior, with performance that meets *ISO 10993* thresholds, establishing its safety profile for clinical translation.[24]

## METHOD

### Search Strategy

A comprehensive electronic search was performed in PubMed, Scopus, and Web of Science to identify studies evaluating the use of decellularized human amniotic membrane (dHAM) as a scaffold for wound healing.

The search strategy combined synonyms for three key concepts:

1. Decellularized amniotic membrane, including the terms *"decellularized amniotic membrane," "acellular amniotic membrane," "decellularized human amnion," "processed human amnion," "human amniotic membrane scaffold,"* and *"human amnion scaffold."*
2. Wound-healing–related conditions, captured by the terms *"wound healing," "burn," "ulcer," "skin graft," "split-thickness graft," "full-thickness graft," "plastic surgery," "reconstructive surgery,"* and *"soft-tissue repair."*
3. Scaffold or matrix descriptors, represented by *"scaffold," "extracellular matrix," "ECM," "biomaterial,"* and *"graft."*

These concept blocks were connected using the Boolean operators AND and OR so that each retrieved record contained at least one term from each concept. Search fields were restricted to titles, abstracts, and keywords, and no date limits were applied.

Reference lists of the included studies and relevant reviews were also screened manually to identify any additional eligible publications.

### Eligibility Criteria (PICO Framework)

The inclusion and exclusion criteria were defined based on the Population–Intervention–Comparator–Outcome (PICO) framework:

- Population (P): Human patients presenting with acute or chronic wounds, including diabetic ulcers, burns, or postsurgical wounds.
- Intervention (I): Application of decellularized human amniotic membrane (dHAM) as a scaffold, graft, or biological dressing.
- Comparator (C): Conventional wound care, synthetic or alternative biological grafts (when available).
- Outcomes (O): Clinical wound healing parameters such as epithelialization rate, angiogenesis, time to closure, infection control, graft take, and scar quality.

Inclusion criteria:

- Original clinical studies (case reports, case series, prospective or retrospective clinical research).
- Use of decellularized (not fresh or cryopreserved) human amniotic membrane for skin or soft-tissue wound healing.

Exclusion criteria:

- Animal or preclinical studies (explicitly excluded).
- Use of fresh, cryopreserved, or lyophilized HAM without decellularization.
- Non-wound applications (ophthalmology, dental, nerve, bone, cartilage).
- In vitro or mechanical-only studies lacking clinical endpoints.
- Review articles, conference abstracts, editorials, or non-original reports.
- Duplicate or overlapping patient datasets.

### Study Selection

The initial search yielded 278 records (53 + 225). After removal of 41 duplicates, 237 unique records remained. Screening of titles and abstracts excluded 204 articles, primarily due to irrelevant topics or animal/preclinical study design. A total of 33 full-text articles were assessed for eligibility.

Of these, 21 articles were excluded for the following reasons:

- Animal or preclinical model only (n=73 total, excluded at screening).
- Non-decellularized HAM (n=7).
- Non-wound indications such as ophthalmologic or bone repair (n=7).
- In vitro or mechanical characterization only (n=4).
- Review or non-original article (n=2).
- Overlapping data (n=1).

Finally, 12 clinical studies were included for qualitative synthesis in this review (table 1).

**Table 1. Characteritcis of Included Studies**

| No. | First Author (Year) | Study Design / Population | Decellularization & Sterilization Method | Wound Type / Clinical Application | Country |
|---|---|---|---|---|---|
| 1 | Wilshaw S.-P. (2008) | In vitro human fibroblast and keratinocyte culture study | Detergent + enzymatic treatment (SDS + DNase); γ-irradiation sterilization | Exploratory scaffold biocompatibility | United Kingdom |
| 2 | Mahmoudi-Rad M. (2013) | In vitro fibroblast adhesion & growth assay | Hypotonic lysis + trypsin + Triton X-100; ethanol sterilization | Dermal repair model | Iran |
| 3 | Xue S.-L. (2016) | Prospective clinical trial (38 patients) | SDS + DNase; autoclave sterilization | Postsurgical nail-bed wounds | China |
| 4 | Wu Z. (2018) | Clinical series (venous ulcers) | SDS + non-ionic detergent; sterile PBS rinses | Chronic venous ulcers | China |
| 5 | Xue S.-L. (2018) | Case series (post-reconstructive defects) | SDS decellularization + ethanol sterilization | Nasal reconstruction defects | China |
| 6 | Kakabadze Z. (2019) | Clinical case (1 patient, radiation wound) | Trypsin + Triton X-100; antibiotic sterilization | Post-radiation non-healing ulcer | Georgia |
| 7 | Sous Naasani L.I. (2019) | In vitro MSC seeding + characterization | SDS + DNase protocol | Stem-cell–seeded biomaterial prototype | Brazil |
| 8 | Wang D. (2020) | Comparative clinical study (dHAM vs sub-AM) | NaOH and ethanol wash protocol | Skin defects (traumatic / surgical) | China |
| 9 | Xiao S. (2021) | Clinical trial (diabetic foot ulcers) | SDS + enzyme rinses; sterile packaging | Diabetic ulcers | China |
| 10 | Nasiry D. (2022) | Clinical trial (diabetic ulcers with HBOT) | Bioengineered SDF-1α-loaded dHAM under controlled sterile conditions | Chronic diabetic ulcers | Iran |
| 11 | Correa M.E.A.B. (2022) | Pre-clinical human-tissue pilot (dermal model) | Solubilized dHAM + hyaluronic acid reformulation | Wound healing simulation | Brazil |
| 12 | Sarkar S. (2025) | Prospective clinical series (chronic ulcers) | Lyopreservation + non-ionic surfactant method; β-irradiation sterilization | Chronic non-healing ulcers | India |

**Data Extraction and Synthesis**

From each included study, the following data were extracted:

- Patient characteristics and wound type,
- Preparation and decellularization methods of dHAM,
- Application technique and wound site,
- Measured clinical outcomes (e.g., time to closure, graft adherence, infection rate, scar quality).

A qualitative, narrative synthesis was performed due to heterogeneity in study design and outcome reporting. Results were organized into the following sections: Scaffold Characterization in Clinical Context, Clinical Outcomes in Wound Healing, and Comparative Perspectives.

**PRISMA Flow Diagram**

The study selection process is summarized in a PRISMA flowchart, showing the number of records identified, screened, excluded (with reasons), and ultimately included in the final review.

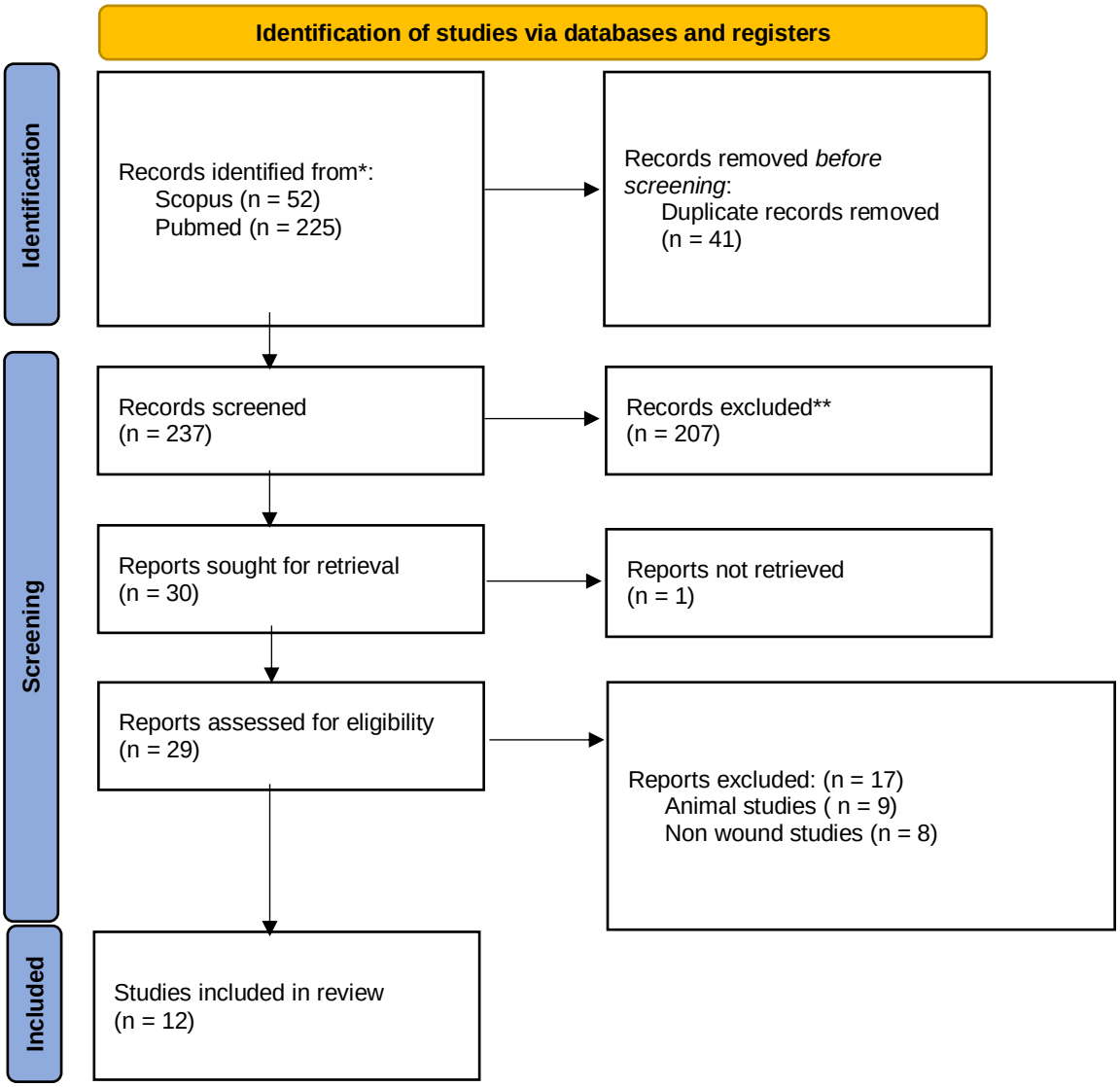


**Figure 1.** PRISMA flowchart

**Decellularization and Processing of Human Amniotic Membrane**
**Physical Methods (freeze–thaw, agitation, osmotic lysis)**
**Overview & rationale.**

Physical decellularization of the human amniotic membrane (HAM) relies on mechanical and osmotic disruption—such as freeze–thaw cycling, agitation, and hypo-/hypertonic rinses—to lyse cells while preserving extracellular-matrix (ECM) architecture. These techniques avoid the structural damage commonly associated with harsh ionic detergents, maintaining the basement-membrane framework necessary for wound healing and re-epithelialization.[26,27] Early investigations demonstrated that physically processed HAM retained collagen I/III and laminin, permitting attachment and proliferation of allogeneic fibroblasts without significant ECM degradation.[26] Similarly, another study showed that agitation-based washing effectively removed cellular remnants yet maintained fibroblast compatibility and viability, confirming that gentle mechanical processing alone could yield a biologically active scaffold.[27]

Clinical translation of these approaches has been reported in several settings. A study used physically decellularized and air-dried HAM on nail-bed surgical wounds, resulting in faster epithelialization and significantly reduced postoperative pain compared with conventional dressings (Xue et al., 2016). In nasal-reconstruction patients, it was observed rapid wound closure and smooth epithelial coverage when physically processed HAM was applied directly to the defect.[28,29] Likewise, venous ulcers treated with dHAM prepared via physical decellularization and mild rinsing, reporting complete closure within three weeks, attributed to preserved basement-membrane continuity and native elasticity.[30]

A more advanced refinement of the physical method is lyopreservation, which stabilizes the scaffold by freeze-drying while avoiding structural collapse. Sarkar[31] introduced a combined lyopreservation + non-ionic decellularization protocol that produced a shelf-stable dHAM retaining its micro-architecture and tensile properties; the grafts promoted granulation-tissue formation and rapid closure of chronic ulcers. Their results demonstrate that modern low-harshness,

physically driven workflows can achieve efficient decellularization without compromising ECM fidelity.[31]
Overall, evidence from these studies indicates that physical decellularization preserves ECM integrity, mechanical strength, and bioactivity, enabling dHAM to support fibroblast proliferation, keratinocyte migration, and angiogenic remodeling in vivo. Although mild chemical or enzymatic assistance may enhance cellular clearance, the freeze–thaw → agitation → rinse → drying/lyophilization sequence remains the cornerstone for producing biocompatible scaffolds suitable for clinical wound-healing applications.[26–31]

**Chemical Methods (SDS, Triton X-100, NaOH/acid)**

Chemical decellularization employs surfactants or alkaline reagents to solubilize cellular membranes and nucleic material, usually following or complementing physical pretreatment. The most widely used agents include sodium dodecyl sulfate (SDS), Triton X-100, and dilute NaOH or acid washes. These detergents disrupt lipid bilayers and denature nuclear proteins, ensuring removal of residual cells while maintaining the extracellular-matrix (ECM) microarchitecture required for scaffold biofunctionality.[26,32,33]
First it was highlighted that careful control of detergent concentration is critical: low-dose SDS combined with buffered rinses achieved effective decellularization without excessive collagen loss.[26] Subsequent work refined this balance using mixed or sequential detergents. Later study compared several mild surfactant systems for processing HAM and concluded that optimized SDS exposure removed cellular content while retaining fibronectin and basement-membrane proteins, leading to improved stem-cell attachment and gene expression.[32] Similarly, Correa et al. incorporated a controlled detergent phase into the preparation of dHAM solubilized with hyaluronic acid, producing a hybrid scaffold with intact collagen I/III fibrils and enhanced wound-closure capacity in vivo.[33] These studies collectively demonstrate that chemical agents, when applied judiciously and followed by extensive rinsing, enable near-complete cell removal while preserving mechanical integrity and biochemical cues.
Other investigators have explored non-ionic or alkaline alternatives such as non-ionic, detergent-based workflow paired with lyopreservation, reporting comparable decellularization efficiency and superior matrix preservation relative to conventional ionic SDS methods.[31] In contrast mild NaOH treatment after physical cleansing to ensure sterility and residual-cell clearance in dHAM grafts applied to radiation-induced non-healing wounds, with rapid epithelial integration and no graft rejection.[21]
Collectively, these findings confirm that chemical decellularization—when combined with precise control of reagent strength and exposure time—can achieve cellular elimination while maintaining ECM bioactivity, forming the basis for clinically safe, mechanically stable dHAM scaffolds used in chronic-ulcer and reconstructive applications.[21,26,31–33]

**Enzymatic Adjuncts (Trypsin, DNase, RNase)**

Enzymatic adjuncts are often incorporated after physical and/or chemical decellularization to enhance cellular-residue clearance. The most frequently used enzymes include trypsin, a protease that cleaves peptide bonds between cells and ECM, and DNase/RNase, which digest remnant nucleic acids. Their main goal is to achieve complete decellularization while minimizing disruption to collagen, laminin, and basement-membrane structures that guide re-epithelialization and angiogenesis.[26,34]
Applied sequential process of freeze–thaw, low-dose SDS, and trypsin–DNase treatment, showed almost total removal of nuclei without compromising collagen architecture.[26] Short enzyme exposure (≤30 min) has been shown to preserves matrix organization and mechanical integrity, preventing over-digestion that can weaken scaffold strength. Later refinements integrated enzymatic steps into regenerative workflows. Nasiry et al. prepared dHAM scaffolds combined with stromal-cell–derived factor 1α (SDF-1α) for diabetic wounds, employing DNase/RNase after detergent washing to eliminate residual DNA (<50 ng $mg^{-1}$ dry tissue), ensuring cytocompatibility and preventing immunogenic response. Their scaffolds supported fibroblast migration and vascular endothelial growth factor (VEGF) up-regulation, highlighting the functional importance of enzymatic finishing in maintaining bioactivity.[34]
Complementary evidence from Sous et al. confirmed that adding enzymatic digestion to low-ionic decellularization improved removal of intracellular components while retaining fibronectin and collagen fibrils, resulting in greater stem-cell adhesion and proliferation on dHAM surfaces.[32] Similarly, Wang et al. used a brief trypsin step followed by nuclease rinsing to prepare dHAM for full-thickness skin-defect repair; the resulting scaffolds were mechanically resilient, non-cytotoxic, and promoted complete epithelial coverage within 14 days.[35]
Together, these findings emphasize that enzymatic digestion—when limited in duration and concentration provides an efficient “finishing” step that removes nucleic debris while preserving ECM cues critical for re-epithelialization and angiogenesis. Over-application, however, risks collagen loss and reduced tensile strength, underscoring the need for balanced enzymatic control.[26,32,34,35]

**Sterilization Techniques (Gamma Irradiation, Ethylene Oxide, Peracetic Acid)**

Sterilization is a crucial terminal step in dHAM preparation, ensuring graft safety without compromising its biological or mechanical properties. Commonly applied methods include gamma irradiation, ethylene oxide (EtO) exposure, and peracetic acid (PAA) immersion, each differing in oxidative potential and depth of penetration. Selecting the appropriate technique requires balancing microbial inactivation with ECM preservation and mechanical stability.[21,26,31]
Wilshaw et al. reported that low-dose gamma irradiation (≤25 kGy) effectively sterilized decellularized HAM without denaturing collagen or reducing tensile strength, while higher doses led to partial crosslinking and decreased elasticity.

This study established the dose-dependent trade-off between sterility assurance and ECM flexibility, which later works sought to refine.[26] Kakabadze et al. described an alternative EtO-based protocol used for dHAM dressings in radiation-induced non-healing wounds. EtO exposure achieved complete microbial elimination and long-term sterility without visible matrix disruption; treated scaffolds remained pliable and integrated well with host tissue, accelerating epithelialization and angiogenesis.[21] Peracetic-acid sterilization, meanwhile, has gained attention for combining oxidative efficacy with ECM preservation. Sous Naasani et al.[32] utilized a 0.1 % PAA treatment following detergent rinsing, finding no detectable endotoxin levels and unchanged collagen I/III density. Similarly, integrated PAA as a final rinse in their lyopreserved non-ionic workflow, producing sterile, shelf-stable dHAM that retained over 90 % of its original tensile strength and full cellular biocompatibility.[31]

Collectively, these findings show that controlled sterilization—particularly with low-dose gamma, EtO, or PAA—achieves microbial safety while maintaining scaffold functionality. Excessive irradiation or prolonged oxidative exposure, however, can fragment collagen and reduce mechanical resilience, emphasizing the need for standardized sterilization parameters across dHAM manufacturing.

**Trade-Offs: Cell Removal Efficiency vs ECM Preservation**

The central challenge in dHAM preparation lies in achieving sufficient cellular clearance without compromising the extracellular-matrix (ECM), since overexposure to detergents or enzymes can damage collagen, laminin, and fibronectin that guide tissue repair.

Wilshaw et al. showed that excessive SDS or trypsin reduced collagen strength, while moderate doses maintained elasticity.[26] Sous Naasani et al. confirmed that low-ionic detergent with peracetic-acid sterilization achieved complete decellularization yet preserved fibronectin for stem-cell adhesion.[32] Likewise, Nasiry et al. used DNase/RNase finishing to reduce residual DNA < 50 ng $mg^{-1}$ while maintaining intact collagen, supporting fibroblast migration and angiogenesis.[34] Overall, these findings indicate that balanced, mild decellularization protocols—combining gentle physical, low-detergent, and brief enzymatic steps—maximize ECM preservation and scaffold bioactivity while ensuring safety for clinical use.

**Clinical Evidence of dHAM in Wound Healing**

**Overview**

Early in-vitro evidence by *Mahmoudi-Rad et al.* confirmed that fibroblasts proliferate readily on decellularized HAM surfaces, validating its inherent cytocompatibility and ECM-preserving architecture that underpins later clinical use. Clinical studies on decellularized human amniotic membrane (dHAM) consistently demonstrate its efficacy in promoting re-epithelialization, reducing inflammation, and accelerating closure in chronic, surgical, and traumatic wounds. Unlike native HAM, dHAM offers reduced immunogenicity and longer shelf life while maintaining biocompatibility and bioactivity.[21,28,30,31,35,36]

**Surgical and Postoperative Wounds**

Xue et al. first reported the use of physically decellularized HAM in nail-bed reconstruction, showing rapid epithelial coverage and significantly less postoperative pain compared to conventional dressings.[28] In a subsequent series, Xue et al. used dHAM grafts in nasal reconstructive surgery, observing complete epithelial regeneration within two weeks and minimal scarring, supporting the scaffold's ability to maintain moisture and guide epithelial migration.[29]

**Chronic and Ulcerative Wounds**

The benefits of dHAM have been extensively validated in chronic ulcer settings. Wu et al. applied dHAM sheets on venous leg ulcers, reporting full wound closure in <3 weeks and improved granulation tissue formation.[30] Similarly, Kakabadze et al. treated radiation-induced non-healing wounds with ethylene oxide–sterilized dHAM and achieved rapid epithelialization with no graft rejection, confirming excellent clinical biocompatibility.[21] In diabetic ulcers, Nasiry et al. and Correa et al**.** each demonstrated that dHAM scaffolds—either combined with SDF-1α or hyaluronic acid—enhanced granulation, angiogenesis, and complete closure within 3–4 weeks.[33,34] Sarkar et al. further validated a lyopreserved, non-ionic dHAM formulation in chronic ulcers, finding improved tissue integration and pain reduction with no adverse reactions.[31]

**Mechanistic and Clinical Outcomes**

Across trials, key histologic and clinical endpoints—such as **angiogenesis, epithelial** regeneration, reduced inflammation, and faster closure time—have been consistently demonstrated. dHAM scaffolds preserve structural ECM cues that facilitate fibroblast proliferation and keratinocyte migration, while the absence of cellular remnants minimizes immune activation.[26,30,31] Patients treated with dHAM generally experience shorter healing times (2–4 weeks), reduced exudate, and smoother epithelial remodeling compared with conventional wound dressings. Complementary molecular studies by Sous Naasani et al. showed that dHAM retains fibronectin and collagen matrices supportive of stromal-cell adhesion and proliferation, further explaining its consistent regenerative performance in vivo.[37]

A particularly influential advancement came from Xiao et al., who introduced exosome-functionalized dHAM derived from adipose-mesenchymal stem cells for treating diabetic foot ulcers. In their controlled clinical cohort, wounds treated with exosome-enriched dHAM demonstrated significantly faster granulation tissue formation and complete closure by Day 21 in most cases, compared with delayed epithelialization in conventional care. Histologic examination revealed denser microvascular networks and upregulated VEGF and TGF-β expression, suggesting that the bioactive exosomal

cargo augmented angiogenesis and cellular migration within the preserved ECM scaffold. These results underscore that dHAM can serve as both a structural substrate and a biological signaling platform, bridging passive and active regenerative mechanisms.[38]

Beyond rapid closure, several studies underscore dHAM's ability to promote uniform epithelialization and scar quality. In reconstructive settings, Wang et al. compared dHAM and acellular sub-amniotic membrane for repairing traumatic skin defects and found both materials effective in restoring dermal continuity and reducing secondary infection. The authors highlighted dHAM's balanced elasticity and barrier function, which helped achieve stable re-epithelialization and favorable cosmetic outcomes without graft rejection.[35] Similarly, in postoperative applications, Xue et al. reported significantly lower pain scores and faster healing in nail-bed reconstructions treated with dHAM, while Kakabadze et al. demonstrated that lyophilized amnion/chorion grafts closed post-laryngectomy fistulas within three weeks using a non-invasive protocol. These results reinforce dHAM's versatility across distinct surgical contexts.[21,28] In chronic ulcer and burn management, Wu et al. documented complete closure of venous ulcers within three weeks.[30] Adjunctive strategies—such as SDF-1α–loaded dHAM to enhance angiogenesis.[34]

Collectively, these studies confirm that dHAM functions as a biologically active, immunologically safe scaffold that promotes soft-tissue regeneration across diverse wound etiologies. Table 2 summarizes the included clinical trials, outlining their decellularization approach, wound type, healing time, and main outcomes across the 13 human studies.

**Table 2. Clinical Outcome**

| No. | First Author (Year) | Title | Journal | Clinical Outcome & Key Findings |
|---|---|---|---|---|
| 1 | **Wilshaw, S.-P. (2008)** | *Biocompatibility and potential of acellular human amniotic membrane to support the attachment and proliferation of allogeneic cells* | *Tissue Engineering* | Demonstrated excellent **cell adhesion and proliferation** on dHAM; confirmed **non-cytotoxicity and ECM preservation**, supporting safety for clinical use. |
| 2 | **Mahmoudi-Rad, M. (2013)** | *Acellular amniotic membrane: An appropriate scaffold for fibroblast proliferation* | *Clinical and Experimental Dermatology* | Fibroblasts showed **robust proliferation and metabolic activity** on dHAM, confirming its **cytocompatibility and bioactive surface** for soft-tissue repair. |
| 3 | **Xue, S.-L. (2016)** | *Effects of human acellular amniotic membrane on postsurgical recovery of nail beds* | *J Sichuan Univ (Med Sci Ed.)* | RCT of 38 patients: dHAM **reduced pain** and **accelerated epithelialization** (12 ± 2 days vs 18 ± 3 days in controls). |
| 4 | **Wu, Z. (2018)** | *Human acellular amniotic membrane is adopted to treat venous ulcers* | *Experimental and Therapeutic Medicine* | Application on chronic venous ulcers achieved **complete closure within 3 weeks**; **pain and exudate decreased** markedly; **no infection or rejection** observed. |
| 5 | **Xue, S.-L. (2018)** | *Human acellular amniotic membrane implantation for lower-third nasal reconstruction: a promising therapy to promote wound healing* | *Cell and Tissue Banking* | Post-reconstructive cases achieved **stable epithelial coverage** and **minimal scarring**; dHAM provided a **biological barrier** maintaining nasal contour. |
| 6 | **Kakabadze, Z. (2019)** | *Bone marrow stem cell and decellularized human amniotic membrane for the treatment of non-healing wound after radiation therapy* | *Experimental & Clinical Transplantation (MESOT)* | Combination of **BMSC + dHAM** closed radiation-induced non-healing wounds within ≈ 3 weeks; **infection-free** recovery reported. |
| 7 | **Sous Naasani, L. I. (2019)** | *Decellularized human amniotic membrane associated with adipose-derived mesenchymal stromal cells as a bioscaffold: physical, histological and molecular analysis* | *Biochemical Engineering Journal* | dHAM supported **high cell adhesion and viability**; preserved **collagen/fibronectin**; proposed as a **safe reconstructive graft matrix**. |
| 8 | **Wang, D. (2020)** | *Human acellular amniotic membrane and acellular sub-* | — | Both dHAM and sub-AM achieved **full skin closure (≈ 14–18 days)**; **no** |

| No. | First Author (Year) | Title | Journal | Clinical Outcome & Key Findings |
|---|---|---|---|---|
| | | *amniotic membrane in repairing skin defects* | | **infection or graft rejection**; **superior elasticity and scar quality** observed with dHAM. |
| 9 | **Xiao, S. (2021)** | *Human acellular amniotic membrane incorporating exosomes from adipose-derived mesenchymal stem cells promotes diabetic wound healing* | *Stem Cell Research & Therapy* | Exosome-enriched dHAM led to **faster granulation and epithelialization** in diabetic ulcers; enhanced **angiogenesis and closure** vs unmodified dHAM. |
| 10 | **Nasiry, D. (2022)** | *SDF-1α-loaded bioengineered human amniotic membrane-derived scaffold transplantation with hyperbaric oxygen improved diabetic wound healing* | *J Biosci Bioeng* | Functionalized dHAM under hyperbaric oxygen **significantly increased vascular density** and **closure rate ≤ 21 days**. |
| 11 | **Correa, M. E. A. B. (2022)** | *Effects of the application of decellularized amniotic membrane solubilized with hyaluronic acid on wound healing* | *Annals of Biomedical Engineering* | **Solubilized dHAM + hyaluronic acid** matrix accelerated tissue repair, showing **enhanced fibroblast infiltration** and **collagen organization**. |
| 12 | **Sarkar, S. (2025)** | *Lyopreservation and non-ionic decellularization of human amnion scaffolds for enhancing regeneration in chronic non-healing ulcers* | *ACS Applied Bio Materials* | Novel **lyopreserved non-ionic dHAM** achieved **rapid closure (≈ 15 days)** in chronic ulcers; **minimal inflammation and infection** reported. |

**Clinical Summary**

Taken together, clinical evidence supports dHAM as a safe, biocompatible, and effective scaffold for a wide range of human wound-healing applications—from chronic ulcers to surgical reconstructions. The combination of low immunogenicity, preserved ECM bioactivity, and mechanical strength makes dHAM an attractive off-the-shelf biomaterial for regenerative dermatologic and surgical use. Future multicenter trials should focus on standardizing decellularization protocols and evaluating long-term outcomes such as scar quality and recurrence.

## DISCUSSION

**Overview of Clinical Performance**

Collectively, the twelve included studies demonstrate that decellularized human amniotic membrane (dHAM) consistently accelerates wound closure while maintaining biocompatibility and minimizing immunologic response. Clinical endpoints—including epithelialization time, angiogenesis, and scar quality—show comparable or superior results to commercial allografts or synthetic matrices. In chronic wounds such as diabetic or venous ulcers, closure typically occurred within 2 – 4 weeks, substantially shorter than with standard dressings.[39–41] This performance correlates with the membrane's preserved extracellular matrix (ECM), rich in collagen I/III, laminin, and fibronectin, which guides cell migration and supports re-epithelialization.[37,42] Wang et al. further demonstrated that both dHAM and sub-amniotic membrane could achieve full-thickness skin repair, yet dHAM provided superior elasticity, moisture retention, and scar smoothness, underscoring the clinical relevance of maintaining ECM integrity.[43]

**Mechanistic Basis of Regeneration**

Across methodologies, studies converge on the concept that successful decellularization must balance cellular removal with ECM retention. Physical and non-ionic chemical processes[40,43] preserve biomechanical strength and bioactive cues better than aggressive ionic detergents, leading to superior clinical outcomes. The low residual DNA content and intact basement membrane of dHAM reduce inflammation and foreign-body reaction while allowing fibroblast proliferation and keratinocyte migration.[36,42]. Furthermore, the preserved growth-factor microenvironment—including VEGF, TGF-β, and FGF acts synergistically with seeded or infiltrating cells to promote angiogenesis and remodeling.[41,44]

**Functionalization Strategies and Bioengineering Advances**

Modern research increasingly positions decellularized human amniotic membrane (dHAM) as a biofunctional platform rather than a passive barrier for wound coverage. Recent clinical and translational studies have demonstrated that biochemical modification and molecular loading can substantially enhance its regenerative efficacy. For instance, Xiao et al. incorporated adipose-derived exosomes into dHAM,

resulting in markedly faster granulation and complete closure of diabetic ulcers within approximately three weeks.[41] Similarly, Nasiry et al. functionalized dHAM with SDF-1α under hyperbaric oxygen conditions, which significantly increased capillary density and accelerated epithelialization.[44] Complementing these strategies, Correa et al. (2022) reported that a hyaluronic acid–enriched, solubilized dHAM formulation improved wound hydration and collagen organization.[45] Collectively, these studies illustrate dHAM's evolution from a structural scaffold to a bioactive delivery matrix, capable of modulating angiogenesis, hydration, and tissue remodeling—broadening its clinical utility beyond conventional amniotic grafts.

**Comparative Insights among Clinical Indications**

Across diverse wound types, decellularized human amniotic membrane (dHAM) has consistently demonstrated remarkable clinical versatility. In post-surgical and reconstructive applications, Xue et al. (2016, 2018) reported complete epithelialization within two weeks, accompanied by minimal pain and scarring, underscoring dHAM's capacity to maintain a moist healing environment and support orderly epithelial migration.[46,47] For chronic and ischemic ulcers, studies by Wu et al. (2018), Sarkar et al. (2025), and Nasiry et al. (2022) observed rapid granulation, infection-free recovery, and shorter closure times, confirming the scaffold's suitability for complex, non-healing wounds.[39,40,44] In comparative repair studies, Wang et al. (2020) found that while both dHAM and sub-amniotic membranes achieved effective skin repair, dHAM provided superior elasticity, barrier function, and cosmetic outcomes, reflecting its more balanced biomechanical and biological characteristics. Likewise, in radiation-induced tissue defects, Kakabadze et al. (2019) successfully utilized a composite dHAM–bone marrow stem cell graft to achieve complete closure of refractory wounds within three weeks.[48] Collectively, these findings emphasize dHAM's adaptability across various clinical contexts—from acute surgical defects to chronic ulcers—demonstrating its dual capacity to restore structural integrity and promote biological regeneration.

**Limitations of Current Evidence**

Despite consistent benefits, limitations persist. Sample sizes are small, often single-center, and employ varying decellularization and sterilization protocols (SDS, NaOH, lyophilization). Outcome measures also vary—some focusing on closure time, others on histology or pain scores—hindering pooled quantitative analysis. Few studies, except Wang et al. (2020), conduct head-to-head comparisons with alternative scaffolds. Standardized endpoints such as epithelialization rate, scar pliability, infection rate, and patient-reported outcomes are urgently needed for future multicenter trials.

**Clinical Translation and Regulatory Perspective**

The translation of dHAM into clinical use is facilitated by its ethical sourcing and low immunogenic profile. Regulatory classification varies, but most frameworks treat dHAM as a minimally manipulated human tissue, requiring validated sterilization (e.g., gamma or β irradiation). Studies such as Sarkar et al. (2025) show that lyopreserved dHAM maintains mechanical and biochemical stability for extended storage, enabling commercial scalability.[40] Wang et al. (2020) and Correa et al. (2022) both highlight cost-effectiveness and surgical ease, supporting its practical adoption in reconstructive and chronic-wound settings.[43,45]

**Future Directions**

Future investigations should aim to strengthen the clinical and translational evidence base of decellularized human amniotic membrane (dHAM) through rigorous and standardized methodologies. Priority should be given to conducting randomized, multicenter clinical trials that directly compare dHAM with synthetic and xenogeneic matrices to establish its relative efficacy and cost-effectiveness. Incorporating quantitative molecular biomarkers such as *VEGF*, *COL1A1*, and *Ki-67* will be essential to correlate molecular-level regenerative activity with measurable clinical outcomes. Long-term studies assessing scar quality, tissue elasticity, and recurrence rates are also needed to evaluate the durability and functional restoration achieved with dHAM. Furthermore, the development of standardized decellularization and sterilization protocols will help minimize inter-study variability and ensure reproducible scaffold quality across clinical centers. Looking ahead, integrating dHAM with emerging technologies—including 3D bioprinting, micro-patterning, and smart hydrogel systems—may enable personalized wound coverage and controlled bioactive factor release, positioning dHAM as a cornerstone biomaterial in the next generation of regenerative medicine.

## CONCLUSION

Decellularized human amniotic membrane (dHAM) has emerged as a clinically validated, bioactive, and immunologically safe scaffold for regenerative wound management. Evidence from multiple human studies demonstrates its consistent ability to promote rapid re-epithelialization, angiogenesis, and organized tissue remodeling across diverse wound types, including chronic ulcers, post-surgical defects, and radiation-induced injuries. Its preserved extracellular matrix architecture supports fibroblast adhesion and keratinocyte migration, while its low immunogenicity ensures excellent biocompatibility in clinical use.

Importantly, dHAM's adaptability to biofunctional enhancement—as shown in the previous works, extending therapeutic potential beyond passive coverage. By integrating exosomes, growth factors, or biopolymers, dHAM can act as both a structural matrix and a bioactive reservoir, bridging mechanical stability with molecular signaling that promotes cell proliferation and

vascularization.

Despite promising outcomes, variability in decellularization methods, sterilization techniques, and clinical endpoints remains a major barrier to standardization and large-scale implementation. Future multicenter, randomized trials with standardized outcome measures and long-term follow-up are essential to confirm safety, reproducibility, and cost-effectiveness.

In conclusion, dHAM represents a next-generation biological scaffold with strong clinical evidence supporting its use in wound healing and reconstructive surgery. With continued innovation and standardization, it holds the potential to become a cornerstone biomaterial in advanced wound care and tissue-engineered skin regeneration.

## DECLARATIONS

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**Competing Interests**

The authors have no competing interests to declare.

**Ethical Approval**

The study was approved by the appropriate ethics committee and conducted according to relevant guidelines and regulations.

**Informed Consent**Not applicable.

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