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Impact of Hyaluronic Acid-Based Therapy on Burn Wound Healing

Abstract

Burn injuries are among the most complex forms of skin trauma, characterized by disruption of tissue integrity, excessive inflammatory response, increased risk of infection, and impaired healing that often leads to scarring and functional impairment. Despite advances in surgical and supportive care, effective strategies to optimize both the rate and quality of burn wound healing remain limited, prompting increasing interest in biomaterial-based regenerative approaches.

Hyaluronic acid (HA), a naturally occurring glycosaminoglycan of the extracellular matrix, has emerged as a multifunctional biomaterial with significant relevance in burn wound management. Its biological activity includes regulation of inflammation, promotion of cell migration and proliferation, stimulation of angiogenesis, and modulation of extracellular matrix remodeling. These effects are strongly influenced by molecular weight and receptor-mediated interactions, particularly via CD44 and RHAMM.

This work provides an overview of HA biosynthesis, biological functions, and its role in burn wound healing, with emphasis on its mechanisms of action and clinical applications. A broad

spectrum of HA-based systems is discussed, including topical formulations, hydrogels, impregnated dressings, dermal scaffolds, sponges, and combination therapies incorporating bioactive agents such as growth factors, polynucleotides, and platelet-rich plasma.
The literature suggests that HA-based therapies may beneficially influence multiple phases of wound healing; however, current evidence remains heterogeneous and limited by a lack of large-scale randomized controlled trials in burn populations. Further research is required to define their optimal clinical use.

Review methods. Data for this paper were gathered using electronic databases like PubMed and Google Scholar, with a focus on papers from the last five years, particularly clinical trials, double-blind randomized studies, meta-analyses, and reviews.

State of Knowledge: According to the World Health Organization (WHO), burns are responsible for an estimated 180,000 deaths annually, while non-fatal burn injuries frequently result in long-term morbidity and functional impairment. Despite advances in surgical management and critical care, current therapeutic strategies remain primarily focused on wound coverage and infection control rather than true tissue regeneration. This limitation has driven increasing interest in biomaterials capable of actively modulating the wound microenvironment and enhancing the quality of tissue repair. Among the promising approaches, the application of hyaluronic acid (HA) in burn wound management has attracted considerable attention. HA has been shown to exert multiple beneficial effects on the wound-healing process, including modulation of inflammation, promotion of cell migration and proliferation, stimulation of angiogenesis, and regulation of extracellular matrix remodeling. A wide range of HA-based products is currently available, including creams, ointments, wound dressings, hydrogels, sponges, scaffolds, and bioengineered skin substitutes. Clinical and experimental evidence supports the efficacy and safety of HA-based therapies, which are generally well tolerated by patients. Nevertheless, several limitations remain, including variability in formulation properties, relatively high production costs, and the need for further high-quality clinical studies to establish standardized treatment protocols.

Introduction and Objective

Burn injuries represent a significant clinical challenge due to their complex pathophysiology and systemic consequences. Depending on depth and extent, they may range from superficial epidermal damage to full-thickness destruction involving deeper tissues. In addition to local injury, severe burns trigger systemic responses such as hypermetabolism, immune

dysregulation, and microvascular impairment, all of which negatively affect wound healing and increase the risk of complications, including infection and sepsis. Despite advances in surgical management and critical care, current therapeutic strategies remain primarily focused on wound coverage and infection control rather than true tissue regeneration. This limitation has driven increasing interest in biomaterials capable of actively modulating the wound microenvironment and enhancing the quality of tissue repair.

Hyaluronic acid (HA) is a naturally occurring, non-sulfated glycosaminoglycan and a fundamental component of the extracellular matrix, widely distributed in skin, connective tissues, and synovial fluid. In physiological conditions, HA contributes to tissue hydration, structural integrity, and biomechanical stability of the extracellular matrix. Beyond its structural role, HA functions as a biologically active molecule involved in the regulation of key cellular processes relevant to wound healing. Due to its multifunctional profile, HA has become an important biomaterial in modern regenerative medicine and wound care.

The aim of this work is to present a comprehensive overview of the role of hyaluronic acid in burn wound healing, including its biological functions, mechanisms of action, and applications in contemporary biomaterial-based therapeutic systems.

1. Burn injuries. Represent some of the most complex and clinically challenging skin lesions, posing substantial therapeutic difficulties. Their management is complicated not only by the inherently protracted and intricate healing process, which is associated with a markedly increased risk of infection, but also by the profound impact on both functional and aesthetic outcomes of the affected tissue. Even in cases of uncomplicated healing, resulting scars may constitute significant functional or cosmetic deficits, adversely affecting patients' daily activities and overall quality of life [1]. When the healing process is disrupted, patients face an elevated risk of severe wound infections, which may necessitate systemic antibiotic therapy and, in extreme instances, can culminate in limb amputation or sepsis.

Consequently, burn wounds represent a major clinical concern, yet their significance is frequently underappreciated in routine medical practice. Despite substantial advances in modern medicine, effective and reliable therapeutic strategies for optimizing burn wound repair remain limited [2, 3].

Recent research has increasingly focused on innovative approaches to enhance wound healing, among which hyaluronic acid (HA) has emerged as particularly promising.

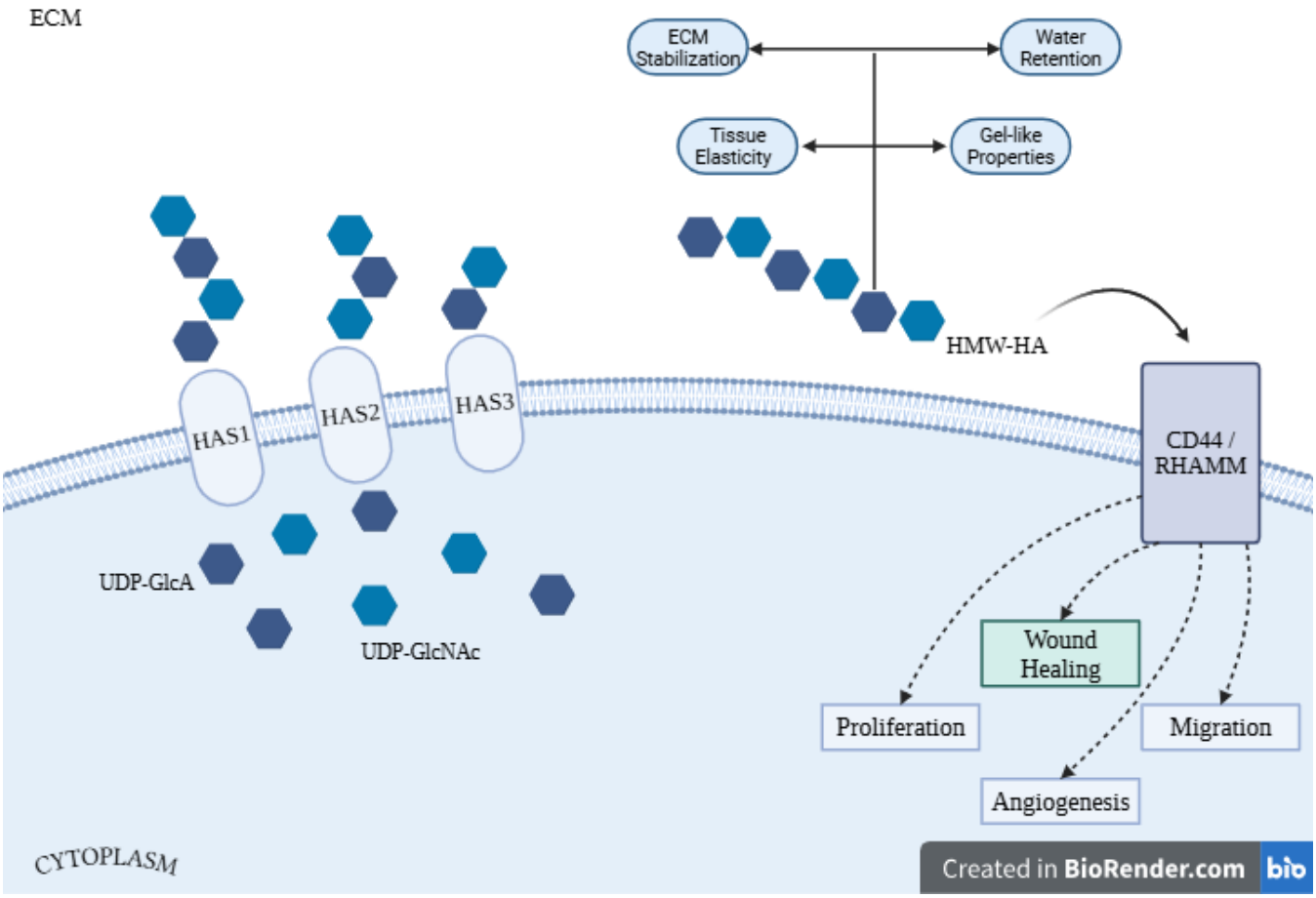
HA, a naturally occurring glycosaminoglycan abundantly present in human skin, contributes not only to tissue hydration and structural integrity but also plays a fundamental role in orchestrating wound repair and tissue regeneration [4]. Due to its biocompatibility and minimal immunogenicity, HA is well-suited for clinical application. Its multifaceted biological activities - including modulation of inflammatory responses, promotion of cellular migration, and facilitation of extracellular matrix remodeling - underpin its therapeutic potential in burn wound management [4, 1].

Clinical observations indicate that HA-based dressings improve healing outcomes in partial-thickness burns, leading to faster wound closure, reduced infection rates, and improved cosmetic results [1]. Preclinical studies have further demonstrated that HA functionalization of polymeric nanoparticles enhances targeted dermal delivery, promoting tissue regeneration and accelerating the healing process compared with non-functionalized controls [4, 5].
Although current clinical and experimental evidence is encouraging, larger, rigorously designed randomized controlled trials are still required to confirm the efficacy, safety, and long-term benefits of HA-based interventions in burn wound treatment and to establish standardized therapeutic protocols [1-5].

2. HA biosynthesis.

Hyaluronic acid (HA) is a non-sulfated, linear glycosaminoglycan composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine, widely distributed in connective tissues, skin, synovial fluid, and the extracellular matrix (ECM) of most organs [6, 7].
The biosynthesis of HA requires two activated sugar nucleotides: UDP-glucuronic acid (UDP-GlcUA) and UDP-N-acetylglucosamine (UDP-GlcNAc). These precursors are generated through interconnected metabolic pathways originating from glucose. UDP-GlcUA is synthesized from UDP-glucose via UDP-glucose dehydrogenase, whereas UDP-GlcNAc is produced through the hexosamine biosynthetic pathway from fructose-6-phosphate [8, 9].
HA synthesis is catalyzed by hyaluronan synthases (HAS1, HAS2, and HAS3), which are integral membrane glycosyltransferases localized in the plasma membrane. These enzymes mediate the alternating addition of UDP-GlcUA and UDP-GlcNAc to the growing polysaccharide chain [10]. Structural and biochemical studies have demonstrated that HAS enzymes function as processive glycosyltransferases, coordinating substrate binding, polymer elongation, and translocation through a membrane-embedded channel [10]. Despite their

conserved function, HAS isoforms differ in enzymatic activity and product characteristics. HAS2 is considered the predominant isoform in most tissues and plays a critical role in development and tissue integrity, whereas HAS1 exhibits lower catalytic efficiency. HAS3, in contrast, typically produces HA with lower molecular weight, which is associated with distinct



biological effects [11].

Diagram 1 Hyaluronian Biosynthesis and Its Biological Functions

A defining feature of HA biosynthesis is its coupling with translocation across the plasma membrane. The polymer is synthesized at the cytoplasmic face of the membrane and simultaneously extruded into the extracellular space through the HAS-associated channel [10]. This mechanism distinguishes HA from other glycosaminoglycans, which are synthesized in the Golgi apparatus and secreted via vesicular transport. The direct extrusion of HA enables rapid remodeling of the pericellular matrix and immediate participation in cell signaling and matrix organization [8].

HA biosynthesis is regulated at multiple levels, including the control of HAS gene expression,

substrate availability, post-translational modifications and external factors such as cytokines and growth factors (e.g., TGF-β, PDGF).

Consequently, HA production is tightly linked to cellular metabolism. Fluctuations in glucose availability or metabolic reprogramming - such as those observed under hypoxia or in rapidly proliferating cells - can significantly influence HA synthesis [9, 12]. Increased HA synthesis is observed during wound healing, inflammatory processes, and in tumors, where it plays an important role in cell migration and proliferation [13, 14]. In particular, inflammatory mediators, oxidative stress, and hypoxic conditions have been shown to modulate HAS expression and activity [11, 12]. Additionally, metabolic regulation plays a crucial role, as intracellular levels of UDP-sugar precursors directly determine HA synthesis rates.

3. HA functions.

HA plays a fundamental role in tissue homeostasis, regeneration, and pathological processes [15,8]. During tissue repair, HA contributes to the formation of a provisional extracellular matrix, facilitating cell migration, proliferation, and angiogenesis [15,16]. Furthermore, HA biological activity is strongly dependent on molecular weight. High-molecular-weight HA (>1000 kDa) is generally associated with anti-inflammatory and tissue-protective effects, whereas fragmented, low-molecular-weight HA (<500 kDa) and oligosaccharides (<10 kDa) can act as danger-associated molecular patterns (DAMPs), promoting inflammatory and pro-angiogenic signaling [15,16,17].

Table 1 Functions of HA Depending on Molecular Size

HA Type	Molecular Weight	Main Biological Functions	Notes / Mechanisms
HMW-HA (High-Molecular-Weight)	> 1,000 kDa	• ECM stabilization • Tissue hydration and elasticity • Anti-inflammatory effects • Protection against tissue damage	Produced mainly by HAS2; Forms gel-like network in ECM; Suppresses immune activation
MMW-HA (Medium-Molecular-Weight)	100–1,000 kDa	• Intermediate roles in tissue repair • Modulation of cell signaling	Can act as a precursor for LMW fragments; Partially pro-inflammatory depending on context
LMW-HA (Low-Molecular-Weight)	10–100 kDa	• Pro-inflammatory signaling • Induction of angiogenesis • Activation of immune cells	Generated by HYAL2/HYAL1 degradation; Binds CD44/RHAMM to trigger signaling pathways
Oligo-HA	< 10 kDa	• Strong immunostimulatory effects • Activation of cytokine production • Modulation of wound healing	Acts as DAMP (damage-associated molecular pattern); Strongly activates TLR2/4 receptors

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HA exhibits remarkable hygroscopic properties, capable of binding large amounts of water (up to several thousand times its weight), forming a viscoelastic hydrogel that provides tissue hydration, mechanical cushioning, and structural support in both physiological and regenerative processes [18].

4. Burn injuries classification

Burn injuries are primarily classified based on the depth of skin and tissue damage, a factor that is critical for determining appropriate treatment strategies and predicting scar quality. The most widely used classification system categorizes burns as superficial (first-degree), partial-thickness (second-degree), full-thickness (third-degree), and those involving subcutaneous and deeper structures (fourth-degree) [19,20]. This classification is anatomically oriented, reflecting the extent of damage to specific layers of the skin, ranging from the epidermis, through the dermal layers, to the subcutaneous tissue and underlying structures [19,20].

The extent of burn injuries is commonly quantified using the Parkland method, which estimates the percentage of total body surface area (TBSA) affected.

First-degree burns involve only the epidermis. They are characterized by erythema and pain without blister formation. Healing typically occurs within several days and generally does not result in scar formation [19].

Second-degree burns extend through the epidermis into the dermis. These injuries are further subdivided into superficial partial-thickness burns, primarily affecting the papillary dermis, and deep partial-thickness burns, which extend into the reticular dermis and may involve sweat glands and hair follicles [20]. Clinically, these wounds present with blisters, moist surfaces, and significant pain. Healing occurs with scar formation and typically requires 10-14 days.

Third-degree burns involve the entire thickness of the skin and often extend into the subcutaneous tissue. These wounds are characterized by a dry, waxy, or leathery appearance with variable coloration and do not blanch under pressure due to destruction of blood vessels and nerve endings. Given the loss of the skin's intrinsic healing capacity, these burns generally necessitate surgical intervention and skin grafting [19,21].

Fourth-degree burns extend beyond the skin into subcutaneous tissue, muscles, tendons, and occasionally bone. These injuries result in tissue charring, and patients typically do not experience pain due to nerve destruction. The wounds appear black and require immediate surgical management. In such cases, the risk of systemic complications and long-term functional impairment is high [19,21].

In clinical practice, classification also considers the etiology of the burn, including thermal, chemical, electrical, and radiation burns. Accurate assessment of burn depth and extent is essential for treatment planning and prognosis. By evaluating both the depth and surface area of the injury, clinicians can more precisely tailor therapeutic interventions and determine the most appropriate course of action, including conservative versus surgical management, as well as the use of advanced biomaterials to support wound healing [19,20].

5. Challenges in the Management of Burn Wounds

The management of burn wounds remains a significant clinical challenge due to the complex interplay of local tissue destruction, systemic metabolic perturbations, immune dysregulation, and heightened susceptibility to infection, distinguishing it from other forms of skin injury. Thermal trauma disrupts the integumentary barrier, a primary defense against microbial colonization. Loss of this protective barrier facilitates rapid microbial invasion and promotes the establishment of polymicrobial communities and biofilms within the wound bed. Biofilms confer enhanced tolerance to antimicrobial agents and host immune effectors, impeding bacterial clearance and prolonging the inflammatory milieu, thereby delaying wound resolution

[22, 23].

Moreover, thermal trauma gives rise to an intricate biological microenvironment saturated with burn wound exudate (BWE) - a fluid-replete milieu characterized by a highly distinct metabolomic and cellular architecture. The intricate biochemical composition and specialized cellular dynamics inherent to this BWE create a fertile substrate and a selective ecological niche, fostering the rapid colonization and proliferation of opportunistic pathogens endowed with extensive metabolic plasticity. [14]. The predominant etiological agents isolated from these lesions include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Acinetobacter baumannii*.These opportunistic pathogens are ubiquitous within nosocomial environments; their clinical eradication from the wound bed remains profoundly challenging due to their potencially multidrug-resistant (MDR) phenotypes, often exacerbated by the systemic immunosuppression characteristically exhibited by severely burned patients [22].

Prophylaxis against microbial colonization and the definitive eradication of bacterial biofilms constitute paramount therapeutic objectives in the clinical management of burn wounds. In patients with severe burns involving more than 40% of the total body surface area (TBSA), up to 75% of all deaths have been attributed to sepsis secondary to burn wound infections and/or infectious and inhalation-related complications. [22] However, the contribution of infection to burn-related mortality varies depending on burn severity, patient population, and advances in critical care, with reported proportions ranging from approximately 50% to 70% in modern clinical settings [24, 25].

In the acute post-injury phase, burn wounds elicit a robust inflammatory response that initially serves to clear necrotic tissue and recruit immune effector cells. However, excessive or prolonged inflammation contributes to secondary tissue injury, delays progression to the proliferative phase of healing, and promotes a dysregulated extracellular matrix remodeling environment. Dysregulated production of pro-inflammatory cytokines (including TNF-α, IL-1β, and IL-6) and reactive oxygen species (ROS) within the burn wound microenvironment drives ongoing extracellular matrix degradation and impairs re-epithelialization [21,26].

Beyond local inflammation, severe burns induce a systemic hypermetabolic response characterized by increased energy expenditure, enhanced proteolysis, insulin resistance, and profound endocrine alterations. This metabolic stress increases nutritional demands while simultaneously impairing nutrient utilization, thereby limiting cellular proliferation, angiogenesis, and collagen synthesis essential for effective wound repair. Inadequate metabolic support in this context further contributes to immunosuppression and malnutrition, collectively compromising the regenerative capacity of the organism [21].

Another critical barrier to effective healing in burn wounds is microvascular dysfunction and tissue hypoxia within both the central burn zone and the surrounding zone of stasis. Disruption of dermal microcirculation limits perfusion, reduces oxygen and nutrient delivery to viable tissues, impairing the migration of keratinocytes and fibroblasts into the wound bed. Sustained hypoxia promotes anaerobic metabolism and may lead to progressive tissue necrosis, a process known clinically as "burn wound conversion," which complicates early wound assessment and often necessitates surgical debridement of non-viable tissue [21].

Severe burns are also associated with systemic immune dysregulation, including impaired neutrophil and lymphocyte function, which increases susceptibility to sepsis and multi-organ dysfunction syndrome. The interaction between local wound repair mechanisms and systemic immune responses is therefore critical but frequently disrupted in major burn injury [26].

Finally, even after re-epithelialization, burn wounds are prone to abnormal extracellular matrix remodeling characterized by excessive collagen deposition and persistent myofibroblast activity. These processes underlie the development of hypertrophic scars and contractures, which not only compromise aesthetic outcomes but also result in significant functional impairment and may necessitate further surgical intervention and prolonged rehabilitation [21].

Collectively, these factors - barrier disruption and infection risk, persistent inflammation, metabolic and immune dysregulation, microvascular hypoxia, and aberrant remodeling - illustrate why effective management of burn wounds remains a major clinical challenge, despite advances in surgical techniques, wound care technologies, and supportive therapies.

6. Benefits of HA

In advanced biomaterial engineering and regenerative medicine, hyaluronic acid (HA) represents a highly versatile glycosaminoglycan that extends beyond its traditional role as a structural component of the extracellular matrix**.** Its biological functionality arises from the synergistic interaction between distinctive physicochemical properties and receptor-mediated cellular signaling, particularly via CD44 and RHAMM pathways [27].

On a macroscopic level, its extraordinary viscoelastic and hygroscopic properties enable the formation of an ideal, homeostatically regulated fluid matrix that mechanically stabilizes the extracellular microenvironment. [28]

On a molecular level, hyaluronic acid (HA) acts as a biologically active ligand capable of engaging specific cell surface receptors, including CD44, RHAMM, and other HA-binding proteins, thereby initiating and modulating intracellular signaling cascades involved in tissue repair. Through these receptor-mediated interactions, HA influences key cellular processes

such as migration, proliferation, angiogenesis, and the regulation of inflammatory responses, all of which are essential for coordinated wound healing. [29, 30]

Importantly, these biological effects are strongly dependent on HA molecular weight distribution, which critically determines its functional role within the tissue microenvironment. High-molecular-weight HA is generally associated with anti-inflammatory and homeostatic functions, whereas lower-molecular-weight fragments often act as bioactive signals that can promote inflammatory and regenerative responses. Consequently, HA dynamically contributes to the temporal regulation of wound healing, supporting the transition between inflammatory, proliferative, and remodeling phases. [31, 28]

As a result, HA plays an integral role in the coordinated orchestration of wound repair processes, including controlled inflammatory modulation, tissue regeneration, and extracellular matrix remodeling. This multifaceted biological activity underlies its extensive investigation as a functional biomaterial in regenerative medicine and tissue engineering, particularly in strategies aimed at optimizing soft tissue repair and restoration [28]

Modulation of Inflammation. Inflammation is a central component of the wound-healing process, particularly in burn injuries where it tends to be disproportionately intense and prolonged, frequently delaying subsequent reparative phases and promoting pathological scarring. In burn wounds, the magnitude and duration of the inflammatory response are driven by abundant damage-associated molecular patterns (DAMPs), oxidative stress, and persistent cytokine production, which together, these factors contribute to a microenvironment that may promote secondary tissue injury, delay progression to the proliferative phase, and increase the risk of infection and pathological scar formation.This excessive inflammatory milieu not only prolongs healing but also predisposes wounds to chronicity and infection [32,33].

Hyaluronic acid (HA) has been implicated in the regulation of inflammatory processes through both its physicochemical properties and receptor-mediated signaling pathways. In the context of inflammation, HA interacts with cell surface receptors such as CD44 and Toll-like receptors (e.g., TLR2/TLR4), thereby influencing leukocyte behavior and cytokine expression in a context-dependent manner. High-molecular-weight HA (HMW-HA) is generally associated with anti-inflammatory effects and has been shown to modulate immune cell activation and reduce the production of pro-inflammatory mediators such as TNF-α and IL-1β, and other mediators implicated in prolonged tissue injury [32,6]. Conversely, controlled generation of low-molecular-weight HA (LMW-HA) fragments during early tissue injury may transiently stimulate inflammatory signaling pathways that contribute to debris clearance and host defense, although these effects appear to depend on fragment size, concentration, and local tissue

conditions, illustrating HA's dual regulatory capacity depending on molecular size and wound stage [33,6].

HA's physicochemical ability to maintain a hydrated extracellular environment may reduce desiccation-related cellular stress and limit further inflammatory amplification. Hydrated tissues exhibit less mechanical stress and reduced leukocyte adhesiveness, contributing to diminished local inflammation. Furthermore, through its interactions with extracellular matrix components and signaling molecules, HA may also influence the local availability and activity of growth factors and chemokines. It helps stabilize the wound microenvironment and orchestrate a shift from pro-inflammatory to pro-healing signaling networks as early inflammation resolves [32,34].

In preclinical and translational contexts, Evidence from preclinical studies and selected translational investigations suggests that HA-based interventions may be associated with reduced inflammatory marker expression, decreased neutrophil infiltration, and earlier progression toward the proliferative phaseof healing compared with wounds lacking HA support. These observations underscore how these findings indicate that HA functions not only as a structural component of the extracellular matrix but also as a biologically active regulator of the wound microenvironment. It influences immune cell recruitment, cytokine gradients, oxidative stress, and tissue hydration in ways that collectively foster a more regulated inflammatory response and improved healing trajectory [32,33,6,34].

Hyaluronic Acid–Mediated Enhancement of Cell Migration and Proliferation. Efficient re-epithelialization and granulation tissue formation are essential components of effective burn wound healing. These processes are fundamentally dependent on the directed migration and proliferation of multiple cell types, including keratinocytes, dermal fibroblasts, endothelial cells, and mesenchymal progenitors. Thermal injury disrupts the extracellular matrix (ECM) architecture and creates a microenvironment that impairs cellular motility, reduces proliferative responsiveness, and hinders coordinated cell signaling. The sum of these factors contribute to delayed wound closure and increased risk of chronic wound development [32,33]. Hyaluronic acid (HA), a glycosaminoglycan ubiquitously present in the ECM, has been shown to contribute to the regulation of these cellular processes during tissue regeneration in these critical cellular processes during tissue regeneration [32,33,6]. At the biochemical level, HA interacts with cell surface receptors such as CD44, which is expressed on keratinocytes and fibroblasts, and with other co-receptors involved in mechanotransduction and cytoskeletal organization. This interaction has been associated with modulation of intracellular signaling pathways, including MAPK and Rho GTPase signaling, which are involved in the regulation of actin polymerization

[32,33]. The engagement of CD44 by HA also may facilitate integrin clustering and enhances cell adhesion dynamics, enabling cells to traverse provisional ECM more effectively. This is particularly important at the leading edge of epithelial wounds where matrix integrity is compromised [32,33].

In addition to receptor-mediated signaling, HA's hydrated, viscoelastic matrix supports a moist wound environment that is permissive for cell motility. Cell migration assays and in vitro studies have generally shown that HA can enhance keratinocyte and fibroblast migration across wound surfaces. This facilitation is achieved, in part, by reducing the physical barriers associated with desiccation and fibrin scab formation. A study utilizing keratinocyte cell lines showed increased migration and proliferative responses in the presence of high-molecular-weight HA, as evidenced by elevated expression of growth factors such as VEGF and increased migratory capacity in scratch wound assays [35]. These effects appear to be dose- and molecular-weight dependent. High molecular weight HA has been reported to promote more robust proliferative and migratory responses under physiological conditions [35]. HA also contributes to growth factor modulation within the wound microenvironment, by binding and stabilizing cytokines and growth factors. Specifically, mediators such as transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF). HA may influence the local availability and activity of these signaling molecules through interactions within the extracellular matrix, potentially supporting mitogenic and chemotactic signaling involved in cell recruitment and proliferation [33,6]. This mechanism is particularly relevant in burn wounds, where endogenous growth factor gradients can be disrupted by thermal denaturation and proteolysis.

Further evidence from recent preclinical studies suggests that HA incorporation into biomaterials and ECM analogs has been associated with enhanced cell proliferation and migration in vivo and with accelerated wound closure and improved tissue organization of regenerating tissue [32,33,6]. These findings support the concept that HA not only contributes to tissue hydration but may also influence cellular behavior through interactions with extracellular and intracellular signaling pathways. Together, these factors promote effective tissue regeneration.

Hyaluronic Acid and Angiogenesis. Angiogenesis (the formation of new blood vessels from existing vasculature) is an essential step in the proliferative phase of wound healing, particularly in burn injuries. Effective angiogenesis restores oxygen and nutrient delivery to hypoxic tissues, supports fibroblast and keratinocyte function, and enables granulation tissue to replace necrotic matrices. In burn wounds, microvascular disruption and prolonged hypoxia are key barriers to

angiogenic progression, impairing reparative processes and leading to chronic wounds or defective healing [32,36].

Hyaluronic acid (HA) has emerged as an important modulator of angiogenic responses. It is capable of influencing both vascular endothelial cell behavior and the local expression of angiogenic growth factors. HA exists as a heterogeneous population of polymers with a wide range of molecular weights, and its angiogenic activity is molecular weight-dependent. Low-molecular-weight HA (LMW-HA) fragments are generally associated with pro-angiogenic activity, including enhanced endothelial proliferation and sprouting, whereas HMW-HA is more commonly associated with tissue homeostasis and matrix stabilization [32,7].

Recent literature highlights that LMW-HA fragments can interact with endothelial cells via receptors such as CD44 and RHAMM This interaction has been associated with activation of intracellular signaling pathways, including MAPK and PI3K/AKT signaling, which may contribute to the upregulation of pro-angiogenic genes, including that of vascular endothelial growth factor (*VEGF*) and other mediators essential for capillary morphogenesis. These signaling events have been reported to promote endothelial cell proliferation, migration, and tube formation, all critical steps in neovascularization within the wound bed [32]. These effects are particularly relevant in the hypoxic microenvironments characteristic of burn wounds, where effective angiogenesis is necessary to overcome oxygen diffusion limitations and support tissue regeneration.

Moreover, HA's role in regulating the local concentrations of growth factors augments angiogenic signaling. Through its interactions with extracellular matrix components and signaling molecules, HA may influence the local availability and activity of growth factors such as VEGF and FGFs, thereby supporting angiogenic signaling within the wound microenvironment. This growth factor stabilization contributes to the amplification of angiogenic cascades and supports a sustained angiogenic response needed for adequate granulation tissue formation [32,36].

In addition to molecular interactions, HA's hydration properties influence angiogenesis indirectly by maintaining a moist wound environment that favorably alters interstitial pressure gradients, promoting endothelial cell infiltration and sprouting. A hydrated extracellular matrix may support molecular transport and cell migration within the wound environment, further mitigating hypoxic stress and improving the functional integration of newly formed microvessels [32,36].

Translational and mechanistic studies in cutaneous wound models (inclusive of wounds with

burn-like hypoxic conditions) have reported that HA administration, particularly when optimized for molecular weight distribution, correlates with increased microvessel density and enhanced angiogenic marker expression compared with controls lacking HA support. These findings support the concept that HA is not merely a passive matrix component but may function as a biologically active regulator of angiogenic responses during wound repair that helps coordinate vascular responses essential for effective burn wound repair [32,7].

Hyaluronic Acid in Extracellular Matrix Remodeling. Extracellular matrix (ECM) remodeling is a critical determinant of functional and aesthetic outcomes in burn wound healing. Following the inflammatory and proliferative phases, the ECM undergoes dynamic restructuring to restore tissue architecture, mechanical stability, and tensile strength. In burn injuries, thermal insult causes extensive ECM denaturation, collagen fragmentation, and disruption of glycosaminoglycan networks, resulting in impaired scaffold function and abnormal deposition of fibrotic tissue. These alterations can lead to hypertrophic scarring, contractures, and compromised dermal elasticity [32,33].

Hyaluronic acid (HA) plays a multifaceted role in ECM remodeling, acting both as a structural component and as a regulator of cellular behavior. HA contributes to the hydration and viscoelasticity of the ECM, providing a scaffold that facilitates fibroblast infiltration, orientation, and deposition of collagen and other ECM proteins. High-molecular-weight HA contributes to tissue integrity and matrix organization, whereas its degradation products may exert distinct biological activities depending on their molecular size, whereas controlled fragmentation of HA generates bioactive fragments that may influence fibroblast proliferation, migration, and extracellular matrix synthesis [32,6].

HA also modulates ECM remodeling through receptor-mediated signaling, predominantly via CD44 and RHAMM on fibroblasts and mesenchymal progenitor cells. Engagement of these receptors has been associated with activation of intracellular signaling pathways, including MAPK/ERK and PI3K/AKT signaling, which may contribute to the regulation of collagen, fibronectin, and glycoprotein synthesis during matrix remodeling. HA has been reported to influence matrix metalloproteinase (MMP) expression and activity, thereby contributing to the balance between ECM degradation and deposition, a process essential for preventing excessive fibrosis or persistent ECM disorganization [32,34].

Another key function of HA in ECM remodeling is its ability to modulate mechanical cues within the wound bed. The hydrated HA-rich matrix may influence local mechanical properties of the wound environment, including tissue stiffness and cellular mechanotransduction influencing fibroblast phenotype and potentially limiting excessive myofibroblast

differentiation associated with fibrotic remodeling. This mechanical modulation may contribute to a reduced of hypertrophic scar formation and supports more organized collagen alignment. Ultimately, this optimization improves the biomechanical properties, architectural integrity, and aesthetic outcomes of the healed tissue [33,34].

Preclinical studies in burn and full-thickness wound models have demonstrated that HA-enriched scaffolds enhance ECM deposition and remodeling. By doing so, HA-enriched scaffolds have been associated with improved dermal architecture restoration and reduced scar formation in preclinical models. Incorporation of HA into biomaterials may influence the local retention and activity of growth factors such as TGF-β1 and VEGF, which synergistically stimulate fibroblast activity and angiogenesis. The resulting benefit is supporting coordinated tissue reconstruction [32, 6, 34]. These findings suggest that HA is not merely a passive ECM filler but an active modulator of ECM homeostasis, regulating both biochemical and biomechanical signals to optimize burn wound repair.

7. Hyaluronic Acid-Based Preparations in Burn Wound Management

The clinical application of hyaluronic acid (HA) in burn wound care has evolved from simple topical supplementation toward a spectrum of structurally and biologically engineered delivery systems. Contemporary wound management no longer treats HA as a single active compound, but rather as a platform material whose therapeutic performance is determined by its molecular weight, formulation type, degree of chemical modification, and integration with other bioactive agents.

In burn injuries, where tissue architecture is disrupted across multiple layers and the inflammatory response is both intense and prolonged, the selection of an appropriate HA-based formulation is highly dependent on wound depth, exudate level, and the regenerative potential of the residual tissue. As a result, HA is currently available in multiple clinically distinct forms, ranging from low-viscosity topical creams and hydrogels designed for superficial injuries, to cross-linked scaffolds and bilayer dermal substitutes intended for deep partial-thickness and full-thickness burns.

Importantly, these formulations differ not only in physical structure but also in their biological function. While simple sodium hyaluronate preparations primarily act through hydration and facilitation of keratinocyte migration, more advanced esterified or cross-linked HA matrices function as temporary extracellular scaffolds, actively guiding cellular infiltration, angiogenesis, and dermal remodeling. In addition, combination systems incorporating antimicrobial agents, growth factors, or platelet-derived components further extend the

therapeutic role of HA from passive wound coverage to active modulation of the wound microenvironment.

Given this functional heterogeneity, a structured classification of HA-based preparations is necessary to accurately interpret their clinical utility in burn care. The following section therefore outlines the principal categories of HA-containing products used in burn management, together with their material composition, mechanism of action, and evidence-based clinical indications.

HA forms:

- Topical HA formulations → Ialuset® (0.2% sodium hyaluronate cream)/Connettivina Plus®
- Hydrogels dressings → Hyalofill-F®/ Hylase Wound Gel®
- HA-Impregnated Gauze and Tulle Dressings → Hyalofill®/Prosorb/Zelaffin
- Dermal scaffolds/ skin substitutes → Hyalomatrix®/ Laserskin®
- Sponges / composite dressings → HylaSponge®
- HA + bioactive combinations:

  a. HA + Platelet-Rich Plasma (PRP) systems → HA+PRP gel

  b. HA + polynucleotides (PN-HA gels) → Nucliaskin S™

  c. HA + antibiotics / antiseptics → Connettivina Plus®

Burn Degree	HA Forms	Exaples
I°	▪ Topical HA ▪ Hydrogels dressings ▪ HA-Impregnated Gauze and Tulle Dressings	Ialuset®
II°a	▪ Topical HA ▪ Hydrogels dressings ▪ HA-Impregnated Gauze and Tulle Dressings	Ialuset®, Hyalofill-F®
II°b	▪ Scaffolds	Hyalomatrix®, Laserskin®
III°	▪ Dermal substitute + Graft Support	Hyalomatrix® + STSG

Table 2 Burn Degree and HA Forms

Topical Hyaluronic Acid in Burn Wound Management. Topical hyaluronic acid (HA) is one of the most widely used and clinically accessible biomaterials in wound and burn care,

particularly in the management of superficial and partial-thickness burns. Unlike advanced scaffold-based systems or tissue-engineered constructs, topical HA formulations - including creams, gels, and sprays - exert their therapeutic effects primarily through physicochemical modulation of the wound microenvironment rather than direct structural tissue replacement. Their clinical utility is associated with the maintenance of tissue hydration, promotion of re-epithelialization, reduction of pain, and regulation of inflammatory responses during the healing process.

Burn wounds are characterized by disruption of the epidermal barrier, increased transepidermal water loss, inflammatory cell infiltration, and exposure of nociceptive nerve endings. In such conditions, maintenance of a moist wound environment is essential for effective tissue repair. Hyaluronic acid acts as a highly hygroscopic polymer capable of retaining substantial amounts of water and forming a hydrated protective layer over the wound surface. This microenvironment promotes keratinocyte migration and proliferation, processes that are significantly impaired under dry conditions. Numerous studies have demonstrated that moist wound healing accelerates epithelial regeneration and shortens healing time compared with conventional dry wound management strategies [23].

The biological activity of topical HA is mediated through several complementary mechanisms. High-molecular-weight hyaluronic acid (HMW-HA) exhibits predominantly anti-inflammatory and hydrating properties, whereas low-molecular-weight HA fragments may transiently stimulate regenerative signaling pathways involved in tissue repair. At the cellular level, HA interacts with receptors such as CD44 and RHAMM expressed on keratinocytes, fibroblasts, and immune cells, promoting cell migration, cytoskeletal reorganization, extracellular matrix stabilization, and growth factor retention within the wound bed.

An additional therapeutic benefit results from the formation of a viscoelastic protective film on the wound surface. This layer reduces friction and mechanical stress, protecting newly formed tissue from secondary injury during dressing changes. Improved hydration of exposed nerve endings further contributes to pain reduction and enhanced patient comfort.

Clinical evidence supports the efficacy of topical HA in improving wound healing outcomes. Randomized controlled trials in patients with superficial and partial-thickness wounds have demonstrated significant reductions in wound size and pain intensity after 2-6 weeks of treatment [37]. In burn-related acute wounds, faster epithelial closure has been observed, frequently within 10-14 days in partial-thickness injuries compared with conventional moist dressings. These findings are further supported by systematic reviews indicating that HA-containing preparations enhance epithelial regeneration and reduce inflammatory burden,

particularly in wounds where rapid restoration of epidermal integrity is the primary therapeutic goal [23].

Within this group of formulations, HA-based creams have been most extensively studied in clinical trials involving chronic wound populations. In a multicenter randomized controlled trial including 168 patients with chronic venous or mixed-origin leg ulcers, Mikosinski et al. demonstrated that a 0.2% HA-containing cream significantly improved healing outcomes compared with placebo. Complete wound closure was achieved in 31.3% of patients receiving HA therapy versus 14.8% in the control group, indicating a clinically meaningful enhancement of healing processes associated with topical HA application [38]. Complementary randomized studies evaluating HA-based dressings in similar patient populations have reported substantial reductions in wound surface area-approaching approximately 70% after six weeks of treatment - alongside improved healing rates and reduced pain intensity [39]. Although these effects were observed using different HA delivery systems, they consistently support the role of hyaluronic acid in promoting wound repair through sustained hydration, facilitation of cellular migration, and modulation of local inflammatory activity.

Importantly, these data derive from chronic venous or mixed-etiology ulcers rather than burn injuries. Nevertheless, they provide indirect but relevant evidence supporting the biological plausibility of topical HA in burn wound management, particularly in relation to maintaining a moist wound environment and facilitating re-epithelialization.

Topical HA is also available in gel and spray formulations, each offering distinct clinical advantages. Gels provide higher water content and a cooling effect that may be particularly beneficial in the acute post-burn phase, whereas sprays allow non-contact application, minimizing mechanical irritation in highly sensitive areas. Sodium hyaluronate 0.2% cream formulations have additionally demonstrated significant reductions in wound size and pain scores after 4-6 weeks of treatment, with the greatest benefits observed in superficial partial-thickness burns where epithelial regeneration is the dominant healing mechanism [23].

Despite these advantages, topical HA has several limitations. Its residence time on the wound surface is relatively short due to dilution by exudate and enzymatic degradation, which limits sustained biological activity. Furthermore, topical formulations do not provide structural support required for deep dermal or full-thickness burn regeneration. Variability in molecular weight composition may also influence clinical outcomes, as high-molecular-weight HA predominantly exerts anti-inflammatory effects, whereas lower-molecular-weight fragments may induce transient pro-inflammatory responses.

Overall, topical hyaluronic acid represents a valuable first-line therapeutic option in superficial and partial-thickness burn wounds. Its efficacy is primarily associated with maintenance of a moist wound environment, enhancement of keratinocyte migration, acceleration of epithelial closure, reduction of pain, and modulation of inflammatory signaling. Although clinical evidence from both burn and non-burn wound studies supports its biological activity, its therapeutic potential remains limited by short residence time and lack of structural regenerative capacity. Consequently, topical HA should be regarded as a supportive, environment-modifying therapy that optimizes conditions for natural healing rather than directly reconstructing damaged tissue [40].

Hyaluronic Acid-Based Hydrogels in Burn Wound Management. Hyaluronic acid (HA)-based hydrogels represent an advanced class of topical wound dressings positioned between conventional HA formulations (creams, gels, sprays) and engineered biomaterial scaffolds. Their defining feature is a three-dimensional, water-swollen polymer network capable of maintaining a stable, hydrated wound environment over extended periods, which is particularly relevant in burn injuries characterized by epidermal barrier disruption, increased transepidermal water loss, and progressive tissue dehydration.

From a mechanistic perspective, the primary function of HA hydrogels is the maintenance of a sustained moist microenvironment conducive to tissue repair. The hydrogel matrix retains large amounts of water, absorbs excess exudate, and reduces local tissue desiccation, thereby supporting the physiological conditions required for re-epithelialization. In addition, the cooling and occlusive properties of hydrogels contribute to analgesia and improved patient comfort, which is of particular importance in acute burn management.

Beyond their physicochemical role, HA hydrogels exert biological effects through receptor-mediated interactions with keratinocytes, fibroblasts, and immune cells via CD44 and RHAMM receptors. These interactions regulate cell adhesion, migration, and proliferation, as well as extracellular matrix remodeling, thereby facilitating coordinated tissue regeneration. The biological activity of HA is further influenced by molecular weight distribution, with high-molecular-weight HA primarily contributing to anti-inflammatory and barrier-stabilizing effects, while degradation products may support angiogenesis and tissue remodeling processes. This balance between anti-inflammatory control and regenerative stimulation is particularly relevant in burn wounds, where sequential phase transition from inflammation to proliferation is critical. [41]

An additional functional advantage of HA hydrogels is their potential as drug delivery systems. Their porous polymeric structure enables incorporation and localized release of antimicrobial

agents, growth factors, or anti-inflammatory compounds, which may be particularly beneficial in contaminated or complex burn wounds requiring multimodal therapy [42, 43].

Clinical evidence indicates that HA-based hydrogels improve healing outcomes in superficial and partial-thickness burns, with accelerated epithelial closure typically observed within approximately 10-14 days compared with conventional dressings, depending on injury severity and patient-related factors. Furthermore, commercially available sodium hyaluronate hydrogels (approximately 2-2.5% HA) have demonstrated reductions in wound size and pain intensity over 4-6 weeks of treatment, particularly in exudative burn wounds where fluid balance control is critical [23, 45].

Evidence from broader wound care populations further supports the clinical utility of hydrogel dressings. Systematic reviews consistently report improved healing outcomes compared with dry gauze dressings, including enhanced moisture retention, improved exudate control, and reduced infection risk [46]. Analyses of HA-based technologies also suggest superior performance of hydrogels compared with simpler topical formulations in maintaining a stable wound environment and promoting epithelial regeneration, especially in superficial burns and donor-site wounds [47, 45]. However, the overall certainty of evidence remains limited to low-to-moderate levels due to heterogeneity in study design, product composition, and sample size [39].

From a formulation standpoint, HA hydrogels provide several clinically relevant advantages. Their three-dimensional structure enables simultaneous hydration and exudate management, reducing the risk of both wound desiccation and peri-wound maceration. In addition, their non-adherent properties minimize secondary tissue trauma during dressing changes, while their inherent cooling effect contributes to pain reduction and improved patient tolerance of therapy.

Clinically, HA hydrogels are applied across a broad range of wound types, including venous leg ulcers, pressure ulcers, diabetic foot ulcers, donor-site wounds, and superficial burns. Their ability to maintain a moist environment, regulate exudate, and support cell migration makes them particularly suitable for wounds requiring rapid epithelial regeneration. Their ease of application and removal further supports their use in both inpatient and outpatient care settings [42].

Despite these advantages, several limitations must be considered. In highly exudative or infected wounds, hydrogel integrity may be compromised due to dilution and reduced residence time. Moreover, HA hydrogels do not provide structural support for dermal regeneration, limiting their use in deep partial-thickness and full-thickness burns. Variability in formulation characteristics, including molecular weight distribution, crosslinking density, and additive

composition, may also contribute to differences in clinical performance between products [40]. Overall, HA-based hydrogels represent a clinically important intermediate technology in burn wound management, combining sustained hydration with biologically active wound modulation. Their therapeutic effects are primarily driven by optimization of the wound microenvironment, enhancement of cell migration, and support of re-epithelialization rather than structural tissue replacement. Consequently, they should be regarded as environment-modifying regenerative dressings that facilitate healing processes during the proliferative phase, particularly in superficial and partial-thickness burns where preservation of epidermal regeneration capacity is essential.

HA-Impregnated Gauze and Tulle Dressings in Burn Wound Management. Hyaluronic acid (HA)-impregnated gauze and tulle dressings represent a distinct category of bioactive wound coverings used in burn care, particularly for superficial and partial-thickness injuries. In contrast to topical formulations and hydrogels, which are applied directly to the wound bed, these systems function as sustained-release dressings that combine mechanical protection with gradual delivery of hyaluronic acid. Their primary clinical objective is to support a stable wound environment while minimizing dressing-related trauma and maintaining conditions favorable for epithelial regeneration [42, 43].

Burn wounds are particularly susceptible to secondary injury during dressing changes, as newly formed epithelial tissue can adhere to conventional gauze and be disrupted upon removal. HA-impregnated dressings address this limitation by providing a non-adherent interface while simultaneously delivering HA to the wound surface. This dual function supports both physical protection and biologically active wound modulation [23].

The therapeutic effects of HA-impregnated gauze and tulle dressings arise from controlled release of hyaluronic acid upon contact with wound exudate. Once activated, HA forms a hydrated interface that reduces friction, limits adherence to regenerating tissue, and supports a moist wound environment conducive to epithelial migration. At the molecular level, released HA interacts with CD44 and RHAMM receptors on keratinocytes and fibroblasts, promoting cell migration, proliferation, and extracellular matrix remodeling. In addition, HA modulates local inflammatory responses by influencing cytokine activity, thereby facilitating progression from the inflammatory to the proliferative phase of healing [40].

Unlike hydrogels, which provide intrinsic hydration through high water content, HA-impregnated dressings depend on wound exudate for activation and sustained release. As a result, they are most effective in low-to-moderate exudating wounds, where moisture balance can be maintained without excessive fluid accumulation [43].

Clinical evidence for HA-impregnated gauze and tulle dressings is derived primarily from chronic wound populations, with limited burn-specific randomized controlled trials. However, available studies provide relevant insights into their biological activity. In a double-blind randomized controlled trial including patients with venous or mixed-etiology ulcers, HA-impregnated gauze dressings were associated with significant improvements in wound healing parameters compared with standard gauze. Humbert et al. reported greater reductions in wound area, lower pain scores, and higher rates of complete healing in the HA-treated group, with particularly notable improvements in patient-reported comfort and analgesia during treatment [44].

Additional RCT-level data from venous ulcer populations further support the clinical efficacy of HA-impregnated gauze. In one study, wound area reduction after approximately 45 days reached around 73% in the HA group compared with 46% in controls, while complete healing rates at later follow-up were also significantly higher. These findings, although not derived from burn populations, represent some of the strongest clinical evidence for HA-based dressings in wound care and demonstrate consistent effects on wound contraction, pain reduction, and healing progression [44].

In burn management, HA-impregnated gauze and tulle dressings are most commonly applied in superficial partial-thickness and selected deeper partial-thickness burns, particularly in anatomically sensitive areas where dressing adherence and repeated mechanical trauma may significantly impair healing. Commercial examples include sodium hyaluronate-impregnated gauze pads (e.g., Ialuset® gauze, ~0.05% HA) and HYAFF®-based tulle dressings, which have been widely described in wound-care literature.

A related technology is represented by esterified HA-based materials such as Hyalofill®-F, which transforms into a gel upon contact with wound fluid, thereby creating a moist interface that promotes cellular migration and tissue regeneration. While most clinical studies on these systems focus on chronic wounds, their biological principles are directly applicable to partial-thickness burn management [42,43].

The main advantages of HA-impregnated gauze and tulle dressings include their non-adherent properties, which reduce trauma to regenerating epithelium and minimize pain during dressing changes. In addition, they provide sustained local delivery of HA without the need for frequent reapplication, while maintaining a balance between moisture preservation and exudate control. Their compatibility with secondary absorbent dressings further allows flexible adjustment to wound exudate levels and clinical requirements [42, 43, 44]

Despite these benefits, several limitations must be acknowledged. The total amount of HA

delivered is generally lower than in hydrogel systems, which may reduce biological activity in more complex wounds. Their effectiveness is also dependent on the presence of wound exudate, limiting performance in dry wound environments. Furthermore, the lack of burn-specific randomized controlled trials limits the strength of direct clinical conclusions in this population, as most available evidence originates from chronic ulcer or mixed-wound cohorts. Finally, variability in product composition-including HA concentration, molecular weight, and carrier material - complicates direct comparison between formulations [40].

Overall, HA-impregnated gauze and tulle dressings occupy an intermediate position within HA-based wound therapies. They provide a combination of mechanical protection and biological activity that is superior to conventional passive dressings, while remaining simpler and more accessible than hydrogel or scaffold-based systems. Their primary clinical value lies in the management of superficial and partial-thickness burns, where protection of fragile epithelium, pain reduction, and maintenance of a controlled moist environment are key therapeutic goals. Although burn-specific high-quality clinical evidence remains limited, existing data from broader wound populations support their role as effective, biologically active dressings that enhance wound healing conditions.

Hyaluronic Acid-Based Dermal Scaffolds and Skin Substitutes. Severe burn injuries, particularly deep partial-thickness and full-thickness burns, involve extensive destruction of both epidermal and dermal structures, including the extracellular matrix (ECM), vascular networks, adnexal structures, and resident regenerative cell populations. In such wounds, spontaneous re-epithelialization is insufficient to restore normal skin architecture, and healing typically occurs through fibrotic repair, leading to hypertrophic scarring, contractures, and long-term functional impairment. As a result, modern burn care increasingly emphasizes not only wound closure but also dermal regeneration and restoration of tissue architecture. Within this context, hyaluronic acid (HA)-based dermal scaffolds and skin substitutes have been developed as regenerative biomaterials designed to replace or mimic the native ECM and support organized tissue reconstruction [23].

Unlike topical formulations or hydrogel dressings, which primarily optimize the wound environment, HA-based dermal scaffolds function as temporary three-dimensional ECM analogues. They provide a structural framework that supports cellular infiltration, angiogenesis, and extracellular matrix deposition, thereby guiding the formation of a neodermis prior to definitive wound closure. The intrinsic properties of hyaluronic acid - particularly its biocompatibility, hydrophilicity, and ability to modulate cell signaling - make it a suitable component for such regenerative constructs.

From a biological perspective, HA-based scaffolds act as provisional matrices into which fibroblasts, endothelial cells, keratinocytes, and inflammatory cells migrate following implantation. HA interacts with cell surface receptors such as CD44 and RHAMM, activating signaling pathways involved in cell proliferation, migration, and angiogenesis. As the scaffold undergoes gradual biodegradation, HA-derived fragments contribute to tissue remodeling and vascular development, while newly synthesized ECM progressively replaces the biomaterial. In addition, HA contributes to hydration regulation within the wound bed, facilitating nutrient diffusion and maintaining favorable conditions for cell survival and migration. Another relevant property is its ability to bind and stabilize growth factors, thereby prolonging their local activity and enhancing regenerative signaling during the proliferative phase of healing [55, 56].

The most extensively studied HA-derived scaffold systems in burn care are based on HYAFF® technology, a benzyl ester derivative of hyaluronic acid designed to improve mechanical stability and slow degradation compared with native HA. This modification allows prolonged scaffold persistence while maintaining biological compatibility. One of the most widely used clinical systems is Hyalomatrix®, a bilayer dermal substitute consisting of an inner HYAFF® scaffold and an external silicone layer. The inner layer functions as a biodegradable dermal template that supports granulation tissue formation, while the outer layer provides temporary epidermal protection and limits water loss. Hyalomatrix® has been used in the management of deep partial-thickness and full-thickness burns, including complex wounds with exposed tendon or poorly vascularized tissue. Clinical experience suggests that it can promote the formation of a vascularized neodermis, improving wound bed quality prior to autologous skin grafting. Observational studies and case series have reported enhanced granulation tissue formation, improved graft take conditions, and reduced need for repeated debridement procedures in selected patients [23]. However, it should be emphasized that much of the available clinical evidence derives from older studies, while more recent publications primarily provide translational or review-based insights rather than large-scale randomized controlled burn trials. Another HA-based system is Laserskin®, a perforated HYAFF® scaffold designed to facilitate keratinocyte delivery and epithelial regeneration. Its microperforated structure allows cell migration and nutrient diffusion and has been explored in both chronic wound and reconstructive applications, including burn-related tissue repair [23]. Similarly, fibrous HA-based dressings such as Hyalofill®-F have been developed to transform into a gel-like matrix upon contact with wound fluid, thereby creating a moist regenerative environment.

Clinical outcomes associated with HA-based dermal substitutes indicate that their primary benefit lies in improving the quality of tissue regeneration rather than merely accelerating

wound closure. This distinction is particularly important in burn surgery, where long-term functional and cosmetic outcomes are critical. Reports in the literature describe improved dermal architecture, enhanced vascularization, and more organized epithelial regeneration following treatment with HA-based scaffolds. Some studies also suggest reduced scar contracture formation and improved tissue pliability, although the strength of evidence is limited by small sample sizes and the predominance of non-randomized study designs.

A recent systematic review of HA-based wound technologies supports their role in managing partial- and full-thickness wounds, including burns, highlighting improved granulation tissue formation, facilitation of grafting procedures, and enhanced dermal regeneration outcomes [23]. Nevertheless, the overall certainty of evidence remains moderate to low due to methodological heterogeneity and limited high-quality randomized controlled trials.

From a clinical perspective, HA-based dermal scaffolds offer several advantages. They provide a temporary ECM-like structure that actively participates in tissue regeneration by supporting cell migration, angiogenesis, and organized collagen deposition. Their biodegradability ensures gradual replacement by native tissue, while their biocompatibility reduces the risk of chronic inflammatory reactions. Additionally, pre-grafting use of these scaffolds may improve wound bed quality and increase the success rate of subsequent skin grafting procedures, particularly in complex burn wounds.

Despite these benefits, important limitations remain. HA-based dermal substitutes are costly and often require specialized surgical expertise, including staged procedures and subsequent grafting. Their effectiveness is highly dependent on appropriate wound bed preparation, infection control, and adequate vascularization. In contaminated or poorly perfused wounds, regenerative outcomes may be significantly compromised. Moreover, high-quality burn-specific randomized controlled trials remain scarce, limiting the ability to draw definitive comparative conclusions against alternative dermal substitutes [57].

Overall, HA-based dermal scaffolds and skin substitutes represent advanced regenerative technologies in burn wound management. Their therapeutic value lies in their ability to function as temporary extracellular matrix replacements that actively guide dermal reconstruction rather than simply covering the wound. Although clinical evidence supports their beneficial role in selected burn populations, particularly in complex deep injuries, the current literature is largely base on clinical experience and observational studies, with contemporary research focusing primarily on mechanistic and translational development rather than large-scale randomized clinical validation.

Hyaluronic Acid–Based Sponges and Composite Dressings in Burn Wound Management.

The management of burn wounds requires not only physical protection of injured tissue but also the establishment of a biologically favorable microenvironment that supports cellular migration, angiogenesis, extracellular matrix (ECM) remodeling, and controlled inflammation. While topical formulations and hydrogel dressings are widely used in superficial burns, more complex or highly exudative wounds often require advanced materials capable of simultaneously maintaining hydration, absorbing wound exudate, and providing structural support. In this context, hyaluronic acid (HA)-based sponges and composite dressings represent an important class of advanced wound-care biomaterials [23].

HA-based sponges are porous three-dimensional scaffolds designed to mimic aspects of the native ECM while enabling fluid absorption and sustained hydration of the wound bed. Composite dressings extend this concept by combining HA with additional natural or synthetic polymers or bioactive agents in order to improve mechanical stability and expand biological functionality. These systems are particularly relevant in burn wound care, where multiple pathological processes-including inflammation, dehydration, microbial contamination, and impaired cellular migration-occur simultaneously.

From a biological perspective, burn injury leads to disruption of the dermal ECM and creates an environment characterized by high protease activity, oxidative stress, and fluid loss. HA-based sponge systems interact directly with this environment. Their porous architecture enables controlled absorption of wound exudate while maintaining sufficient moisture to support cell survival and migration. In addition, HA released from the scaffold interacts with CD44 and RHAMM receptors expressed on keratinocytes, fibroblasts, endothelial cells, and immune cells, thereby promoting re-epithelialization, fibroblast activation, angiogenesis, and extracellular matrix deposition [43].

High-molecular-weight HA contributes primarily to anti-inflammatory and barrier-stabilizing effects, whereas degradation products may participate in signaling pathways involved in angiogenesis and tissue remodeling. This dual biological activity is considered relevant in burn wounds, where successful healing requires a balance between inflammation control and regenerative activation [40].

One of the earliest HA sponge systems described in the literature is HylaSponge®, a porous HA-based scaffold designed to absorb exudate while maintaining a hydrated wound environment. As summarized in recent reviews, such systems have been applied in both acute and chronic wound management, where their primary role is to support granulation tissue formation and tissue regeneration through maintenance of a biologically active

microenvironment [23]. The high porosity and surface area of these scaffolds facilitate oxygen diffusion, nutrient exchange, and cellular infiltration, which are key processes in the formation of granulation tissue, particularly in partial-thickness burns.

Because native hyaluronic acid is rapidly degraded and mechanically weak, modern approaches increasingly rely on composite materials that combine HA with other biopolymers such as chitosan, alginate, or carboxymethylcellulose. These combinations improve mechanical stability, water retention, and handling properties while preserving the biological activity of HA [23]. However, current evidence for these systems is largely derived from experimental and preclinical studies, and burn-specific clinical validation remains limited.

In particular, HA–chitosan and HA-alginate composite systems have demonstrated promising regenerative, antimicrobial, and anti-inflammatory properties in experimental wound models. These effects include enhanced cell migration, improved exudate management, and modulation of inflammatory cytokine activity. Nevertheless, robust clinical data in burn populations are still insufficient, and further translational research is required before definitive clinical conclusions can be drawn. More advanced composite strategies include the incorporation of bioactive molecules into HA-based sponge matrices. For example, platelet-rich plasma (PRP)-loaded HA scaffolds have been associated with enhanced epithelial proliferation and improved dermal regeneration in experimental settings, likely due to the sustained release of growth factors such as VEGF, PDGF, and TGF-β. Similarly, incorporation of epidermal growth factor (EGF) has been shown in preclinical studies to enhance epidermal thickness and accelerate re-epithelialization. Antimicrobial-loaded systems, including HA-chitosan dressings incorporating antibiotics such as mupirocin, have also demonstrated antibacterial activity alongside regenerative potential in infected wound models [51].

The principal advantage of HA-based sponges and composite dressings lies in their multifunctionality. Unlike passive dressings, they simultaneously provide hydration, exudate management, structural support, and biologically active signaling. Their porous architecture facilitates oxygen diffusion and cellular infiltration, while HA-mediated signaling promotes fibroblast activity, angiogenesis, and extracellular matrix remodeling. Composite formulations further expand these functions by integrating antimicrobial or growth factor-based therapies.[40,43].

Despite these advantages, several limitations must be considered. Most available evidence originates from preclinical studies, biomaterials research, or mixed wound populations rather than burn-specific randomized controlled trials. As a result, the overall certainty of clinical evidence remains limited. In addition, manufacturing complexity, variability in scaffold

composition, and differences in HA molecular weight and crosslinking methods contribute to heterogeneity in reported outcomes. Some sponge systems may also require secondary fixation and can be difficult to apply in anatomically challenging or highly mobile regions.[40, 57].

Overall, HA-based sponges and composite dressings represent a promising but still evolving category of regenerative wound-care technologies. Their therapeutic potential lies in their ability to bridge the gap between simple topical formulations and advanced dermal substitutes by combining structural support with biological activity. Current evidence suggests that they may be particularly useful in partial-thickness burns with moderate to high exudate levels, where both moisture control and support for granulation tissue formation are required. However, their role in clinical burn care remains primarily supportive and investigational, pending further high-quality clinical validation.

Examples of HA-Based Sponges and Composite Dressings Relevant to Burn Wound Care				
Product / Technology	**Composition**	**Potential Burn Application**	**Advantages**	**Limitations**
HylaSponge®	Porous HA sponge	Partial-thickness burns, acute wounds	Hydration, exudate absorption, ECM support	Requires secondary dressing
HA–Chitosan Sponge	HA + chitosan	Experimental burn wound scaffolds	Antimicrobial, anti-inflammatory, regenerative	Mainly preclinical evidence
HA–Alginate Composite	HA + alginate	Exudative burns	Superior fluid management	Limited burn-specific clinical data
HA–PRP Scaffold	HA + platelet-rich plasma	Deep burns, regenerative applications	Enhanced angiogenesis and cell proliferation	Higher cost, limited clinical evidence
HA–EGF Scaffold	HA + epidermal growth factor	Experimental burn repair	Increased epidermal regeneration	Mostly preclinical studies

HA–Mupirocin Composite	HA + antimicrobial agent	Infected burns (experimental)	Antibacterial and regenerative activity	Not widely available clinically

Table 3 Examples of HA-based Sponges and Composite Dressings

Hyaluronic Acid in Bioactive Combination Systems for Burn Wound Management. The use of hyaluronic acid (HA) in burn wound management has progressively evolved from simple topical application toward multifunctional combination systems designed to address the complex and multi-phase pathophysiology of thermal injury. Burn wounds are characterized by sustained inflammation, impaired angiogenesis, elevated proteolytic activity, and increased susceptibility to infection, all of which contribute to delayed epithelialization and pathological scar formation. In this context, HA serves not only as a hydrating biomaterial but also as a biophysical and biochemical matrix that can stabilize, localize, and modulate the activity of co-administered therapeutic agents.

Across combination strategies, HA primarily functions as a viscoelastic extracellular matrix (ECM)-mimetic platform that enhances wound hydration, supports cellular migration, and improves the retention of biologically active molecules within the wound bed. Its therapeutic effects in combination systems are therefore largely indirect, acting through improved bioavailability and sustained activity of adjunctive agents rather than isolated pharmacological action [52].

One of the most extensively studied approaches involves the combination of *HA with platelet-rich plasma (PRP)*. PRP contains high concentrations of growth factors, including VEGF, PDGF, and TGF-β, which regulate angiogenesis, fibroblast proliferation, and tissue remodeling. When incorporated into HA-based matrices, PRP benefits from prolonged local retention and reduced enzymatic degradation due to the viscoelastic properties of HA. Clinical evidence from burn-related donor site wounds indicates that PRP-based interventions can accelerate epithelial closure and reduce pain during early healing phases [34]. Meta-analytical data further support improved healing rates and reduced healing time in burn populations treated with PRP-based therapies [53]. In combined HA-PRP systems, observational studies suggest enhanced granulation tissue formation and faster peri-wound epithelialization, although outcomes vary depending on preparation protocols and platelet concentration [37]. However, the lack of standardization in PRP preparation remains a major limitation affecting reproducibility and clinical comparability.

Another emerging strategy involves the combination of *HA with polynucleotides (PN-HA systems)*. Polynucleotides are DNA-derived biomolecules that support cellular metabolism and extracellular matrix synthesis. In these systems, HA provides hydration and structural support, while polynucleotides contribute to fibroblast activation and tissue regeneration. Clinical studies conducted in chronic wound populations, particularly venous leg ulcers, have reported improved healing outcomes, including higher complete closure rates and substantial reductions in wound area within approximately 45 days of treatment [37]. Although these findings indicate strong regenerative potential, they are derived primarily from non-burn populations, and their applicability to thermal injury remains limited. Variability in polynucleotide composition and processing further contributes to heterogeneous biological responses.

HA is also frequently combined with antimicrobial agents in order to address the high infection risk associated with burn wounds. Such systems include *combinations with silver-based compounds, iodine, or antibiotic-loaded formulations.* These hybrid dressings aim to simultaneously support tissue regeneration and reduce microbial burden. Available evidence suggests that HA may mitigate some of the cytotoxic effects associated with certain antimicrobial agents by maintaining a hydrated extracellular environment and reducing direct cellular exposure. Nevertheless, the balance between antimicrobial efficacy and cytotoxicity remains highly dependent on formulation design and concentration of active agents [47].

More advanced experimental systems incorporate HA into scaffolds loaded with growth factors such as epidermal growth factor (EGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF). In these constructs, HA acts as a controlled-release matrix that prolongs growth factor stability and enhances receptor-level signaling within the wound environment [48, 49]. Preclinical studies indicate that such systems can improve angiogenesis, endothelial proliferation, and dermal organization, leading to accelerated re-epithelialization compared with non-functionalized scaffolds. However, clinical translation remains limited due to high production costs, instability of recombinant growth factors, and regulatory challenges associated with combination biologic-device products [49, 50].

Another promising approach involves *HA-functionalized nanoparticle drug delivery systems*. In these systems, hyaluronic acid serves as a carrier that facilitates the targeted delivery and dermal penetration of bioactive compounds, thereby increasing their local retention and concentration within the wound bed, ultimately enhancing their therapeutic efficacy [54]. A representative example of an advanced HA-based drug delivery system was presented by Hussain et al., who developed hyaluronic acid-functionalized chitosan nanoparticles co-loaded with curcumin and quercetin for burn wound treatment. Functionalization with HA significantly

enhanced dermal retention of both bioactive compounds and enabled sustained drug release for up to 48 h. In an in vivo rat burn model, the HA-functionalized formulation achieved 98.2 ± 0.4% wound closure after 28 days, outperforming non-functionalized nanoparticles **(**94.5 ± 0.8%**),** silver sulfadiazine cream (89.3 ± 0.9%**),** and the untreated control group **(**79.8 ± 1.2%**).** Histological evaluation further demonstrated nearly complete re-epithelialization, increased collagen deposition, enhanced neovascularization, and markedly reduced inflammatory cell infiltration in animals treated with the HA-functionalized nanoparticles. These findings indicate that hyaluronic acid not only serves as a biologically active component supporting tissue regeneration but also functions as an effective carrier that enhances local drug delivery and improves therapeutic outcomes in burn wound healing [54].

Across all combination strategies, HA primarily functions as a structural and biochemical facilitator that enhances the stability, localization, and efficacy of adjunctive therapeutic agents. The most consistent biological effects are observed in systems combining HA with autologous biological products such as PRP, whereas scaffold-based growth factor systems demonstrate strong regenerative activity predominantly in experimental models.

Despite promising preclinical and early clinical results, a major limitation across HA-based combination therapies is the scarcity of large-scale, burn-specific randomized controlled trials. Most available evidence is derived from mixed wound populations, including chronic ulcers and surgical wounds, which limits direct translation to acute thermal injury management. As a result, HA-based combination systems should currently be regarded as emerging regenerative technologies with strong mechanistic rationale but limited high-level clinical validation in burn populations.

Conclusions

Hyaluronic acid constitutes a key component of contemporary burn wound management strategies, integrating the role of a structural element of the extracellular matrix with an active function as a modulator of biological processes. Its effects encompass the regulation of inflammatory responses, enhancement of cell migration and proliferation, stimulation of angiogenesis, and orchestration of extracellular matrix remodelling, thereby establishing it as a relevant biomaterial in regenerative medicine. The broad spectrum of available HA-based formulations - including topical preparations, hydrogel dressings, sponges, dermal scaffolds, and composite system - enables its application to be tailored according to the depth and characteristics of tissue damage. Of particular interest are multi-component delivery systems in which hyaluronic acid serves as a carrier and stabilising matrix for bioactive agents such as

growth factors, polynucleotides, and antibiotics.

In summary, hyaluronic acid should be regarded as a highly promising biomaterial; however, the current body of evidence remains insufficient. Effective and reliable methods for the treatment of burn injuries are still lacking. A holistic approach to wound care is required to address the diverse needs of patients. While some existing methods are beneficial, they remain insufficient to ensure satisfactory treatment progress. The development of new therapeutic strategies would significantly improve patients' ability to cope with mobility-restricting scars or life-threatening infections. However, most current approaches demonstrate only moderate efficacy or are still undergoing clinical trials and further studies are required to fully elucidate its therapeutic potential in the management of burn injuries.

Disclosure

Author's contribution:

Conceptualization: IO, AL

Methodology: ZS, AL

Software: DM, NS, DZ

Check: ZS, JG, GM

Formal analysis: DM, MŁ

Investigation: NS, AL, IO

Resources: NS, AL, IO

Data curation: MŁ, GM, JG

Writing-rough preparation: IO, DM

Writing-review and editing: AL, ZS

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During the preparation of this work, the authors used ChatGPT and Google's Gemini for the purpose of improving the grammatical correctness, academic style, and readability of the text. After using these tools, the authors reviewed and edited the content as needed and take(s) full responsibility for the substantive content of the publication.

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