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Antimicrobial Peptides in Wound Healing: Multifunctional Mechanisms, Therapeutic Potential, and Emerging Delivery Strategies

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ABSTRACT

Wound healing is a highly coordinated biological process involving hemostasis, inflammation, proliferation, re-epithelialization, angiogenesis, extracellular matrix deposition, and tissue remodeling. Persistent microbial infection, biofilm formation, excessive inflammation, and impaired vascularization can disrupt these processes and contribute to chronic non-healing wounds. Antimicrobial peptides (AMPs), also referred to as host-defense peptides, have attracted increasing attention as multifunctional therapeutic molecules because their biological effects extend beyond direct antimicrobial activity. In addition to disrupting microbial membranes, AMPs can modulate inflammatory signaling, promote keratinocyte migration and proliferation, stimulate fibroblast activity, enhance angiogenesis, and influence extracellular matrix remodeling. Among the most extensively investigated peptides, human cathelicidin LL-37 and human β-defensins have demonstrated both antimicrobial and tissue-regenerative properties in cellular, animal, and early clinical studies. However, rapid proteolytic degradation, susceptibility to the wound microenvironment, cytotoxicity at high concentrations, short residence time, and difficulties in achieving controlled local delivery remain major barriers to clinical translation. Consequently, hydrogels, nanofibers, nanoparticles, self-assembling systems, and stimuli-responsive wound dressings are being explored to improve AMP stability and therapeutic efficacy. This mini-review summarizes the biological roles of AMPs in wound healing, their mechanisms of action, representative therapeutic candidates, current delivery strategies, and major challenges that must be addressed for successful clinical translation.

Keywords

Antimicrobial peptides, Host-defense peptides, LL-37, β-defensin, Wound healing, Diabetic wound, Biofilm, Angiogenesis, Hydrogel, Nanomedicine.

Introduction

Wound healing is a dynamic and highly coordinated biological process through which damaged tissue restores structural integrity and physiological function. Rather than occurring as a series of strictly independent events, wound repair involves overlapping phases of hemostasis, inflammation, proliferation, re-epithelialization, granulation tissue formation, angiogenesis, and tissue remodeling [1]. These processes are regulated through complex interactions among keratinocytes, fibroblasts, endothelial cells, macrophages, neutrophils, extracellular matrix (ECM) components, cytokines, chemokines, and growth factors [1,2]. Effective wound closure therefore depends on the precise temporal coordination of inflammatory and regenerative responses, with disruption of any major component potentially resulting in delayed or pathological healing.

Infection is one of the major factors capable of disrupting this tightly regulated process. Following tissue injury, microorganisms can colonize the wound and establish persistent infections, particularly when local immune defense and tissue perfusion are compromised. Bacterial persistence can prolong the inflammatory phase, increase production of tissue-damaging proteases and reactive oxygen species (ROS), impair keratinocyte migration and proliferation, and interfere with fibroblast function, angiogenesis, and extracellular-matrix deposition [1,3]. The formation of

biofilms, in which microorganisms are embedded within a protective extracellular polymeric matrix, further increases treatment difficulty because biofilm-associated bacteria can exhibit substantially greater tolerance to antimicrobial agents and host immune responses than their planktonic counterparts [4]. These problems are particularly relevant to chronic wounds such as diabetic foot ulcers, where vascular insufficiency, neuropathy, metabolic dysfunction, persistent inflammation, and impaired immune responses frequently coexist and create a pathological environment that prevents normal progression through the wound-healing cascade [3,5]. Current management of infected wounds commonly relies on systemic or topical antibiotics, antiseptics, debridement, and appropriate wound dressings. However, increasing antimicrobial resistance, biofilm-associated tolerance, limited penetration into infected tissue, and the potential disruption of host-associated microbial communities have stimulated interest in alternative antimicrobial strategies. Antimicrobial peptides (AMPs) have consequently attracted considerable attention as potential therapeutic agents. AMPs are evolutionarily conserved components of innate immunity and are produced by diverse organisms, including mammals, insects, amphibians, and microorganisms. They are generally short peptides with variable sequence composition and frequently possess a net positive charge and amphipathic structure that facilitate interaction with microbial surfaces [6,7]. The classical antimicrobial activity of many AMPs begins with electrostatic attraction between positively charged peptide residues and negatively charged components of microbial envelopes. Following surface association, AMPs may insert into bacterial membranes and induce membrane thinning, transient defects, pore formation, lipid reorganization, or extensive membrane destabilization, ultimately causing leakage of intracellular contents and loss of cellular viability. However, membrane disruption does not represent the complete spectrum of AMP activity. Several peptides can translocate across microbial membranes and interact with intracellular targets, including nucleic acids, ribosomes, enzymes, and other essential cellular components [6]. The ability of AMPs to act through multiple mechanisms may provide an advantage against pathogens that have developed resistance to conventional single-target antibiotics. Importantly, the biological functions of AMPs extend beyond direct antimicrobial activity. Several AMPs, particularly those referred to as host-defense peptides (HDPs), can interact with host cells and modulate inflammatory signaling, leukocyte recruitment, cytokine production, angiogenesis, keratinocyte migration, fibroblast activity, and tissue remodeling [6,7]. The human cathelicidin LL-37, for example, exhibits antimicrobial activity while also influencing chemotaxis, epithelial-cell behavior, angiogenesis, and innate immune signaling. Similarly, human β-defensins can contribute to microbial defense while affecting epithelial-cell proliferation, migration, and inflammatory responses [8]. These multifunctional properties distinguish AMPs from conventional antibiotics, whose primary therapeutic objective is generally pathogen elimination.

The ability of AMPs to simultaneously influence infection, inflammation, and tissue regeneration is particularly relevant to chronic wound management. Successful treatment of a chronic infected wound requires more than bacterial killing because persistent inflammation, impaired angiogenesis, defective re-epithelialization, and abnormal extracellular-matrix remodeling may continue even after the microbial burden has been reduced. An AMP-based therapeutic strategy could therefore potentially address several pathological processes simultaneously. However, therapeutic application of AMPs is complicated by proteolytic degradation, relatively short residence time, concentration-dependent cytotoxicity, interactions with proteins and ions in wound exudate, and reduced efficacy against mature biofilms [4,9].

These limitations have encouraged increasing interest in biomaterial-assisted AMP delivery, in which peptides are incorporated into hydrogels, nanoparticles, electrospun nanofibers, films, scaffolds, microneedles, or other delivery platforms. Such systems can potentially protect AMPs from enzymatic degradation, improve local retention, regulate release kinetics, and maintain therapeutic peptide concentrations at the wound site. Among emerging biomaterials, silk fibroin (SF) is particularly attractive because it combines biocompatibility, biodegradability, tunable β-sheet-dependent stability, mechanical properties, and versatility in fabrication. Recent experimental studies have demonstrated that SF can function as a carrier for antimicrobial peptides while simultaneously providing a structural environment conducive to tissue repair [10,11].

Therefore, the therapeutic potential of AMPs in wound healing lies not simply in their ability to kill bacteria, but in their capacity to serve as multifunctional regulators of the infected wound microenvironment. Integrating AMP biology with advanced biomaterials may provide a strategy capable of maintaining localized antimicrobial activity while supporting re-epithelialization, angiogenesis, immunomodulation, and tissue regeneration. This mini-review therefore focuses on the antimicrobial and wound-healing mechanisms of AMPs, their immunomodulatory and regenerative functions, major delivery strategies, the emerging role of silk fibroin as an AMP delivery platform, and the principal challenges that must be addressed for clinical translation.

Antimicrobial Peptides as Multifunctional Wound-Healing Molecules

The therapeutic significance of Antimicrobial Peptides (AMPs) in wound care management arises from their unique biological profile, as they function simultaneously as broad-spectrum antimicrobials and versatile immune-tissue modulators [12,13]. Rather than acting merely as traditional bactericidal agents, AMPs operate as dynamic host defense peptides that directly bridge early microbial clearance to subsequent stages of tissue repair and regeneration [14]. At the wound bed, cationic AMPs rapidly reduce microbial burden through electrostatic attraction with negatively charged bacterial wall components—such as lipopolysaccharides (LPS) in Gram-negative organisms and teichoic acids in Gram-positive bacteria—leading to membrane permeabilization and cell lysis via carpet, pore-forming, or barrel-stave mechanisms [12].

Beyond direct cell lysis, AMPs exhibit diverse host-mediating functions critical to overcoming stalled healing phases. Peptides such as IDR-1018, Pexiganan, and Nisin actively penetrate and disaggregate dense extracellular polymeric substances (EPS) within recalcitrant bacterial biofilms (Table 1) [12]. Concurrently, AMPs bind free circulating endotoxins like LPS, thereby downregulating pro-inflammatory cascades driven by Toll-like receptors and blunting excessive pro-inflammatory cytokine release, such as TNF-α and IL-1β [12]. During tissue reconstruction, cathelicidins like LL-37 recruit monocytes and neutrophils to clear cellular debris while inducing neo-angiogenesis via vascular endothelial cell activation (Table 1). Concurrently, human β-defensins (hBD-2 and hBD-3) accelerate re-epithelialization by inducing keratinocyte proliferation and migration across the lesion. Salivary peptides such as Histatin-2 further facilitate extracellular matrix remodeling by stimulating dermal fibroblast migration with minimal inflammatory stimulation (Table 1), while sweat-derived anionic peptides like DCD-1L maintain continuous surface protection through oligomeric ion channel formation [15].

This pleiotropic functionality is especially vital in managing non-healing chronic wounds—such as diabetic foot ulcers and pressure sores—where persistent microbial infection and defective tissue repair reinforce each other in a destructive pathological loop [12,13]. Consequently, modern tissue engineering leverages peptide-engineered hydrogels, smart wound dressings, and advanced biomaterial platforms to deliver these multifunctional peptides efficiently to the infected site, thereby resolving recalcitrant infection while actively triggering tissue regeneration [12,14].

Mechanisms of Antimicrobial Activity

Antimicrobial peptides (AMPs) exert antimicrobial effects through a complex and multifaceted series of molecular events [22,23]. Although electrostatic membrane interaction and pore formation are traditionally considered the primary mechanisms for many AMPs, accumulating evidence demonstrates that their lethal activity often involves intracellular targeting, cell-wall interference, metabolic disruption, and inhibition of biofilm matrix development [12,24]. Importantly, these pathways are not mutually exclusive. A single AMP may initially target negatively charged bacterial surface lipids to compromise membrane integrity before translocating across the lipid bilayer to bind cytoplasmic targets like DNA, RNA, or essential enzymes [12,24]. The precise biophysical contribution of each mode of action is ultimately governed by the peptide's primary sequence, net positive charge, hydrophobicity, amphipathic secondary structure, concentration, and the specific membrane lipid composition of the target microorganism [12,22].

Membrane disruption

The primary antimicrobial mechanism of action for most cationic antimicrobial peptides (AMPs) initiates with selective surface attraction and electrostatic accumulation at the microbial cell envelope [12,23]. Cationic AMPs exhibit a distinct, high-affinity selectivity for negatively charged bacterial membranes, driven by strong electrostatic interactions with lipopolysaccharides (LPS) in Gram-negative bacteria and teichoic/lipoteichoic acids as well as anionic phosphatidylglycerol in Gram-positive species. This selective target recognition depends heavily on surface charge differentials; host mammalian cell membranes are predominantly composed of zwitterionic phospholipids (such as phosphatidylcholine and sphingomyelin) and stabilizing cholesterol, which substantially diminish initial electrostatic peptide adsorption and confer host cell protection (Figure 1) [23,25]. Following initial surface association, amphipathic AMPs undergo conformational reorientation and insert into the hydrophobic lipid core, proceeding through several well-established biophysical modes of membrane permeabilization and structural collapse

Table 1: Representative antimicrobial peptides investigated for wound healing.

AMP	Source/Type	Major Antimicrobial Activity	Wound-Healing Effects	Evidence Level	Citations
LL-37	Human cathelicidin (CAMP)	Broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria	Promotes keratinocyte migration, endothelial-cell activity, angiogenesis, re-epithelialization, and immune modulation	Cell, animal, clinical	[16,17]
hBD-2	Human β-defensin-2	Antibacterial activity targeting common skin pathogens	Stimulates keratinocyte migration and proliferation; promotes epithelial repair	Cell, animal	[16,18]
hBD-3	Human β-defensin-3	Broad-spectrum antimicrobial activity against multidrug-resistant bacteria	Improves re-epithelialization and reduces bacterial burden in infected diabetic wound models	Animal	[16,17]
IDR-1018	Synthetic innate-defense-regulator peptide	Antimicrobial and broad-spectrum anti-biofilm effects	Accelerates healing in infected and non-infected wound models; promotes immunomodulation	Animal	[19]
Histatin-2	Human salivary peptide	Antimicrobial and antifungal activity	Promotes fibroblast migration with limited inflammatory stimulation	Cell	[18]
Pexiganan	Magainin-derived synthetic peptide	Broad-spectrum topical antimicrobial activity	Reduces microbial burden; investigated in infected skin ulcers (e.g., diabetic foot ulcers)	Preclinical, clinical	[20]
Nisin	Lantibiotic bacteriocin (*Lactococcus lactis*)	Strong activity against susceptible Gram-positive bacteria	Reduces bacterial burden, disrupts bio-films, and aids tissue repair in experimental models	Preclinical	[21]
DCD-1L	Dermcidin-derived human peptide	Antibacterial and anti-biofilm activity in human sweat	Investigated in infected wound models and sweat-mediated cutaneous innate immunity	Preclinical	[15]

[23]. In the classic barrel-stave model, hydrophobic regions of perpendicular peptides insert into the bilayer to align parallel with fatty acid tails, while their hydrophilic residues face inward to form a stable, stave-like transmembrane aqueous pore through which intracellular solutes leak (Figure 1) [23]. Conversely, the toroidal-pore model involves peptides inducing localized physical strain and curvature in the lipid bilayer, forcing phospholipid headgroups to bend continuously inward so that both lipid headgroups and peptides line the transmembrane channel [25,26]. Alternatively, the carpet model describes a process where AMPs accumulate parallel across the outer membrane surface; upon reaching a critical threshold concentration, the peptides exert a detergent-like solubilization effect that causes membrane thinning, extensive lipid disorder, and micellization without necessitating discrete transmembrane pores [12,23]. Furthermore, the aggregate-channel (interfacial) model proposes that peptides and lipids assemble into dynamic, disordered complexes that transiently disrupt barrier function, promoting rapid peptide translocation and interfacial lipid shuffling [27]. These pore-forming, carpet-like, and interfacial mechanisms collectively induce severe bioenergetic collapse, marked by the rapid dissipation of the transmembrane potential ($\Delta\Psi$) and proton motive force, uncoupling of oxidative phosphorylation, efflux of essential potassium ions and metabolites, and cellular lysis (Figure 1) [23,25]. Crucially, these mechanistic pathways are non-exclusive; individual AMPs often transition dynamically between surface carpet accumulation, discrete pore formation, or cell translocation depending on localized peptide-to-lipid ratios, peptide concentration, membrane lipid composition, and environmental ionic strength [23,27]. Protein synthesis is another important intracellular target. Certain proline-rich AMPs can enter bacterial cells through specific uptake systems and interact with ribosomes, thereby inhibiting translation. Bac7 (1–35), for example, has been reported to target the bacterial ribosome and inhibit protein synthesis [23]. Other AMPs may interfere with protein folding, protease activity, enzymatic pathways, or cell division. These mechanisms demonstrate that AMP activity can extend beyond physical membrane damage to disruption of essential intracellular biochemical processes. AMPs may also affect cell-wall biosynthesis and bacterial metabolic pathways. Some peptides interact with cell-wall precursors or interfere with processes required for maintenance of peptidoglycan integrity. In addition, AMP-mediated perturbation of intracellular homeostasis can influence energy metabolism, oxidative stress, and cellular signaling. Therefore, AMP-mediated killing is increasingly viewed as a network of interconnected events rather than a single molecular mechanism [28]. The existence of multiple antimicrobial targets may also have implications for antimicrobial resistance. Conventional antibiotics frequently act on one dominant molecular target, whereas some AMPs can simultaneously perturb membranes and intracellular pathways. This mechanistic multiplicity may reduce the probability that a single genetic alteration will completely eliminate susceptibility, although AMP resistance can nevertheless emerge through changes in membrane composition, surface charge, efflux systems, proteolytic degradation, and biofilm-associated adaptations [23,28].

Anti-biofilm activity

Biofilm formation represents a major challenge in chronic wound management, as bacteria become embedded within a self-produced extracellular polymeric substance (EPS) matrix primarily composed of polysaccharides, extracellular DNA (eDNA), proteins, and lipid components [28,29]. This viscous structural matrix provides spatial stability and acts as a physical and chemical barrier that restricts conventional antibiotic diffusion, neutralizes charged therapeutic agents, and fosters phenotypic tolerance, allowing embedded sessile microbes to exhibit up to 1000-fold higher resistance than their planktonic counterparts [29]. Antimicrobial peptides (AMPs) disrupt biofilms across all critical developmental phases, including initial bacterial adhesion, microcolony assembly, EPS matrix maturation, and persistent biofilm maintenance [29,30]. Specific AMPs prevent early surface attachment by neutralizing bacterial cell-surface charges, modulating surface hydrophobicity, or downregulating motility appendages such as flagella and pili [28]. Once biofilms are established, small amphipathic AMPs diffuse through the EPS matrix to induce membrane permeabilization and bioenergetic collapse in metabolically dormant persister cells, while simultaneously destabilizing matrix biopolymers to enhance the penetration and bio-accessibility of co-administered antimicrobial therapeutics [25,29].

In addition to structural matrix degradation, AMPs target intercellular communication cascades and metabolic stress regulators essential for biofilm coordination [28]. Numerous natural and synthetic peptides suppress quorum sensing (QS) signaling pathways, downregulating key gene networks that govern adhesion, exopolysaccharide secretion, and virulence factor expression [28,29]. Furthermore, targeted AMPs induce the degradation of matrix polysaccharides and interfere with the bacterial stringent-response system by stimulating the degradation of signaling alarmones—specifically guanosine tetraphosphate and pentaphosphate ((p)ppGpp)—which are required for microbial survival under nutrient deprivation and hyper-osmotic stress [28,29]. In non-healing cutaneous wounds, eradicating persistent biofilms alleviates non-resolving inflammatory cascades and re-establishes a favorable microenvironment for keratinocyte re-epithelialization, neo-angiogenesis, and extracellular matrix remodeling [25,29]. However, because anti-biofilm efficacy depends heavily on peptide sequence, net charge, biofilm age, microbial species, EPS composition, and local wound conditions, strong bactericidal activity against planktonic bacteria cannot automatically be equated with equivalent activity against mature wound biofilms [29]. Overall, conceptualizing AMP activity as a coordinated, multistage process involving surface recognition, membrane perturbation, intracellular targeting, and biofilm interference provides essential design principles for rational peptide engineering and the development of biomaterial-based delivery systems capable of maintaining therapeutically effective peptide concentrations at the wound bed [25,28].

The figure illustrates the interconnected membrane-disrupting and non-membrane-disrupting pathways through which AMPs exert bactericidal effects. ***Membrane-level mechanisms*** *begin*

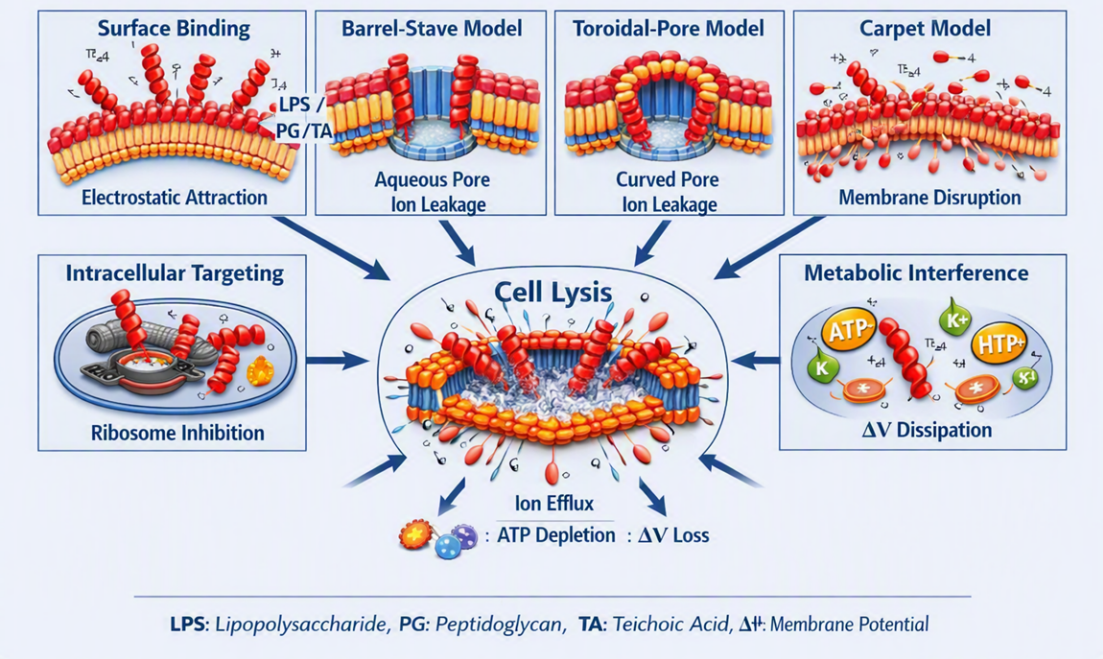

Figure 1: Schematic representation of the multifaceted mechanisms of Antimicrobial Peptide (AMP)-induced bacterial cytotoxicity.

*with **Surface Binding** mediated by electrostatic interactions with negatively charged outer membrane components (LPS in Gram-negative or PG/TA in Gram-positive bacteria). Subsequent permeabilization occurs via **Pore Formation**—including the Barrel-Stave Model (transmembrane aqueous pore formation) and the Toroidal Pore Model (inducing lipid curvature leading to ion leakage)—as well as **Carpet Disruption** (solubilization and complete membrane disintegration). **Non-membrane mechanisms** involve peptide translocation to target essential cytoplasmic components, leading to **Intracellular Targeting** (inhibition of protein synthesis via ribosomal targeting) and **Metabolic Interference** (disruption of energy metabolism, ATP loss, and metabolite leakage). The synergistic culmination of these events induces bioenergetic collapse, leading to bacterial **Cell Lysis** and death. A legend defining individual structural and molecular components is provided at the bottom.*

Immunomodulatory Functions

One of the defining characteristics that distinguishes antimicrobial peptides (AMPs) from conventional antibiotics is their ability to regulate the host immune response. While traditional antibiotics primarily eliminate microorganisms, many AMPs function as host-defense peptides (HDPs) that simultaneously eradicate pathogens and orchestrate the cellular and molecular events required for tissue repair [7,31]. This dual functionality is particularly important in wound healing because successful regeneration depends not only on microbial clearance but also on a precisely controlled inflammatory response [7]. Excessive inflammation results in tissue destruction and chronic wound formation, whereas insufficient inflammation compromises pathogen elimination and delays healing [31].

Immediately after tissue injury, neutrophils and macrophages infiltrate the wound and initiate innate immune responses. Endogenous AMPs—including LL-37 and human β-defensins (hBD-2 and hBD-3)—actively participate in this phase by modulating chemokine and cytokine production rather than functioning solely as antimicrobial molecules [32]. These peptides regulate the release of inflammatory mediators such as interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1) and transforming growth factor-β (TGF-β), thereby tuning leukocyte recruitment and activation [31].

Regulation of Immune Cell Recruitment

LL-37 is one of the best-characterized immunomodulatory AMPs in skin biology. It functions as a chemoattractant for neutrophils, monocytes, macrophages, mast cells, and T lymphocytes through interaction with formyl peptide receptor 2 (FPR2/ALX) [31,33]. Activation of FPR2 promotes directed migration of immune cells toward the wound, enhancing early pathogen clearance while simultaneously initiating tissue regeneration [33]. In addition to FPR2, LL-37 can activate the P2X7 purinergic receptor, stimulating ATP-dependent signaling pathways that contribute to cytokine secretion and inflammasome regulation [31]. Human β-defensins exhibit similar chemotactic properties. Both hBD-2 and hBD-3 recruit immature dendritic cells and memory T cells through the chemokine receptor CCR6, thereby linking innate and adaptive immunity [32]. This coordinated recruitment of immune cells is essential for the efficient removal of invading microorganisms and preparation of the wound environment for the proliferative phase [7,32].

Modulation of Inflammatory Cytokines

Rather than simply amplifying inflammation, AMPs act as immune homeostatic regulators [7]. LL-37 suppresses excessive Toll-like receptor (TLR)-mediated inflammatory responses induced by bacterial lipopolysaccharide (LPS). By directly binding LPS, LL-37 prevents its interaction with TLR4 and reduces downstream activation of NF-κB signaling, thereby decreasing production of pro-inflammatory cytokines such as TNF-α and IL-1β [7,31]. Simultaneously, LL-37 can promote the expression of anti-inflammatory mediators, creating a balanced inflammatory environment that favors tissue repair [31]. This immunomodulatory balance is particularly relevant in chronic diabetic wounds, where persistent inflammation is a major pathological feature [34,35]. Experimental studies demonstrate that AMP treatment reduces prolonged inflammatory infiltration while improving macrophage polarization toward the reparative M2 phenotype, which supports angiogenesis, extracellular matrix deposition, and tissue remodeling [34].

Receptor-Mediated Signaling Pathways

The biological activities of AMPs are mediated through several cell-surface receptors rather than nonspecific membrane interactions alone [31,33]. Among these, FPR2, EGFR (epidermal growth factor receptor), P2X7, and Toll-like receptor-associated pathways are particularly important during wound healing [31,36]. LL-37 indirectly transactivates EGFR through metalloproteinase-dependent shedding of EGFR ligands [36]. This signaling stimulates keratinocyte proliferation and migration while simultaneously enhancing epithelial survival. Activation of EGFR also promotes downstream MAPK/ERK signaling, contributing to rapid restoration of the epidermal barrier [31,36].

Promotion of Re-Epithelialization

Re-epithelialization is the fundamental biological process responsible for restoring the integrity of the skin barrier following injury [32]. During this stage, keratinocytes located at the wound edge detach from neighboring cells, migrate across the provisional extracellular matrix, proliferate to replace lost tissue, and subsequently differentiate to reconstruct the epidermis [36]. Delayed keratinocyte migration is one of the principal causes of chronic non-healing wounds, making this process an attractive therapeutic target for AMP-based interventions [34,36].

Keratinocyte Migration and Proliferation

Among endogenous AMPs, LL-37 demonstrates strong evidence for promoting keratinocyte migration [33,36]. Rather than acting merely as a growth factor, LL-37 activates intracellular signaling pathways that increase cytoskeletal remodeling, cell motility, and proliferation [36]. Experimental studies indicate that LL-37 enhances keratinocyte migration primarily through EGFR transactivation and subsequent activation of the ERK1/2 and PI3K signaling cascades, leading to accelerated wound closure [33,36]. Human β-defensins also contribute significantly to epithelial repair [34,35]. Both hBD-2 and hBD-3 stimulate epithelial-cell proliferation while enhancing migration across injured surfaces. Unlike antibiotics, these peptides actively participate in the reconstruction of the epithelial barrier by regulating cellular behavior rather than merely eliminating infection [34].

Experimental Evidence

The regenerative potential of LL-37 has been validated in several animal models [33]. Ramos et al. demonstrated that topical administration of synthetic and recombinant LL-37 significantly accelerated wound closure compared with untreated controls [33]. Histological analysis revealed enhanced epithelial thickness, increased vascularization, and more rapid re-epithelialization in LL-37-treated wounds [33]. These findings confirm that LL-37 influences both epithelial regeneration and underlying dermal repair. Similarly, studies involving hBD-3 in diabetic wound models reported improved epithelial coverage accompanied by reduced bacterial burden, indicating that antimicrobial and regenerative mechanisms operate simultaneously during healing [35].

Restoration of the Epidermal Barrier

Successful re-epithelialization requires coordinated interactions between keratinocytes, extracellular matrix proteins, fibroblasts, and inflammatory cells [34]. AMPs contribute indirectly by reducing microbial contamination and excessive inflammation while directly stimulating epithelial migration and proliferation [34]. Consequently, AMP therapy shortens the inflammatory phase and accelerates the transition toward the proliferative stage of wound healing, particularly in infected or diabetic wounds where epithelial regeneration is severely impaired [34,35].

Angiogenesis and Fibroblast Activity

Formation of new blood vessels and activation of dermal fibroblasts are essential components of the proliferative phase of wound healing [33,37]. Newly formed capillaries supply oxygen, nutrients, growth factors, and immune cells to regenerating tissue, whereas fibroblasts synthesize collagen, elastin, fibronectin, and other extracellular matrix (ECM) components that provide structural support [33,38]. Increasing evidence indicates that several AMPs regulate both angiogenesis and fibroblast function, extending their therapeutic role beyond antimicrobial defense [34,37].

AMP-Mediated Angiogenesis

LL-37 is widely recognized as a pro-angiogenic peptide [37]. It stimulates endothelial-cell proliferation, directional migration, and organization into capillary-like tubular structures [33,37]. These effects are mediated through activation of FPR2 and downstream signaling pathways involving ERK and PI3K/Akt, ultimately promoting vascular endothelial growth factor (VEGF)-associated responses [37]. Enhanced angiogenesis improves oxygen delivery to hypoxic wounds and supports formation of healthy granulation tissue [33,37]. The angiogenic activity of LL-37 is particularly valuable in diabetic ulcers, where impaired neovascularization contributes to chronic ischemia and delayed healing [33]. Experimental wound models consistently show increased microvessel density and improved vascular organization following topical LL-37 treatment [33,37].

Fibroblast Migration and Extracellular Matrix Remodeling

Fibroblasts are responsible for producing the collagen-rich extracellular matrix that replaces damaged tissue during repair [38]. Several AMPs directly influence fibroblast behavior [34,38]. Histatin-2, a naturally occurring salivary peptide, stimulates fibroblast migration without inducing excessive inflammatory activation [38]. LL-37 similarly enhances dermal fibroblast motility and promotes expression of genes associated with matrix remodeling and tissue regeneration [33]. In addition to increasing fibroblast migration, AMPs regulate the balance between matrix metalloproteinases (MMPs) and their endogenous inhibitors, thereby controlling extracellular matrix turnover [34]. Controlled remodeling is essential because excessive matrix degradation weakens granulation tissue, whereas insufficient remodeling can lead to fibrosis and scar formation [34].

Integration of Regenerative Processes

The regenerative effects of AMPs represent an integrated biological network rather than isolated cellular events [7,34]. By simultaneously reducing microbial burden, modulating inflammation, stimulating keratinocyte migration, promoting angiogenesis, and activating fibroblasts, AMPs create a wound microenvironment that favors rapid and organized tissue regeneration [31,34]. This multifunctionality distinguishes host-defense peptides from conventional antimicrobial agents and underscores why AMP-based biomaterials are leading candidates for next-generation chronic wound therapeutics [7,34].

LL-37 as a Prototype Wound-Healing AMP

LL-37 is the only currently recognized human cathelicidin and is generated via enzymatic cleavage from the precursor protein hCAP-18 [16,39]. It is constitutively expressed or rapidly induced across diverse immune and epithelial cell populations—including neutrophils, monocytes, keratinocytes, and inflammatory macrophages—and accumulates at biologically active concentrations within human wound fluids during tissue repair [16,40]. LL-37 serves as a key clinical prototype because it integrates broad-spectrum direct antimicrobial activity with complex immunomodulatory, pro-angiogenic, and tissue-regenerative functions [41,42]. Extensive functional evaluations confirm that LL-37 directly drives keratinocyte directional migration, activates microvascular endothelial cells, promotes both blood vessel assembly and lymphangiogenesis via ERK and Akt signaling cascades, and accelerates epidermal barrier restoration in vitro and in vivo[40,42].The translational momentum of LL-37 has led to clinical evaluations for non-healing cutaneous lesions, particularly chronic diabetic foot ulcers [41,43]. Specifically, a randomized double-blind placebo-controlled trial evaluating topical LL-37 formulation demonstrated a statistically significant reduction in wound surface area across multiple follow-up intervals compared to placebo control groups, supporting the clinical potential of targeted LL-37 administration in diabetic wound environments [41,43]. However, these findings should not be interpreted as evidence that LL-37 constitutes a fully established standard-of-care regimen [16]. Overcoming native peptide instability and proteolytic degradation requires larger, rigorously controlled Phase III trials, optimal concentration profiling, improved clinical stratification, and advanced biomaterial carriers—such as lipidized PLGA nanocarriers or protective hydrogel matrices—to preserve peptide integrity and achieve sustained therapeutic release at the wound bed [16,41].

Human β-Defensins in Wound Repair

Human β-defensins are another important group of endogenous antimicrobial peptides. They are expressed by epithelial cells and participate in barrier defense and immune signaling [44]. Among them, hBD-3 has attracted considerable interest because of its relatively broad antimicrobial activity and its effects on wound repair [45]. In an infected diabetic porcine wound model, hBD-3 expression resulted in improved re-epithelialization and a substantial reduction in bacterial burden during the early phase of infection. Hirsch et al. reported approximately 75% wound closure in hBD-3-treated wounds compared with approximately 50% in controls at the evaluated time point [44,45]. These findings demonstrate an important principle: the therapeutic value of an AMP may arise from the combined effect of antimicrobial and regenerative mechanisms rather than antimicrobial activity alone.

AMP Delivery Systems for Wound Therapy

Despite promising biological properties, free AMPs often have unfavorable pharmacological characteristics. Proteolytic degradation, rapid diffusion from the wound site, sensitivity to ionic conditions, adsorption to biological components, and potential cytotoxicity can limit therapeutic performance (Table 2). Consequently, delivery systems have become a major research direction.

Silk Fibroin as a Potential AMP Delivery Platform

Silk fibroin (SF), the major structural protein of *Bombyx mori* silk, has emerged as a versatile biomaterial for wound-management applications because its physicochemical properties can be tailored through control of molecular weight, concentration, crystallinity, and β-sheet content. SF can be processed into hydrogels, films, membranes, electrospun nanofibers, porous scaffolds, and micro/nanoparticles, allowing the same protein platform to be adapted to different wound geometries and therapeutic requirements. Its combination of biocompatibility, tunable biodegradation, aqueous processability, mechanical robustness, and ability to stabilize bioactive molecules makes SF particularly attractive for localized delivery of antimicrobial agents and regenerative therapeutics [56,57]. Importantly, recent studies have moved beyond the use of SF as a passive wound scaffold and demonstrated that it can serve as an active carrier for antimicrobial peptides (AMPs), creating an integrated material capable of providing both structural support and antimicrobial functionality [57]. A particularly relevant example was reported by Aye et al., who developed a silk fibroin hydrogel functionalized with the cationic AMP polymyxin B through electrostatic interactions [10]. Because SF carries negatively charged groups while polymyxin B is highly cationic, strong peptide–protein interactions occurred within the hydrogel network. The authors demonstrated changes in nanofibril organization, gelation kinetics, ζ-potential, fluorescence

Table 2: Biomaterial-based delivery platforms for antimicrobial peptides in wound healing.

Delivery platform	Potential advantages	Major limitations
Hydrogels	High water content and maintenance of a moist wound environment; intimate contact with irregular wound surfaces; local retention of AMPs; tunable and sustained release; injectable/in situ-forming formulations are possible. Self-assembling peptide hydrogels can additionally provide ECM-mimetic structures and spatiotemporal control of wound treatment [12,46,47].	Burst release can occur depending on peptide–matrix interactions; peptide activity may be altered by crosslinking or the local physicochemical environment; relatively weak mechanical strength can limit use in mechanically demanding wounds; formulation and sterilization require careful optimization [46,47].
Nanoparticles	Protect AMPs from enzymatic degradation; improve peptide stability and local bioavailability; enable controlled or sustained release; surface functionalization can improve interaction with bacterial biofilms or target cells; nanoparticles can be incorporated into secondary wound dressings or hydrogels [12,48].	Nanoparticle formulation can involve complex preparation and characterization; particle size, surface charge, aggregation, and peptide loading strongly influence biological performance; potential cytotoxicity and long-term safety require systematic evaluation; scale-up and reproducibility remain important translational challenges [12,48].
Electrospun nanofibers	ECM-like fibrous architecture; high specific surface area; interconnected porosity; ability to encapsulate or immobilize AMPs; tunable morphology and release profiles; favorable platform for simultaneous antimicrobial activity and tissue regeneration [48-50]	Initial burst release may occur for surface-associated peptides; electrospinning parameters can affect peptide stability and bioactivity; scale-up, batch-to-batch reproducibility, fiber uniformity, and process optimization remain challenging; some organic solvents used during fabrication may be incompatible with sensitive peptides [49,50].
Silk fibroin systems	Excellent biocompatibility and biodegradability; tunable β-sheet-dependent stability and degradation; good mechanical properties; can be fabricated as films, membranes, hydrogels, sponges, scaffolds, nanofibers, and micro/nanoparticles; capable of serving as a carrier for bioactive molecules and providing structural support for wound regeneration [48,51,52].	Peptide loading and release depend strongly on SF structure, β-sheet content, and peptide–protein interactions; excessive crystallinity may reduce release; formulation conditions require optimization to preserve AMP activity; manufacturing, sterilization, and reproducible control of degradation/release kinetics remain translational challenges [51,52].
Self-assembling peptide systems	Can form injectable or in situ-forming nanofibrous hydrogels; excellent biomimetic potential; intrinsic biocompatibility and biodegradability; ECM-like architecture can support cell migration and proliferation; assembly can be regulated by pH, temperature, ionic strength, or enzymes; some systems possess intrinsic antimicrobial activity [46,53].	Self-assembly is highly sequence- and environment-dependent; peptide aggregation and gelation kinetics can be difficult to control; mechanical properties may be insufficient for some wound sites; stability, storage, sterilization, manufacturing scale-up, and reproducibility remain important challenges [46,53].
Stimuli-responsive dressings	Enable on-demand or site-specific AMP release in response to wound-associated stimuli such as pH, bacterial enzymes, ROS, temperature, glucose, or externally applied NIR light; can minimize unnecessary peptide exposure and potentially improve therapeutic efficiency; particularly attractive for infected chronic wounds [48].	More complex formulation and fabrication; simultaneous control of sensitivity, release kinetics, mechanical stability, and AMP bioactivity is difficult; wound-to-wound variability may alter stimulus response; external stimuli such as NIR may require additional equipment; clinical validation and regulatory translation remain limited [48].
Microneedle systems	Localized transdermal delivery; enhanced penetration into infected tissue and biofilms; bypasses some barriers associated with topical administration; dissolvable microneedles can provide controlled/localized AMP release; can be combined with nanoparticles, nanofibers, or responsive materials for multifunctional wound treatment [50,54,55].	Fabrication requires precise control of needle geometry, mechanical strength, drug loading, and insertion performance; fragile needles may fracture or deform; large-scale manufacturing and quality control can be challenging; tissue penetration and safety must be carefully evaluated, particularly for compromised or infected skin [54,55].

Recent research increasingly focuses on combining AMPs with biomaterials rather than administering peptides as free molecules. Hydrogels, nanofibers, nanoparticles, and smart dressings can potentially improve peptide retention, protect against enzymatic degradation, and provide sustained or stimulus-responsive release.

characteristics, and rheological properties following peptide incorporation. Importantly, the polymyxin-B-loaded SF hydrogel retained antimicrobial activity against two Gram-negative bacterial strains, and physicochemical analysis indicated an optimal polymyxin B:SF molar ratio of approximately 1:2.5 [10]. This finding is important for AMP delivery because it demonstrates that electrostatic association can be exploited to immobilize or retain cationic peptides within negatively charged SF matrices without requiring extensive chemical conjugation [10]. The interaction between AMP charge and SF is particularly relevant to the design of controlled-release systems. Rather than simply entrapping the peptide within a polymeric matrix, electrostatic attraction can provide a reversible retention mechanism that influences peptide diffusion and release (Table 2) [10]. However, excessively strong peptide–SF interactions may also reduce peptide availability, meaning that the balance between loading efficiency, retention, release kinetics, and preservation of antimicrobial activity must be experimentally optimized. Therefore, the optimal SF formulation cannot be defined solely by the amount of AMP incorporated; the bioavailable fraction of peptide released into wound fluid is likely to be more relevant to therapeutic efficacy [10].

Direct evidence for AMP-loaded SF wound dressings has also been obtained using electrospun scaffolds. Moosazadeh Moghaddam et al. Developed an amniotic-membrane/SF electrospun nanofibrous scaffold containing the antimicrobial peptide CM11 [11]. The scaffold was evaluated against antibiotic-resistant *Pseudomonas aeruginosa* and *Staphylococcus aureus*, while its mechanical properties, biodegradation, peptide release, cytotoxicity, and in vivo biocompatibility were also investigated. Notably, the formulation containing 32 μg/mL CM11 produced significantly greater wound closure in a mouse full-thickness wound model. The treatment was also associated with increased relative expression of collagen I, collagen III, TGF-β1, and TGF-β3, indicating that the AMP-loaded SF scaffold was not limited to bacterial suppression but also influenced molecular processes associated with tissue regeneration [11].

More recently, Zhang et al. developed a transparent regenerated SF film incorporating the antimicrobial peptide KR-12, together with other antimicrobial agents, including curcumin and silver nanoparticles[58]. Incorporation of 2.5% Pluronic F127 into the SF film improved its mechanical properties, hydrophilicity, and optical transparency. The resulting medicated SF films demonstrated sustained release of the incorporated antimicrobial agents and retained antibacterial activity [58]. Importantly, in an infected wound model, the medicated SF films were able to eliminate methicillin-resistant *Staphylococcus aureus* (MRSA) from the wound region while reducing inflammatory responses and promoting both angiogenesis and re-epithelialization [58]. These findings provide direct evidence that an AMP-containing SF matrix can simultaneously address infection and several biological processes involved in wound repair [58].

The regenerative contribution of the SF matrix itself is also important. SF provides a proteinaceous three-dimensional environment that can support cell adhesion, migration, and proliferation, while its β-sheet-rich crystalline domains can increase structural stability and slow degradation [56,57]. By adjusting the degree of β-sheet formation, researchers can therefore modulate the balance between mechanical stability and biodegradation. This is particularly advantageous for chronic wounds because a dressing may need to remain at the wound site for substantially longer than a rapidly dissolving topical formulation. In addition, SF can be fabricated into highly porous electrospun structures that partially reproduce the architecture of native extracellular matrix (ECM), providing a physical substrate for fibroblast and keratinocyte activity [56,57]. An additional advantage of SF is its potential to provide multifunctional wound therapy rather than acting simply as a drug reservoir. For example, recent SF films containing KR-12 demonstrated antibacterial activity while simultaneously improving fibroblast adhesion, modulating macrophage polarization, promoting angiogenesis, and enhancing re-epithelialization [58]. Similarly, CM11-loaded SF electrospun scaffolds produced both antimicrobial effects and enhanced expression of collagen- and TGF-β-associated wound-healing markers [11]. These findings support a model in which SF acts as the structural/regenerative component while the AMP provides targeted antimicrobial and potentially immunomodulatory activity.

Accordingly, an AMP-loaded SF system can theoretically provide three complementary therapeutic functions. First, the SF matrix can provide physical wound coverage and a moist, biocompatible scaffold that protects the injured tissue. Second, incorporation of an AMP can increase local peptide residence time and provide sustained or controlled antimicrobial exposure, potentially reducing the rapid loss of free peptide from wound exudate [59]. Third, the SF matrix itself can support cellular adhesion and tissue regeneration, while the AMP may additionally modulate inflammation and microbial burden. This combination is particularly attractive for chronic infected wounds, where persistent infection, biofilm formation, prolonged inflammation, and impaired tissue regeneration occur simultaneously (Table 2) [59].

However, several parameters must be systematically optimized before AMP-loaded SF systems can be translated into clinically useful wound therapeutics. These include AMP loading capacity, peptide–SF binding affinity, encapsulation efficiency, release kinetics, retention under simulated wound-fluid conditions, preservation of peptide secondary structure and antimicrobial activity, cytocompatibility, degradation behavior, and mechanical stability [59]. Importantly, the demonstration that SF itself can inhibit growth of common wound pathogens at sufficiently high concentrations also suggests that the biological activity of the SF matrix should be distinguished from the activity of the incorporated AMP when evaluating therapeutic mechanisms [59].

Challenges and Translational Barriers

Proteolytic degradation

Proteolytic degradation is a major barrier to the clinical translation of antimicrobial peptides (AMPs) for chronic wound therapy.

Chronic wounds, particularly diabetic and infected wounds, often exhibit elevated protease activity, including matrix metalloproteinases (MMPs) and serine proteases, which can degrade exogenously administered peptides and endogenous host-defense peptides [1,60]. Rapid enzymatic cleavage can substantially shorten the AMP half-life and reduce its local bioavailability, causing peptide concentrations to fall below the levels required for effective antimicrobial or immunomodulatory activity. Moreover, proteolysis may generate fragments with altered or unpredictable biological activities. Strategies such as D-amino-acid substitution, peptide cyclization, terminal modification, incorporation into hydrogels or nanoparticles, and controlled-release biomaterials may improve protease resistance and prolong local peptide activity [7,9]. Therefore, proteolytic stability should be evaluated under physiologically relevant wound-fluid conditions during AMP development.

Cytotoxicity

Although antimicrobial peptides (AMPs) are attractive therapeutic candidates because of their potent activity against pathogenic microorganisms, the same physicochemical properties responsible for microbial membrane disruption can potentially cause undesirable interactions with mammalian cells. Most membrane-active AMPs depend on a combination of positive charge, hydrophobicity, and amphipathicity to associate with and perturb lipid membranes [6]. At sufficiently high concentrations, these properties may reduce the selectivity between bacterial and mammalian membranes, resulting in membrane damage, mitochondrial dysfunction, hemolysis, or reduced viability of keratinocytes, fibroblasts, and other cells involved in tissue repair [6,9]. AMP cytotoxicity is strongly dependent on peptide sequence and physicochemical characteristics. Increasing hydrophobicity can enhance membrane insertion and antimicrobial potency, but excessive hydrophobicity may also increase nonspecific interaction with mammalian membranes. Similarly, increasing cationicity can improve electrostatic association with negatively charged bacterial surfaces but may increase cellular uptake and cytotoxicity when the peptide concentration becomes excessive[9]. Therefore, AMP development requires optimization of the therapeutic index, defined broadly as the separation between the concentration required for effective antimicrobial activity and the concentration associated with toxicity to host cells [9]. The wound environment further complicates this relationship because keratinocytes, fibroblasts, endothelial cells, macrophages, and other cells are actively proliferating and migrating during repair. A formulation that is strongly bactericidal but cytotoxic to these cells could ultimately delay wound closure despite successful reduction of bacterial burden [9]. For this reason, evaluation of AMP candidates should include not only minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), but also cytotoxicity assays using relevant skin and wound-associated cell types [9]. The selectivity index, often calculated from cytotoxic concentration and antimicrobial concentration, can provide a more meaningful indication of therapeutic potential than antimicrobial potency alone [9].

Complex Wound Microenvironment

A major limitation in translating AMP activity from laboratory experiments to clinical wound treatment is the biochemical complexity of the wound microenvironment. Unlike standard antimicrobial assays, wounds contain a heterogeneous mixture of wound exudate, plasma proteins, electrolytes, proteolytic enzymes, extracellular DNA, lipids, degraded extracellular matrix components, cytokines, and cellular debris. These components can substantially modify AMP structure, availability, diffusion, and antimicrobial activity [7,31]. One important mechanism is peptide sequestration. AMPs may bind to serum proteins, extracellular matrix components, or nucleic acids present in wound exudate, reducing the concentration of freely available peptide that can interact with bacterial membranes. Electrostatic interactions that facilitate AMP binding to bacteria can also promote nonspecific binding to negatively charged host-derived molecules [9]. Consequently, an AMP exhibiting a low MIC in a simple physiological buffer may require a substantially higher concentration to produce comparable activity in wound fluid [9]. Ionic strength is another important factor. Increasing concentrations of Na^+ and other ions can shield electrostatic interactions between cationic peptides and bacterial membranes, reducing peptide adsorption and membrane activity [31]. Similarly, divalent cations such as Ca^{2+} and Mg^{2+} can alter bacterial surface charge and influence AMP binding, particularly in Gram-negative organisms where these ions stabilize the LPS layer [31]. Proteolytic degradation represents another major challenge. Chronic wounds frequently contain elevated levels of proteases, including matrix metalloproteinases and serine proteases. These enzymes can degrade peptide therapeutics and shorten their residence time at the wound site [1]. The problem can become particularly pronounced in chronic diabetic wounds, where dysregulated protease activity contributes to impaired tissue repair [1]. Therefore, AMP evaluation should progressively move from conventional buffer-based assays toward more physiologically relevant experimental models. Testing in simulated wound fluid, human wound exudate, protein-rich media, polymicrobial communities, and three-dimensional tissue models can provide more realistic information about peptide performance. Delivery systems that protect AMPs from proteolysis and maintain local concentrations above the effective threshold may consequently be essential for successful clinical translation.

Biofilm Penetration

Biofilm-associated infection is one of the most significant barriers to successful treatment of chronic wounds. Unlike planktonic bacteria, biofilm-associated microorganisms are embedded within an extracellular polymeric substance (EPS) matrix composed of polysaccharides, proteins, extracellular DNA, lipids, and other biomolecules [4]. This matrix provides structural organization and can restrict penetration of antimicrobial agents while simultaneously creating nutrient and oxygen gradients that promote metabolically heterogeneous bacterial populations [4]. AMPs can exhibit considerable anti-biofilm activity, but strong activity against planktonic bacteria does not necessarily translate into equivalent activity against mature biofilms. The EPS matrix can bind and sequester cationic peptides before they reach bacterial cells. In

addition, electrostatic interactions between AMPs and extracellular DNA or polysaccharides may reduce the effective concentration of peptide within deeper regions of the biofilm. Consequently, an AMP may demonstrate a low MIC against planktonic bacteria but require substantially higher concentrations to eradicate an established biofilm [4,28]. Biofilm-associated physiological heterogeneity further contributes to therapeutic resistance. Bacteria located in nutrient-limited and oxygen-depleted regions of mature biofilms can enter slow-growing or metabolically altered states that make them less susceptible to antimicrobial mechanisms dependent on active cellular metabolism. In polymicrobial wound biofilms, interactions between different bacterial species can additionally modify matrix composition, quorum-sensing behavior, virulence, and antimicrobial susceptibility [61]. For AMP-based wound therapy, therefore, it is important to distinguish minimum inhibitory concentration (MIC), minimum biofilm inhibitory concentration (MBIC), and minimum biofilm eradication concentration (MBEC) [4]. Evaluating only planktonic MIC values can substantially overestimate the likely clinical effectiveness of an AMP against chronic wound infection. Future AMP formulations should ideally combine direct membrane activity with mechanisms that improve biofilm penetration, disrupt the EPS matrix, interfere with quorum sensing, or sensitize biofilm-associated bacteria to antimicrobial treatment [4]. Nanoparticles, hydrogels, electrospun nanofibers, and stimuli-responsive systems may help address this limitation by improving peptide retention and penetration. In particular, delivery systems capable of releasing AMPs in response to bacterial enzymes, acidic pH, or elevated reactive oxygen species could potentially generate higher local peptide concentrations within infected regions while limiting unnecessary exposure to surrounding healthy tissue.

Manufacturing and Cost

The clinical translation of AMPs is also constrained by manufacturing and economic considerations. Unlike many small-molecule antibiotics that can be produced through relatively inexpensive chemical synthesis or microbial fermentation, therapeutic peptides may require multiple stages of synthesis, purification, folding or structural control, formulation, sterilization, and quality assessment [9]. Solid-phase peptide synthesis (SPPS) is widely used for laboratory-scale production, but increasing peptide length and structural complexity can reduce synthesis yield and increase purification requirements [9]. Manufacturing costs can become particularly significant when peptides contain non-natural amino acids, terminal modifications, cyclization, lipidation, or other structural modifications designed to improve stability and activity [7]. In addition, the final therapeutic product must retain antimicrobial potency during storage and remain stable under clinically relevant temperature and humidity conditions [7]. Formulation adds another layer of complexity. AMP-loaded hydrogels, nanoparticles, electrospun fibers, silk fibroin matrices, or microneedles require reproducible control of peptide loading, particle or fiber characteristics, release kinetics, sterility, mechanical properties, and degradation [7]. Small changes in formulation parameters may influence peptide conformation and biological activity. Therefore, scale-up from laboratory fabrication to Good Manufacturing Practice (GMP)-compatible production is a significant translational step [7]. One potential solution is the development of recombinant AMP production systems, optimized fermentation processes, shorter synthetic AMP sequences, and scalable biomaterial manufacturing techniques [7]. Computational design and high-throughput screening may also reduce development costs by identifying peptides with favorable antimicrobial potency, selectivity, stability, and manufacturability before extensive experimental optimization [7]. For wound applications, local delivery may additionally improve economic feasibility because a controlled-release dressing could reduce the amount of peptide required compared with repeated administration of soluble peptide. However, this advantage must be demonstrated experimentally through pharmacokinetic, dose-response, stability, and cost-effectiveness studies.

Dose Optimization

Dose optimization represents a critical determinant of AMP therapeutic efficacy. AMP activity is generally concentration-dependent, but the relationship between peptide concentration and therapeutic benefit is not necessarily linear. An insufficient concentration may fail to suppress bacterial growth or biofilm formation, whereas excessive concentrations may increase cytotoxicity, inflammatory signaling, or nonspecific membrane interactions [9]. The effective concentration of an AMP in vivo may also differ substantially from its experimentally determined MIC. Factors such as protein binding, ionic strength, proteolytic degradation, biofilm formation, wound exudate, and local tissue distribution can reduce the fraction of peptide that remains biologically active. Consequently, dose selection based exclusively on conventional in vitro MIC values may underestimate the concentration required to achieve therapeutic activity in a chronic wound [7]. An additional challenge is the distinction between antimicrobial and regenerative concentrations. Some AMPs exhibit biological effects on keratinocytes, fibroblasts, endothelial cells, and immune cells at concentrations that may differ from those required for direct bacterial killing [7]. LL-37 provides an important example because its concentration-dependent effects can include antimicrobial activity, chemotaxis, angiogenesis, and epithelial-cell signaling [7]. Thus, an optimal wound-healing dose may need to balance microbial killing with immunomodulatory and regenerative activity rather than simply maximize bactericidal potency [7]. Controlled local delivery therefore represents a particularly attractive strategy. Hydrogels, silk fibroin matrices, nanoparticles, nanofibers, and microneedles can potentially maintain AMP concentrations within the therapeutic window for extended periods while reducing systemic exposure. A sustained-release system may also minimize the fluctuations in local peptide concentration associated with repeated administration of free peptide.

Ultimately, dose optimization should consider AMP concentration, exposure duration, release kinetics, wound volume, bacterial burden, biofilm maturity, protease activity, tissue penetration, and host-cell tolerance. Future studies should therefore use pharmacodynamic models that connect local peptide concentration

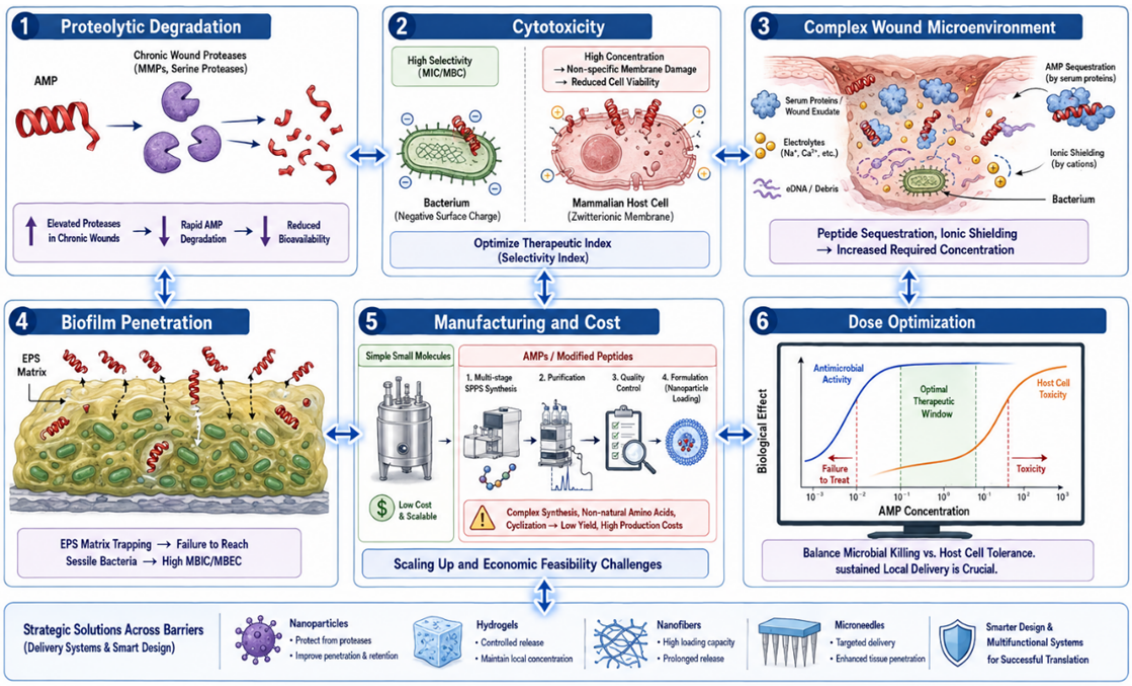

Figure 2: Translational barriers and potential delivery strategies for antimicrobial peptide (AMP)-based wound therapy.

with microbial killing and tissue-regenerative outcomes. Such an approach may allow AMP formulations to achieve a more favorable balance between efficacy and safety than conventional administration of free peptides.

The infographic summarizes six major challenges limiting the clinical translation of AMPs for chronic wound treatment: (1) proteolytic degradation by elevated wound proteases, resulting in reduced peptide stability and bioavailability; (2) cytotoxicity arising from nonspecific interactions with mammalian cell membranes at higher concentrations, emphasizing the need to optimize the therapeutic/selectivity index; (3) the complex wound microenvironment, where protein sequestration, ionic shielding, extracellular DNA, and wound exudate can reduce AMP availability and activity; (4) limited penetration into mature biofilms due to trapping within the extracellular polymeric substance (EPS) matrix, leading to increased MBIC and MBEC requirements; (5) manufacturing and economic challenges associated with multistep peptide synthesis, purification, structural modification, formulation, and scale-up; and (6) dose optimization, requiring a balance between antimicrobial efficacy and host-cell tolerance within an appropriate therapeutic window. Nanoparticles, hydrogels, nanofibers, microneedles, and other controlled-delivery platforms may help overcome these barriers by protecting AMPs, enhancing tissue and biofilm penetration, and maintaining effective local peptide concentrations.

Future Perspectives

Future research on antimicrobial peptides (AMPs) for wound healing should move beyond conventional antimicrobial screening toward the development of multifunctional and microenvironment-responsive therapeutic systems. Traditional AMP studies often emphasize minimum inhibitory concentration (MIC), bacterial killing, and membrane-disruption mechanisms; however, successful treatment of chronic wounds requires simultaneous control of infection, inflammation, biofilm formation, oxidative stress, and impaired tissue regeneration. Host-defense peptides such as LL-37 already demonstrate that antimicrobial, immunomodulatory, angiogenic, and regenerative functions can coexist within a single therapeutic molecule [7,31]. Future AMP development should therefore evaluate these functions together rather than considering antimicrobial activity as the sole therapeutic endpoint.

One particularly promising direction is the development of AMP-loaded smart biomaterials capable of responding to pathological characteristics of the wound microenvironment. Chronic infected wounds frequently exhibit altered pH, elevated reactive oxygen species (ROS), increased protease activity, bacterial enzymes, and other biochemical abnormalities. These characteristics can be exploited as endogenous triggers for controlled drug release. For example, pH-responsive materials could release AMPs preferentially under the mildly acidic conditions associated with infected wounds, whereas enzyme- or ROS-responsive systems could provide localized peptide release in regions of active infection or inflammation [48]. Such systems could potentially reduce premature AMP release and maintain therapeutically relevant peptide concentrations at the site of infection.

Combination therapy represents another important avenue for future development. AMPs could be combined with conventional antibiotics to produce synergistic antimicrobial effects and potentially reduce the required dose of individual agents. In addition, combining AMPs with anti-biofilm molecules, growth-factor mimetics, extracellular-matrix components, antioxidants, or

immunomodulatory compounds may simultaneously target several pathological mechanisms involved in chronic wound persistence. Such combinations may be particularly valuable for polymicrobial and biofilm-associated infections, where a single therapeutic mechanism is often insufficient [4,28].

Rational AMP sequence engineering is also expected to play an increasingly important role. Modification of net charge, hydrophobicity, amphipathicity, secondary structure, protease resistance, and peptide length can substantially alter antimicrobial potency and mammalian-cell selectivity. Computational approaches, molecular dynamics simulations, machine learning, and high-throughput peptide screening may facilitate identification of sequences with improved therapeutic indices. An important objective will be to maximize antimicrobial and anti-biofilm activity while minimizing cytotoxicity and nonspecific inflammatory activation [7].

Nanotechnology provides an additional opportunity to address several limitations simultaneously. Encapsulation of AMPs within nanoparticles can protect peptides against proteolytic degradation, improve local retention, and permit controlled release. Similarly, incorporation into electrospun nanofibers can provide an extracellular-matrix-like architecture while maintaining localized antimicrobial activity. Hydrogels can provide a hydrated wound interface and prolonged peptide residence, whereas microneedle systems may improve penetration into infected tissue and biofilms [12,48].

Among these approaches, silk fibroin (SF)-based AMP delivery deserves particular attention because SF can combine structural support with controlled bioactive delivery. SF can be fabricated into hydrogels, films, electrospun fibers, nanoparticles, and porous scaffolds, while its β-sheet content can be modulated to control mechanical stability and degradation. Recent experimental studies have demonstrated AMP-containing SF systems with antibacterial and wound-regenerative effects, including polymyxin-B/SF hydrogels, CM11-loaded SF nanofibers, and KR-12-containing SF films [10,11]. Future studies should investigate whether SF can be engineered as a stimuli-responsive AMP reservoir, in which peptide release is triggered by bacterial enzymes, pH, ROS, or protease activity. Such an approach could transform SF from a passive wound dressing into an active and programmable therapeutic platform.

Ultimately, the field should adopt a design-to-translation framework in which peptide sequence, biomaterial composition, release kinetics, antimicrobial efficacy, immunomodulation, cytocompatibility, and wound regeneration are optimized simultaneously. More physiologically relevant experimental models, including polymicrobial biofilms, diabetic wound models, human wound-fluid conditions, organotypic skin models, and eventually well-designed clinical trials, will be essential to determine whether the promising results observed in simplified laboratory systems can be reproduced in complex clinical wounds.

Conclusion

Antimicrobial peptides represent a distinctive class of therapeutic molecules for wound management because their biological activities extend beyond direct microbial killing. In addition to disrupting bacterial membranes and interfering with intracellular targets, several AMPs function as host-defense peptides that regulate inflammation, leukocyte recruitment, keratinocyte migration, angiogenesis, fibroblast activity, and extracellular-matrix remodeling [7,31]. LL-37 and human β-defensins are particularly well-characterized examples, with experimental studies demonstrating antimicrobial, immunomodulatory, and regenerative effects in different wound models [33,44].

Despite this multifunctionality, translation of AMPs into clinically effective wound therapeutics remains challenging. Proteolytic degradation, physicochemical instability, concentration-dependent cytotoxicity, limited residence time, protein and ion interactions within wound exudate, biofilm-associated tolerance, manufacturing costs, and uncertainty regarding optimal dosing can all reduce therapeutic efficacy [4]. Therefore, increasing the dose of free AMP alone is unlikely to provide a universal solution. Instead, therapeutic success will probably depend on maintaining an appropriate local concentration while simultaneously protecting the peptide from degradation and minimizing exposure of healthy cells.

Biomaterial-assisted delivery provides a promising strategy to overcome these limitations. Hydrogels can provide hydrated wound coverage and sustained peptide release, nanoparticles can protect AMPs and improve local delivery, electrospun nanofibers can reproduce aspects of the extracellular-matrix architecture, and microneedle systems can facilitate localized penetration. Among these platforms, silk fibroin-based systems are particularly attractive because SF combines biocompatibility, biodegradability, tunable β-sheet-dependent stability, mechanical properties, and diverse processing capabilities. Emerging studies involving AMP-loaded SF hydrogels, nanofibers, and films suggest that these systems can simultaneously provide antimicrobial activity and support tissue regeneration [10,11].

The future of AMP-based wound therapy is therefore likely to involve a transition from antimicrobial peptide as a drug to AMP-integrated regenerative therapeutic platform. Such platforms could combine antimicrobial and anti-biofilm activity with immunomodulation, controlled drug release, angiogenesis, re-epithelialization, and extracellular-matrix regeneration. The integration of rational peptide engineering with smart biomaterials and nanotechnology may ultimately enable site-specific, sustained, and responsive AMP delivery for chronic infected wounds. Nevertheless, rigorous validation in clinically relevant models and well-controlled clinical trials remains necessary before these multifunctional systems can be considered established therapeutic approaches.

References

1. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: Mechanisms, signaling, and translation. Sci

Transl Med. 2014; 6: 265sr266.

2. Gurtner GC, Werner S, Barrandon Y, et al. Wound repair and regeneration. Nature. 2008; 453: 314-321.
3. Frykberg RG, Banks J. Challenges in the Treatment of Chronic Wounds. Adv Wound Care (New Rochelle). 2015; 4: 560-582.
4. Yasir M, Willcox MDP, Dutta D. Action of Antimicrobial Peptides against Bacterial Biofilms. Materials (Basel). 2018; 11: 2468.
5. Armstrong David G, Boulton Andrew JM, Bus Sicco A. Diabetic Foot Ulcers and Their Recurrence. New England Journal of Medicine. 2017; 376: 2367-2375.
6. Hancock REW, Sahl HG. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol. 2006; 24: 1551-1557.
7. Mookherjee N, Anderson M, Haagsman HP, et al. Antimicrobial host defence peptides: functions and clinical potential. Nat Rev Drug Discov. 2020; 19: 311-332.
8. Niyonsaba F, Ushio H, Hara M, et al. Antimicrobial peptides human beta-defensins and cathelicidin LL-37 induce the secretion of a pruritogenic cytokine IL-31 by human mast cells. J Immunol. 2010; 184: 3526-3534.
9. Mahlapuu M, Håkansson J, Ringstad L, et al. Antimicrobial Peptides: An Emerging Category of Therapeutic Agents. Front Cell Infect Microbiol. 2016; 6: 194.
10. Aye SSS, Zhang ZH, Yu X, et al. Silk Hydrogel Electrostatically Functionalized with a Polycationic Antimicrobial Peptide: Molecular Interactions, Gel Properties, and Antimicrobial Activity. Langmuir. 2021; 38: 50-61.
11. Moosazadeh Moghaddam M, Farhadie B, Mirnejad R, et al. Evaluation of an antibacterial peptide-loaded amniotic membrane/silk fibroin electrospun nanofiber in wound healing. Int Wound J. 2023; 20: 3443-3456.
12. Patrulea V, Borchard G, Jordan O. An Update on Antimicrobial Peptides (AMPs) and Their Delivery Strategies for Wound Infections. Pharmaceutics. 2020; 12: 840.
13. Kanaujia KA, Mishra N, Rajinikanth PS, et al. Antimicrobial peptides as antimicrobials for wound care management: A comprehensive review. Journal of Drug Delivery Science and Technology. 2024; 95: 105570.
14. Zhang C, Meng L, Sethi G, et al. Peptide-driven approaches in advanced wound healing materials. Drug Discov Today. 2025; 30: 104440.
15. Paulmann M, Arnold T, Linke D, et al. Structure-activity analysis of the dermcidin-derived peptide DCD-1L, an anionic antimicrobial peptide present in human sweat. J Biol Chem. 2012; 287: 8434-8443.
16. Wu Y, Liu T, Jin L, et al. Antimicrobial Peptides for Skin Wound Healing. Biomolecules. 2025; 15: 11.
17. Guryanova SV, Belogurova-Ovchinnikova OY, Ovchinnikova TV. Human and Marine Host Defense Peptides for Healthy Skin. Mar Drugs. 2026; 24: 134.
18. De Smet K, Contreras R. Human antimicrobial peptides: defensins, cathelicidins and histatins. Biotechnology letters. 2005; 27: 1337-1347.
19. Steinstraesser L, Hirsch T, Schulte M, et al. Innate defense regulator peptide 1018 in wound healing and wound infection. PLoS One. 2012; 7: e39373.
20. Ge Y, MacDonald DL, Holroyd KJ, et al. In vitro antibacterial properties of pexiganan, an analog of magainin. Antimicrob Agents Chemother. 1999; 43: 782-788.
21. Branco P, Muchagato Maurício E, Raposo LR, et al. Antimicrobial Peptides, Bacteriocins and Mycocins as Natural Antimicrobials: Applications in Food Safety, Agriculture and Healthcare. Antibiotics (Basel). 2026; 15: 649.
22. Verma DP, Tripathi AK, Thakur AK. Innovative Strategies and Methodologies in Antimicrobial Peptide Design. J Funct Biomater. 2024; 15: 11.
23. Li J, Koh JJ, Liu S, et al. Membrane Active Antimicrobial Peptides: Translating Mechanistic Insights to Design. Front Neurosci. 2017; 11: 73.
24. Wu YZ, Wang J, Hu YH, et al. Antimicrobial Peptides: Classification, Mechanism, and Application in Plant Disease Resistance. Probiotics Antimicrob Proteins. 2025; 17: 1432-1446.
25. Min KH, Kim KH, Ki MR, et al. Antimicrobial Peptides and Their Biomedical Applications: A Review. Antibiotics (Basel). 2024; 13: 794.
26. Sengupta D. Leontiadou H, Mark AE, et al. Toroidal pores formed by antimicrobial peptides show significant disorder. Biochim Biophys Acta. 2008; 1778: 2308-2317.
27. Wimley WC. Describing the mechanism of antimicrobial peptide action with the interfacial activity model. ACS Chem Biol. 2010; 5: 905-917.
28. Luo Y, Song Y. Mechanism of Antimicrobial Peptides: Antimicrobial, Anti-Inflammatory and Antibiofilm Activities. Int J Mol Sci. 2021; 22: 11401.
29. Naaz T, Lahiri D, Pandit S, et al. Antimicrobial Peptides Against Microbial Biofilms: Efficacy, Challenges, and Future Prospect. International Journal of Peptide Research and Therapeutics. 2023; 29: 48.
30. Freitas ED, Bataglioli RA, Oshodi J, et al. Antimicrobial peptides and their potential application in antiviral coating agents. Colloids Surf B Biointerfaces. 2022; 217: 112693.
31. Hancock RE, Haney EF, Gill EE. The immunology of host defence peptides: beyond antimicrobial activity. Nat Rev Immunol. 2016; 16: 321-334.
32. Gallo RL, Hooper LV. Epithelial antimicrobial defence of the skin and intestine. Nat Rev Immunol. 2012; 12: 503-516.
33. Ramos R, Silva JP, Rodrigues AC, et al. Wound healing activity of the human antimicrobial peptide LL37. Peptides. 2011; 32: 1469-1476.
34. Mangoni ML, McDermott AM, Zasloff M. Antimicrobial peptides and wound healing: biological and therapeutic considerations. Exp Dermatol. 2016; 25: 167-173.

35. Hirsch T, Spielmann M, Zuhaili B, et al. Human beta-defensin-3 promotes wound healing in infected diabetic wounds. J Gene Med. 2009; 11: 220-228.
36. Heilborn JD, Nilsson MF, Kratz G, et al. The cathelicidin anti-microbial peptide LL-37 is involved in re-epithelialization of human skin wounds and is lacking in chronic ulcer epithelium. J Invest Dermatol. 2003; 120: 379-389.
37. Koczulla R, von Degenfeld G, Kupatt C, et al. An angiogenic role for the human peptide antibiotic LL-37/hCAP-18. J Clin Invest. 2003; 111: 1665-1672.
38. Oudhoff MJ, Bolscher JG, Nazmi K, et al. Histatins are the major wound-closure stimulating factors in human saliva as identified in a cell culture assay. FASEB J. 2008; 22: 3805-3812.
39. Moreno-Angarita A, Aragón CC, Tobón GJ. Cathelicidin LL-37: A new important molecule in the pathophysiology of systemic lupus erythematosus. J Transl Autoimmun. 2020; 3: 100029.
40. Verjans ET, Zels S, Luyten W, et al. Molecular mechanisms of LL-37-induced receptor activation: An overview. Peptides. 2016; 85: 16-26.
41. De Soricellis C, Laigle C, Spinelli L, et al. Lipidized LL37-loaded PLGA nanocarriers: Bioengineered peptide delivery systems for enhanced wound healing. Int J Pharm. 2025; 677: 125668.
42. Yanagisawa T, Ishii M, Takahashi M, et al. Human cathelicidin antimicrobial peptide LL-37 promotes lymphangiogenesis in lymphatic endothelial cells through the ERK and Akt signaling pathways. Mol Biol Rep. 2020; 47: 6841-6854.
43. Miranda E, Bramono K, Yunir E, et al. Efficacy of LL-37 cream in enhancing healing of diabetic foot ulcer: a randomized double-blind controlled trial. Arch Dermatol Res. 2023; 315: 2623-2633.
44. Hirsch T, Spielmann M, Zuhaili B, et al. Human beta-defensin-3 promotes wound healing in infected diabetic wounds. J Gene Med. 2009; 11: 220-228.
45. Mahlapuu M, Sidorowicz A, Mikosinski J, et al. Evaluation of LL-37 in healing of hard-to-heal venous leg ulcers: A multicentric prospective randomized placebo-controlled clinical trial. Wound Repair Regen. 2021; 29: 938-950.
46. Guan T, Li J, Chen C, et al. Self-Assembling Peptide-Based Hydrogels for Wound Tissue Repair. Adv Sci (Weinh). 2022; 9: e2104165.
47. Cross ER, Coulter SM, Pentlavalli S, et al. Unravelling the antimicrobial activity of peptide hydrogel systems: current and future perspectives. Soft Matter. 2021; 17: 8001-8021.
48. Firdous SO, Sagor MMH, Arafat MT. Advances in Transdermal Delivery of Antimicrobial Peptides for Wound Management: Biomaterial-Based Approaches and Future Perspectives. ACS Appl Bio Mater. 2024; 7: 4923-4943.
49. Dart A, Bhave M, Kingshott P. Antimicrobial Peptide-Based Electrospun Fibers for Wound Healing Applications. Macromol Biosci. 2019; 19: e1800488.
50. Liu X, Xu H, Zhang M, et al. Electrospun Medicated Nanofibers for Wound Healing: Review. Membranes. 2021; 11: 10.
51. Farokhi M, Mottaghitalab F, Fatahi Y, et al. Overview of Silk Fibroin Use in Wound Dressings. Trends Biotechnol. 2018; 36: 907-922.
52. Patil PP, Reagan MR, Bohara RA. Silk fibroin and silk-based biomaterial derivatives for ideal wound dressings. Int J Biol Macromol. 2020; 164: 4613-4627.
53. Yuan L, Zhang Y, Shuai Y. Self-Assembly Peptide Hydrogel and its Application in the Biomedical Field. Current drug delivery. 2026; 23: 279-299.
54. Su Y, Mainardi VL, Wang H, et al. Dissolvable Microneedles Coupled with Nanofiber Dressings Eradicate Biofilms via Effectively Delivering a Database-Designed Antimicrobial Peptide. ACS nano. 2020; 14: 11775-11786.
55. Haidari H, Bright R, Yu Y, et al. Development of Microneedles for Antimicrobial Drug Delivery: A Comprehensive Review on Applications in Wound Infection Management. Small Sci. 2024; 4: 2400158.
56. Kundu B, Rajkhowa R, Kundu SC, et al. Silk fibroin biomaterials for tissue regenerations. Adv Drug Deliv Rev. 2013; 65: 457-470.
57. Ma L, Dong W, Lai E, et al. Silk fibroin-based scaffolds for tissue engineering. Front Bioeng Biotechnol. 2024; 12: 1381838.
58. Zhang J, Wang L, Xu C, et al. Transparent silk fibroin film-facilitated infected-wound healing through antibacterial, improved fibroblast adhesion and immune modulation. J Mater Chem B. 2024; 12: 475-488.
59. Egan G, Hannah AJ, Donnelly S, et al. The Biologically Active Biopolymer Silk: The Antibacterial Effects of Solubilized Bombyx mori Silk Fibroin with Common Wound Pathogens. Adv Biol (Weinh). 2024; 8: 2300115.
60. Gurjala AN, Geringer MR, Seth AK, et al. Development of a novel, highly quantitative in vivo model for the study of biofilm-impaired cutaneous wound healing. Wound Repair Regen. 2011; 19: 400-410.
61. Donné J, Dewilde S. Chapter Five - The Challenging World of Biofilm Physiology in Poole, R.K. (Ed.). Advances in Microbial Physiology. 2015; 235-292.