

Application of Antimicrobial Peptides in Wound Dressings

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Background: Growing antibiotic misuse and the rise of antimicrobial resistance have driven interest in antimicrobial peptides (AMPs) as therapeutic agents for wound dressings and clinical wound management. AMPs are short, cationic peptides with broad-spectrum activity and diverse mechanisms of action that confer a low propensity for resistance development.

Methods: We performed a focused literature synthesis to review AMP classification, structural features, antimicrobial mechanisms, and strategies for integrating AMPs into wound dressings. We emphasize materials and delivery approaches reported for hydrogels, electrospun fibers, films, scaffolds, and sponges, and we summarize advances in hybrid systems that combine AMPs with functional materials.

Results: AMP-loaded dressings promote infection control and tissue repair by maintaining a favorable wound microenvironment, enabling controlled peptide release, reducing biofilms, and stimulating cell proliferation and angiogenesis. Hybrid platforms—polysaccharide and stimuli-responsive hydrogels, metal-nanoparticle composites, exosome carriers, and cryogels—improve peptide stability and bioavailability while introducing functionalities such as real-time bacterial sensing, antioxidant activity, and electrical conductivity for electrostimulation. In chronic wounds and burns, AMP-based dressings show promise for anti-biofilm activity, immunomodulation, enhanced re-epithelialization, and reduced risk of resistance compared with conventional antibiotics.

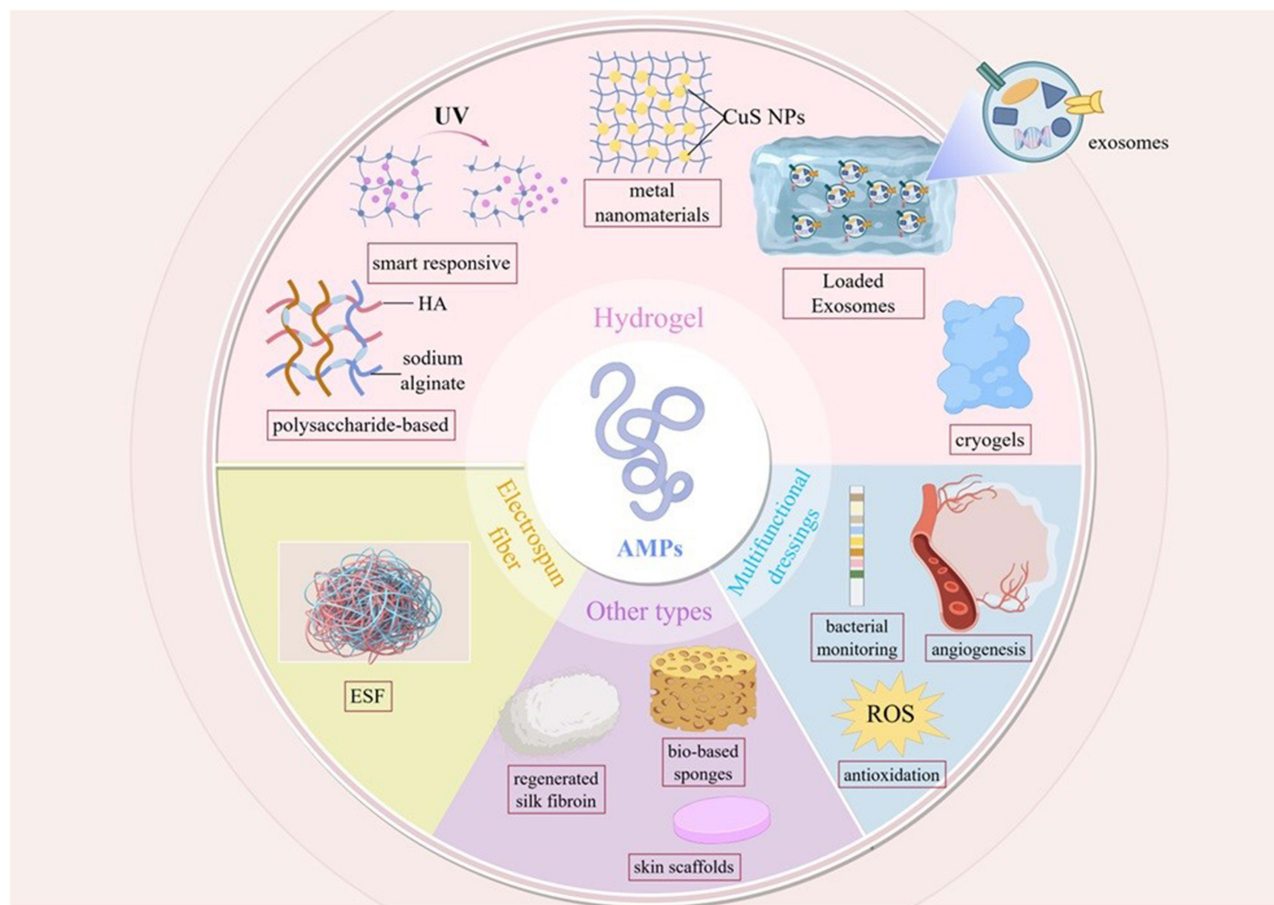
Conclusion: We identify key challenges and propose future directions: rational design of tailored AMPs, smart controlled-release carriers, nanotechnology-enabled formulations, and strategies to accelerate clinical translation. Advances in these areas are expected to expedite the clinical adoption of AMP-based wound therapies, offering safer, more effective, and personalized treatment options.

Keywords: antibiotics, antimicrobial peptides, wound healing, bacterial infection, drug resistance, wound dressings, antimicrobial materials

Introduction

Skin is the body's largest organ, composed of the epidermis, dermis, and subcutaneous tissues, and serves as a primary barrier against environmental insults. Wound healing restores tissue integrity and barrier function through coordinated stages—hemostasis, inflammation, proliferation, and remodeling—supporting skin homeostasis.¹ The skin microbiome contributes to repair, in part via host- and microbiome-derived antimicrobial peptides (AMPs) that shape microbial balance and host defense.² Antibiotic-resistant infections in chronic wounds increasingly impede repair, raise complication rates, and create a major public health burden worldwide.³ As conventional antibiotics lose efficacy, there is an urgent need for new antimicrobial strategies suitable for wound-site delivery.⁴ Infection, dysregulated inflammation, and biofilms can disrupt healing, leading to delayed recovery, higher complication rates, and increased healthcare costs.⁵

Graphical Abstract



AMPs—short, often cationic and amphipathic molecules of the innate immune system—have emerged as promising candidates because of broad-spectrum activity, rapid killing kinetics, and a low tendency to induce resistance. Beyond direct microbicidal effects, many AMPs modulate inflammation, promote cell migration and proliferation, and stimulate angiogenesis, all of which can accelerate tissue repair. Accordingly, a growing number of studies have integrated AMPs into wound-dressing platforms (hydrogels, electrospun fibers, films, scaffolds, sponges) to enable local delivery and multifunctional therapy.⁶ Notably, recent *in vitro* and *in vivo* studies demonstrate the efficacy of AMP-loaded nanofiber and hydrogel platforms in eradicating biofilms and promoting re-epithelialization, which highlight AMP-nanomaterial hybrids and translational challenges.^{7,8} Successful translation requires careful peptide selection, compatible dressing materials, controlled release profiles, thorough biocompatibility testing, and standardized wound assessment protocols. Importantly, many earlier studies — including foundational reports on host antimicrobial peptides and peptide antibiotics (Steiner 1981; Ganz et al 1985; Hancock & Chapple 1999) — also revealed recurrent translational vulnerabilities that persist in contemporary literature: linear L-amino-acid peptides are rapidly degraded in protease-rich wound fluids, many reports rely on small-animal or single-strain assays that poorly model human chronic wounds and biofilms, and study endpoints and biofilm challenge protocols are highly heterogeneous. To address these limitations we suggest integrating standardized *in vitro* mechanistic assays (membrane versus intracellular action, protease stability), well-defined multi-species biofilm challenges, and higher-fidelity preclinical models (diabetic/ischemic and large-animal wounds) early in development to improve reproducibility and reduce bias. Integrating AMPs with advanced biomaterials can still combine

infection control with regenerative support, but doing so requires attention to these historical weaknesses and adoption of harmonized experimental pipelines linking bench mechanistic data to clinically predictive models.

This review synthesizes current knowledge on AMP classification, mechanisms of action, and strategies for their incorporation into diverse dressing platforms, highlights multifunctional hybrid systems, and outlines remaining challenges and future directions to accelerate clinical translation. We conducted a focused literature search in PubMed, Web of Science and Scopus for articles published from 2000 through 2024 using combinations of keywords including “antimicrobial peptide”, “AMP”, “wound dressing”, “hydrogel”, “electrospun”, “nanoparticle”, and “wound healing”. We prioritized primary studies describing AMP integration with wound-dressing materials and in vitro or in vivo evaluations, together with recent relevant reviews. Non-English articles and studies not related to wound applications were excluded.

Definition and Classification of AMPs

Definition

AMPs are a class of short peptides with broad-spectrum antimicrobial activity, composed of oligopeptides made up of amino acid residues (up to 100 in length) arranged in either linear or cyclic forms. They are typically composed of L-amino acids and exhibit antimicrobial activity through secondary structures, such as α -helices, β -sheets, or a combination of both.⁹ Due to their unique multifaceted mechanisms of action, AMPs have attracted increasing attention as a potential novel strategy for treating chronic wound infections. These peptides are inherently cationic¹⁰ and are small molecules produced by the innate immune system of organisms, forming an integral part of the biological defense system.⁹ These biomolecules are cationic, hydrophobic, or amphipathic, and exhibit varying biological activities against Gram-positive and Gram-negative bacteria, viruses, fungi, protozoa, and even tumors.¹¹ When humans encounter potentially harmful pathogens through contact, inhalation, or ingestion, one defense strategy is producing AMPs.¹² Unlike the adaptive immune response activated by T cells and B cells to combat specific antigens after pathogen invasion,¹³ endogenous peptides (expressed or induced) provide a rapid and effective method for defending against pathogens.¹⁴

Classification

AMPs are commonly classified by origin, structure, and amino-acid composition. By origin, AMPs derive from plants (eg, thionins, plant defensins), animals (insects, amphibians and vertebrates — eg, cecropins, magainins, defensins, cathelicidins such as human LL-37) or microorganisms (bacteriocins and related peptides). Microbial AMPs are particularly diverse and may be ribosomally or non-ribosomally synthesized; this diversity and the relative ease of microbial production make them attractive for scalable manufacturing and translational applications.^{15,16} Microbial AMPs (bacteriocins and related peptides) are especially diverse and may be ribosomally or non-ribosomally synthesized; they include bacterial, fungal and actinobacterial peptides with high potential for biotechnological production. Structurally, AMPs are grouped into canonical classes— α -helical,^{17,18} β -sheet stabilized (often with disulfide bonds),¹⁹ looped/cyclic peptides,^{20,21} and extended or proline/glycine-rich peptides—each class conferring distinct membrane-interaction modes. Classification by amino-acid composition identifies proline-rich, histidine-rich, tryptophan-rich or cationic-rich peptides; composition influences cellular uptake, intracellular targets, and spectrum of activity. For example, proline-rich peptides often translocate into the bacterial cytoplasm to inhibit protein synthesis or chaperone function, whereas amphipathic α -helical peptides commonly destabilize microbial membranes. Because many AMPs also modulate inflammation, angiogenesis and cell migration, their combined antimicrobial and pro-regenerative properties make them especially attractive for wound-dressing applications. Over 100 human AMPs have been described, including α - and β -defensins,^{22,23} cathelicidins (such as LL-37),²⁴ and histatins (such as Histatin-1, Histatin-5), many of which display both antimicrobial activity and wound-modulatory effects.

Antimicrobial Mechanisms of AMPs

AMPs act via diverse, often complementary mechanisms that can be broadly grouped into membrane-targeting processes and intracellular mechanisms; understanding these modes of action is essential for rational peptide design and formulation for wound dressings (Figure 1). In membrane-targeting mechanisms, AMPs interact with microbial membranes to cause destabilization, permeabilization and leakage of cellular contents that can lead to rapid bacterial death; the

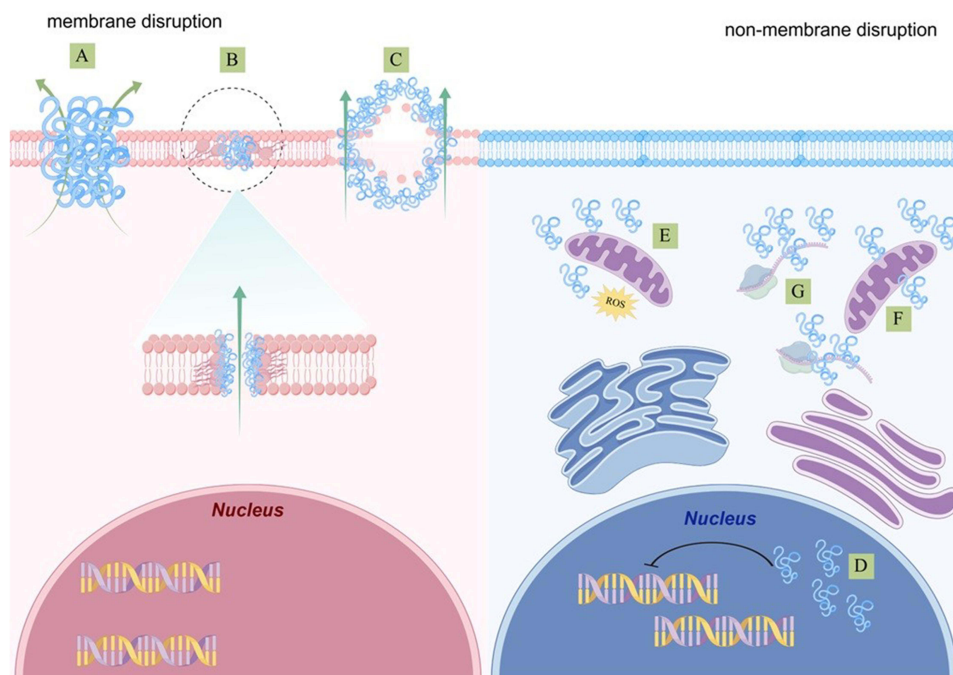


Figure 1 Two core mechanisms of action of antimicrobial peptides: membrane disruption and non-membrane disruption mechanisms. Mechanisms of membrane disruption include the formation of (A) the barrel-stave model, (B) the toroidal-pore model and (C) the carpet model. Non-membrane disruption mechanisms include (D) blocking RNA synthesis, (E) targeting mitochondria to inhibit cellular respiration and induce reactive oxygen species (ROS) formation, (F) disrupting mitochondrial membrane integrity and (G) inhibiting protein synthesis. Drawn using Figdraw (www.home-for-researchers.com).

molecular pathway to membrane failure depends on peptide sequence, concentration and membrane composition.¹⁹ Biophysical descriptions of membrane action have crystallized into three canonical models — barrel-stave pores, toroidal pores, and carpet-like disruption — each describing distinct peptide–lipid arrangements: (a) barrel-stave — amphipathic helices insert and assemble into peptide-lined channels; (b) toroidal pore — peptides induce strong bilayer curvature so pores are lined by both peptide and lipid headgroups; (c) carpet — peptides coat the membrane surface and, at high coverage, cause micellization or membrane fragmentation rather than discrete pore formation.²⁰ Which physical mechanism predominates in a given setting depends on peptide sequence and structure, local concentration, and the lipid composition of the target membrane — factors that also determine bacterial versus host-cell selectivity and thus safety for wound applications.

Beyond membrane permeabilization, many AMPs also act via intracellular or cell-wall mechanisms. Representative non-membrane actions include: (i) inhibition of cell-wall synthesis — eg, lantibiotics such as nisin bind lipid II and block peptidoglycan assembly while also forming pores in Gram-positive membranes; (ii) inhibition of protein synthesis — proline-rich peptides (PRPs) such as Bac7 and oncocin are internalized via bacterial uptake systems (for example SbmA) and interact with ribosomes or translation factors to block protein synthesis; (iii) nucleic-acid targeting — tryptophan-rich peptides such as indolicidin can bind DNA/RNA and disrupt nucleic-acid functions; and (iv) induction of oxidative stress or metabolic perturbation — certain peptides increase microbial ROS or disturb energy metabolism, which contributes to killing and may affect fungal/eukaryotic pathogens at higher doses.²² The multiplicity of mechanisms — including combinations of membrane and intracellular actions — reduces single-target vulnerability and is one reason AMPs often show a lower propensity to select for classical resistance mechanisms compared with many single-site antibiotics.

Importantly for wound healing, many AMPs have secondary functions beyond direct microbicidal action. Experimental studies increasingly show that AMPs can modulate inflammation, recruit or polarize immune cells, stimulate angiogenesis, and promote keratinocyte and fibroblast migration — effects that support tissue repair as well as infection control^{22,25} Thus, AMPs are attractive candidates for multifunctional dressings that simultaneously reduce bioburden and actively promote tissue regeneration. At the molecular level AMPs can down-regulate excessive pro-inflammatory cytokines, up-regulate

reparative mediators, act as chemoattractants and modulate macrophage polarization — net effects that can limit tissue damage while supporting clearance and repair.²⁶ Collectively, these antimicrobial and immunomodulatory properties position AMPs as promising agents for dressings that both control infection and actively promote wound healing and barrier restoration.²⁷ The diversity of AMP mechanisms and bioactivities creates opportunities for rational design of tailored peptides and multifunctional formulations optimized for specific wound microenvironments and pathogens. Design objectives include increased pathogen selectivity, improved bacterial versus host selectivity, optimized protease resistance and controlled release; AMPs can also be used as antibiotic adjuvants to enhance activity or mitigate resistance.²⁴ However, practical translation is hindered by vulnerabilities including peptide instability in protease-rich wound fluids, delivery and controlled-release challenges, potential cytotoxicity, manufacturing and scale-up cost barriers, and limited clinical data—issues discussed elsewhere in this paper.¹⁸ This review summarizes recent advances in AMP-based wound dressings, synthesizes mechanistic and translational evidence, highlights current limitations, and outlines actionable research priorities to accelerate clinical translation. With coordinated advances in peptide engineering, delivery platforms, standardized preclinical models and manufacturing strategies, AMP-based composite dressings have strong potential to become important clinical tools for managing infected and hard-to-heal wounds.

Application Strategies of AMPs in Wound Dressings

Several advanced wound dressings, such as hydrogels,²⁸ nanofibers,²⁹ films,³⁰ skin scaffolds,³¹ and sponges,³² not only support wound healing by maintaining low oxygen tension at the wound site and activating factors such as hypoxia-inducible factor-1, but also release AMPs when combined with them (Table 1). These dressings can diffuse, swell, and undergo chemical degradation to release AMPs. Providing therapeutic delivery systems that address infection, inflammation, and other wound-related issues has been a critical solution for enhancing wound care.³³ To guide material selection we also compared the principal wound-dressing platforms (hydrogels, electrospun fibers, films, skin scaffolds, and sponges) across key performance dimensions including antimicrobial control, protection from proteolysis and controlled release, mechanical/handling properties, anti-biofilm efficacy, translational maturity and typical side effects (Table 2). In brief: hydrogels typically provide excellent hydration, local sustained release and co-delivery of soluble factors but can show limited mechanical strength and require design for protease protection; electrospun fibers mimic the extracellular matrix and afford high surface area for peptide loading and gradient release but require careful control to avoid burst release and cytotoxicity; films and coatings are simple to apply and can deliver surface-immobilized AMPs with low systemic exposure but are less able to release soluble growth factors; skin scaffolds and sponges provide three-dimensional structure and hemostatic function but vary widely in porosity, degradation and manufacturing complexity.

Hydrogel Wound Dressings

Hydrogels are widely used AMP carriers because their hydrated 3D polymer networks mimic soft tissue, maintain a moist wound milieu, and can be engineered for tunable, sustained or stimulus-responsive release. Natural (hyaluronic acid, alginate, chitosan) and synthetic (PEG, polyacrylamide, PNIPAM) hydrogels can physically entrap or chemically conjugate AMPs, reduce direct protease exposure, slow peptide wash-out, and provide an anti-fouling microenvironment that preserves activity in wound fluid. Tunable crosslink density and mesh size control diffusion-driven release, while affinity interactions (electrostatic binding between cationic AMPs and anionic polysaccharides or specific peptide-binding domains) can prolong residence time and maintain sustained local antimicrobial pressure. Hydrogel matrices readily enable co-delivery of growth factors, metal ions, ROS scavengers or cell-derived exosomes, allowing combination antimicrobial and pro-regenerative activities in a single dressing.^{53,86}

Integration of AMPs with Polysaccharide-Based Hydrogels

Polysaccharide-based hydrogels, such as hyaluronic acid (HA) and sodium alginate, have become invaluable matrix materials in the field of wound care due to their excellent moisturizing ability and injectability. When these hydrogels are combined with AMPs, the resulting dressings not only demonstrate broad-spectrum antimicrobial efficacy but also exhibit exceptional biocompatibility. They efficiently eliminate bacteria, stimulate angiogenesis, and promote cell proliferation, significantly accelerating the wound healing process.⁸⁷

Table 1 Carrier Platforms and Representative AMPs

Carriers	AMP	Antimicrobial Activity	Ref.
Electrospun nanofiber, Collagen-based biomaterials, collagen scaffold	LL37	MRSA, S. aureus, E. coli and P. aeruginosa	[34–40]
Hydrogel Bacterial-derived, Hydrogels, electrospun nanofiber	ϵ -PL	E. coli, S. aureus, and MRSA	[41–44]
Sponge, hydrogel	Tet213	E. coli and S. aureus	[45–48]
Cryogel, Bacterial-derived, cellulose, RSF films	KR-12	E. coli, P. aeruginosa, MRSA and S. aureus	[49–52]
Hydrogel	EPL	MRSA, E. coli, P. aeruginosa, C. albicans and Aba	[53–55]
Electrospun nanofiber, biological-based sponge, silk fibroin Electrospun fibers	CM11	S. aureus, E. coli, P. aeruginosa and Aba	[31,32,56]
Hydrogel, electrospun nanofiber	V-Os	E. coli and S. aureus	[57–59]
Hydrogel	HHC36	S. aureus, STAPH, P. aeruginosa and E. coli	[60,61]
Hydrogel	DP7	E. coli, P. aeruginosa, and S. aureus	[3]
Cryogel		P. aeruginosa, E. coli and S. aureus	[62]
Polyurethane material	TCP-25	S. Aureus, P. aeruginosa and E. coli	[63]
Hydrogel	SIKVAV	E. coli and S. aureus	[5]
Hydrogels	RRP9W4N	STAPH, S. aureus and P. aeruginosa	[64]
Electrospun nanofibers	RGD	STAPH and P. aeruginosa	[65]
Cellulose membranes	CBP-RGD	S. aureus	[66]
Hydrogel	Ponericin G1	E. coli, P. aeruginosa and MRSA	[67]
Electroactive antibacterial	PonG1	E. coli and S. aureus	[68]
Hydrogels	Pln 149	S. aureus and MRSA	[69]
PLDA film	P5S9K	S. aureus and E. coli	[70]
Hydrogel	PI, W8	STAPH and P. aeruginosa	[71]
Electrospun fiber membrane	OH-CATH30	E. coli and S. aureus	[72]
Hydrogel	NZ2114	S. aureus	[73]
Cellulose materials	MPI96	E. coli, P. aeruginosa and S. aureus	[74]
Hydrogel	MDPI	VRSA and MRSA	[75]
Hydrogels	L9	E. coli and S. aureus	[76]
Nanofibers	LfcinB (21–25) _{Pal}	E. coli	[77]
Hydrogel	HHC10	E. coli and S. aureus	[78]
Hydrogel	C8G2	MRSA	[79]
Foam film coating	HEWL	E. coli, S. aureus and C. albicans	[80]
Hydrogel	Chol-37 (F34-R)	P. aeruginosa	[53]
Hydrogel	HX-12C	E. coli and S. aureus	[28]
Hydrogel	AC	E. coli and S. aureus	[81]
Hydrogel	C14R	P. aeruginosa	[82]
Natural latex film	G (LLKK)3L	E. coli and S. aureus	[83]
Nanofiber	I7BIPHE2	Kpn and Aba	[84]
Electrospun nanofiber	W379	MRSA, Kpn, Aba and P. aeruginosa	[85]

Through carefully designed strategies, several composite dressings have been successfully developed. For example, Zefeng Lin's research team⁸⁸ ingeniously anchored the AMP AMP-Tet213 within a composite matrix of alginate, HA, and collagen. The resulting ALG/HA/COL-AMP dressing not only exhibited excellent physical properties and biodegradability but also displayed potent antimicrobial activity against various pathogens. Furthermore, it effectively promoted the active proliferation of fibroblasts and accelerated wound closure. Another team led by Mahsa Ahmadi⁸⁹ employed an innovative approach by encapsulating the AMP LL37 within microsphere carriers, which were then embedded in an activated carbon-chitosan hydrogel. This design not only protected LL37 but also enabled targeted action against bacterial toxins, offering a new avenue for the treatment of chronic wound infections. Additionally, the clever combination of HA with the AMP Plantaricin 149 led to the formation of an injectable and adhesive antimicrobial hydrogel (HAD@AMP). This hydrogel demonstrated excellent antimicrobial efficacy, tissue compatibility, antibiotic

Table 2 Comparative Performance of Dressing Platforms

Platform	Antimicrobial Control	Protease Protection/ Controlled Release	Mechanical/handling	Anti-biofilm Potential	Clinical Readiness	Common Side Effects/Risks
Hydrogels	Good local concentration; sustained release possible	High (with crosslinking/affinity interactions)	Moderate (injectable or patchable)	Moderate–high (if loaded with anti-biofilm peptides)	High (many products)	Maceration if overhydrated; possible burst release without design
Electrospun fibers	High surface area for rapid contact killing or sustained release	Moderate (encapsulation in nanoparticles enhances protection)	Good (flexible mats)	High (fibrillar structure can disrupt biofilms)	Moderate (many preclinical studies)	Residual solvents; potential cytotoxicity if AMP or polymer not optimized
Films / coatings	Good for surface sterilization and localized contact killing	Low–moderate (immobilized peptides have long surface activity)	Excellent (easy to apply)	Low–moderate	High (some clinically used coatings)	Limited fluid handling; may delaminate
Skin scaffolds (porous)	Variable — depends on pore size and peptide loading	Good if peptides immobilized or protected	Good (structural support)	High (3D structure supports host cells and anti-biofilm agents)	Moderate	Immune reaction risk if xenogeneic; manufacturing complexity
Sponges	Good (absorptive plus antimicrobial)	Moderate (can be engineered for release)	Good (conformable, hemostatic)	Moderate	Moderate	Foreign-body reaction; absorption overload risks

resistance, and the ability to inhibit bacterial biofilm formation. Moreover, it could regulate inflammatory responses and promote angiogenesis, providing a novel therapeutic perspective for the rapid recovery of infectious wounds.

Furthermore, Shi et al⁵³ successfully developed a sodium alginate-based hydrogel dressing loaded with the novel AMP Chol-37 (F34-R). This dressing not only exhibited excellent cross-sectional structure and good water absorption and swelling properties but also demonstrated significant antimicrobial effects. It could create an impenetrable barrier between the wound and the external environment, effectively preventing bacterial invasion and showing great potential as a novel dressing for the treatment of infectious wounds. In summary, the combination of polysaccharide-based hydrogels and AMPs provides a new pathway for the development of efficient, biocompatible wound dressings. These dressings show great potential in promoting wound healing and preventing infection, offering novel strategies for skin healing.

Integration of AMPs with Smart Responsive Hydrogels

Smart responsive hydrogels have demonstrated significant potential in wound healing by precisely controlling the release of AMPs, thereby enhancing therapeutic efficiency. These hydrogels are capable of sensing changes in the wound environment, such as light, pH, and temperature, and adjusting their release mechanisms accordingly. pH-sensitive hydrogels, for example, release AMPs in response to the pH changes at the wound site.^{90,91} This responsive design allows the hydrogel to effectively combat infections, especially in cases where the wound's pH is imbalanced.⁹² For instance, Li et al⁷⁹ developed an in situ formed hydrogel by conjugating oxidized β -D-glucan with the AMP C(8)G(2) through a Schiff base reaction. This hydrogel is easy to prepare and has a positive impact on the entire healing process of bacterial-infected wounds, exhibiting significant antimicrobial activity and biocompatibility. The pH-sensitive reversible imine bond enables the hydrogel to self-heal and sustains the release of AMPs, thereby enhancing their bioavailability while reducing toxicity. Photoreponsive hydrogels, which combine AMPs with photosensitizers, enable controlled release under light exposure. This strategy not only improves the precision of the treatment but also reduces unnecessary drug waste and side effects. For example, Fan et al⁷⁸ proposed a novel antimicrobial hydrogel by covalently coupling photosensitizers with AMPs. This hydrogel showed remarkable antimicrobial effects and good efficacy against drug-

resistant bacteria due to the increased treatment precision. Another innovative strategy involves combining thermo-responsive hydrogels with CuS nanoparticles and lysozyme-loaded AMPs. By utilizing photothermal regulation to control the release of AMPs, this hydrogel can effectively combat chronic wound infections.⁹³ In summary, smart responsive hydrogels have broad application prospects in the field of wound treatment. With continued optimization of design and fabrication processes, these hydrogels are expected to provide more efficient, precise, and safe solutions for wound healing.

Combination of AMPs and Metal Nanomaterials

Nanomaterials have emerged as a research frontier in antimicrobial materials due to their remarkable antibacterial properties and their ability to significantly enhance the mechanical strength and stability of wound dressings.⁹⁴ By strategically integrating AMPs with these high-performance metallic nanomaterials, researchers are working to develop innovative metallic nanohydrogel dressings that exhibit synergistically enhanced antimicrobial effects and excellent mechanical properties. These dressings enable precise control over the release of both AMPs and metal nanoparticles, ensuring long-lasting antimicrobial efficacy while accelerating the wound healing process.⁹⁵

Specifically, Xianhao Su⁹³ successfully developed an innovative thermosensitive hydrogel composite material based on poly-N-isopropylacrylamide (PNIPAM) and polyacrylamide (PAM). This hydrogel incorporates CuS nanoparticles (CuS/PP) and one-dimensional lysozyme nanofibers loaded with the AMP melittin (M). Through photothermal regulation, this hydrogel allows for flexible control of melittin release, providing a novel strategy for the treatment of chronic wound infections.

Another notable study by Xinrui Li⁶ designed a dynamic, multifunctional HA-based hydrogel dressing that mimics the extracellular matrix (ECM) and integrates antimicrobial, immunomodulatory, and angiogenic functionalities for the treatment of infected skin wounds. The dynamic network structure of this hydrogel is constructed through reversible metal-ligand coordination between thiol groups and bioactive metal ions, with antimicrobial silver ions and immunomodulatory zinc ions being ingeniously incorporated into thiolated HA and angiogenic peptides. This dressing not only exhibits excellent bioactivity for infected wounds but also possesses self-healing and injectable properties, offering enhanced flexibility and potential for wound care applications.

In summary, the combination of AMPs and metal-based antimicrobial nanomaterials has opened a new avenue for the development of next-generation multifunctional, high-performance wound dressings. These innovations hold significant promise for advancing wound treatment strategies and are expected to play a critical role in future wound care applications.

Combination of AMPs and Exosomes

Exosomes,⁹⁶ as nanoscale carriers naturally secreted by cells, exhibit excellent biocompatibility and efficient delivery capabilities, demonstrating immense potential in biomedical applications. Recent studies have explored a cutting-edge approach: the integration of AMPs with exosomes derived from mesenchymal stem cells (MSCs) to develop composite hydrogel systems that offer long-term storage stability, rapid re-dissolution properties, and high antimicrobial activity.⁹⁶ This innovative strategy not only deepens our understanding of the delivery mechanisms of bioactive molecules but also provides new solutions for tissue repair and regeneration.⁹⁷

The composite hydrogel system exhibits multiple biological effects, effectively regulating the activity of fibroblasts, vascular endothelial cells, and macrophages. Additionally, it demonstrates outstanding performance in inhibiting fibrosis mediated by myofibroblasts, which is crucial for promoting healthy tissue regeneration and reducing scar formation. These findings offer novel perspectives for addressing skin injuries, wound healing, and other tissue repair needs.⁹⁸

Of particular interest, YuLing Yang³ proposed an innovative preparation strategy involving the construction of a macroporous hydrogel (HD-DP7/Exo) containing human umbilical cord mesenchymal stem cell-derived exosomes (HucMSC-Exos) using rapid freeze-drying technology. This hydrogel was further enhanced with an AMP coating on its surface. This method not only achieves stable encapsulation of exosomes within the HA-based macroporous hydrogel but also imparts the hydrogel with long-term storage and transport advantages, as well as the capability for instant re-dissolution for therapeutic use.

Comparative experiments demonstrated³ that hydrogel systems loaded with HucMSC-Exos exhibited similar positive effects in regulating cellular behavior, inhibiting fibrosis, and promoting tissue regeneration compared to hydrogels directly loaded with HucMSCs. These findings further validate the unique therapeutic value of HucMSC-Exos as extracellular communication mediators and highlight their enhanced therapeutic potential when combined with AMPs within hydrogel systems.

In summary, the integration of AMPs and HucMSC-derived exosomes has not only paved the way for efficient bioactive molecule delivery but has also brought revolutionary progress to tissue engineering and regenerative medicine. This approach holds tremendous promise for promoting healthy tissue recovery and reducing complications, with broad applications in future therapeutic scenarios.

Combination of AMPs and Cryogels

Cryogels, as emerging star materials in the biomedical field, are characterized by highly tunable porous structures and outstanding water absorption properties conferred by low-temperature gelation techniques. These features make cryogels ideal carriers for bioactive molecules, ensuring stable release and precise delivery within the body. Their excellent biocompatibility and biodegradability further guarantee their safety in clinical applications.⁹⁹

Wang et al⁶² designed an innovative macroporous hydrogel (DA7CG@C system) that integrates AMPs and stem cells. This hydrogel, constructed through the polymerization of an HA backbone with dopamine, combines the AMP DP7 with placental mesenchymal stem cells (PMSCs), achieving comprehensive wound care from inflammation suppression and tissue regeneration to scar-free healing. The system significantly optimizes the wound healing process.

Similarly, Menglong Liu et al⁴⁹ developed a multifunctional cryogel based on HA, tannic acid, and the AMP KR-12 (HA/TA2/KR2). This cryogel stands out for its shape-memory properties, strong absorption capacity, hemostatic effect, and antimicrobial activities. The intelligent release mechanism of KR-12 effectively eradicates various pathogens, while TA synergistically eliminates reactive oxygen species and regulates immune responses, thereby accelerating wound healing and demonstrating excellent *in vivo* performance.

In conclusion, cryogels, through meticulous design, achieve efficient delivery of bioactive molecules and precise regulation of cellular behavior while promoting healthy tissue regeneration. These advancements represent a revolutionary breakthrough and innovation in the biomedical field.

Electrospun Fiber (ESF) Wound Dressings

ESFs mats provide extracellular-matrix-like architecture that promotes cell attachment and ingrowth while offering very high surface area for AMP loading and contact killing.¹⁰⁰ The fibrous geometry can physically block bacterial penetration and limit biofilm maturation, and fiber porosity supports oxygen and gas exchange essential for healing. However, the same high surface exposure that promotes antimicrobial contact can also accelerate peptide loss and degrade peptide stability unless peptides are encapsulated or immobilized; moreover, residual solvents, polymer choice and high local AMP concentration can contribute to cytotoxicity or local irritation. Common mitigation strategies that have been validated in preclinical studies include core-shell or multilayer fiber architectures, nanoparticle loading and post-spinning crosslinking to reduce burst release, and graded release designs to preserve antimicrobial activity while minimizing host toxicity. When properly designed, ESFs are promising for both acute and chronic wounds, but translation requires explicit attention to solvent removal, peptide stability assays in wound-like fluids, and standardized cytotoxicity testing.

The flexibility of nanofiber fabrication is attributed to its compatibility with a wide variety of polymeric materials and the ability to incorporate bioactive components. This enables the creation of an efficient and precise drug and antimicrobial agent delivery system.²⁹ For instance, the integration of carboxymethyl chitosan nanoparticles with the AMP OH-CATH30 imparts antimicrobial efficacy and wound-healing potential to PVA/CS nanofibers.⁷² Similarly, recombinant LL37 peptide and VEGF encapsulated in chitosan nanoparticles and fabricated through a multilayered electrospinning process result in wound dressings with superior biophysical properties and notable efficacy against drug-resistant pathogens like MRSA.³⁴ Polycaprolactone (PCL) fibers, another highlight, exhibit strong antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* through the physical adsorption of nisin.¹⁰¹ Additionally, the

synergistic strategy of combining cationic bio-based polymers with AMPs offers a novel approach for developing multifunctional ESFs, which demonstrate significant potential in the biomedical field, particularly in wound dressings.¹⁰²

Of particular interest, the incorporation of insulin-like growth factor 1 (IGF1) and AMP Os into PLGA electrospun scaffolds via an innovative small pentapeptide tagging technology fused with 3,4-dihydroxyphenylalanine (DA) yields fibers that mimic the porous structure of natural ECM. These scaffolds provide an optimal microenvironment for cell growth and achieve controlled release of growth factors and AMPs, significantly enhancing wound healing and tissue regeneration.⁵⁷

In summary, the exploration and application of ESFs and their composites in wound healing are rapidly advancing, showcasing their immense potential. With continuous optimization of material design and fabrication processes, ESFs are poised to offer more efficient, safer, and patient-centered solutions for wound care, heralding a new era in wound healing treatments.

Other Types of Dressings

At the forefront of research on AMP-based wound dressings, innovative strategies continue to emerge, optimizing wound management approaches. Jiamei Zhang et al successfully incorporated the AMP KR-12 into regenerated silk fibroin films. This novel design not only enables the sustained release of the AMP but also imparts the dressing with multiple functionalities, including antimicrobial activity, enhanced cell adhesion, and macrophage activity regulation. *In vivo* experiments have demonstrated the significant wound healing effects of this dressing, offering a breakthrough in the field of wound treatment.

Another study, conducted by Mehrdad Moosazadeh Moghaddam et al,³¹ focused on the innovative application of amniotic skin scaffolds. Through enhanced processing of silk fibroin and coating with the AMP CM11, the team developed a dressing with superior antimicrobial performance and excellent biocompatibility. This amniotic skin scaffold exhibited remarkable efficacy in promoting wound closure, providing a novel solution for the treatment of complex wounds.

Hatef Ghasemi Hamidabadi et al³² extracted bio-based sponges from human placental tissue and skillfully loaded them with AMPs to create a skin substitute with high antimicrobial activity. This innovative dressing is currently advancing to preclinical research stages and holds the potential to bring revolutionary changes to future wound care.

Additionally, Wang et al⁸³ developed a glycerol-AMP natural latex film with significant antimicrobial activity and excellent biocompatibility. This dressing effectively promotes the healing of infected wounds, providing new insights and approaches for wound management and expanding the application scope of AMP-based antimicrobial dressings.

In summary, these pioneering studies collectively advance the development of AMP-based antimicrobial dressings, offering unprecedented hope for wound treatment. As research deepens and technologies continue to innovate, it is anticipated that more efficient, safe, and convenient AMP-based antimicrobial dressings will emerge, providing more comprehensive and effective solutions for patient wound care.

Multifunctional Wound Dressings

In recent years, AMP-based multifunctional wound dressings have emerged in the field of wound management, offering comprehensive and efficient solutions by integrating cutting-edge technologies. The core advantage of these dressings lies in their multifunctionality, which includes real-time bacterial monitoring, promotion of angiogenesis and tissue regeneration, antioxidation, and electrostimulation-assisted healing.

First, the real-time bacterial monitoring capability allows dressings to respond rapidly to wound infections.⁴⁵ By incorporating built-in sensors or indicators, healthcare providers can promptly assess bacterial loads in wounds and adjust treatment strategies accordingly, effectively controlling infections.⁹⁰ For instance, certain studies⁴⁶ synthesized composite dressings combining AIEgens mesoporous bioactive glass and AMPs, enabling real-time bacterial detection, broad-spectrum antimicrobial activity, and tissue regeneration, thereby accelerating the healing of chronic wounds.

Second, these dressings are highly effective in promoting angiogenesis and tissue regeneration. By releasing AMPs and other bioactive molecules, they stimulate cell proliferation and migration, accelerate the formation of new blood vessels to supply oxygen and nutrients, and facilitate tissue repair and regeneration.⁷⁰ For example, some multifunctional

hydrogels achieve sequential two-stage release via near-infrared stimulation, enabling precise wound treatment while promoting angiogenesis and collagen deposition.²⁸

Third, these dressings exhibit outstanding antioxidant properties, scavenging free radicals and mitigating oxidative stress-induced cellular damage to create a favorable environment for wound healing. For instance, Dong Yang et al⁶⁷ developed multifunctional dynamic boronic acid-crosslinked hydrogels through specific chemical reactions. These hydrogels not only exhibit rapid gelation properties but also carry cationic AMPs, achieving both antimicrobial and antioxidative effects.

Finally, electrostimulation assistance represents another innovative feature of these dressings.⁶⁸ Mild electric currents can further activate cellular activities, promoting cell proliferation and differentiation to accelerate wound healing. For example, a research team led by Dawei Ren⁵⁸ developed multifunctional conductive gelatin methacrylate hydrogels. By using superior conductive materials as electrodes and incorporating modified AMPs to inhibit bacterial infections, this dressing accelerates skin damage repair through external electrical stimulation, enhancing cell survival rates and upregulating tissue repair-related gene expression.

In conclusion, AMP-based multifunctional wound dressings demonstrate immense potential and broad application prospects in wound management due to their outstanding multifunctionality. With ongoing advancements in technology and deeper clinical applications, these dressings are poised to become a new frontier in wound treatment, offering hope to more patients. Moving forward, we anticipate the emergence of even more innovative AMP-based multifunctional wound dressings, injecting new vitality into wound management.

Clinical Applications and Prospects of AMP-Based Wound Dressings Innovations in Chronic Wound Treatment

Chronic wounds,¹⁰³ such as diabetic foot ulcers and wounds induced by venous or arterial diseases, are often challenging to treat due to persistent infections and impaired blood circulation. In addressing these complexities, AMPs have demonstrated their unique therapeutic value. AMPs are highly effective against both Gram-negative bacteria (eg, *Pseudomonas aeruginosa*) and Gram-positive bacteria (eg, *Staphylococcus aureus*), which are major culprits in chronic wound infections.³⁵ By inhibiting bacterial communication, reducing biofilm formation, and immobilizing bacterial cells to prevent proliferation, AMPs play a critical role in infection control.¹⁰⁴ For instance, methacrylated chitosan (MECs) hydrogels coated with melittin-derived peptide 1 (MDP1)⁷⁵ utilize an “explosive release” strategy to rapidly eliminate planktonic bacteria while exhibiting anti-biofilm activity. Moreover, AMPs are not limited to their antimicrobial function; they also modulate host immune responses, promote cell migration and proliferation, and thereby accelerate wound healing.¹⁰⁵ A prominent example is human β -defensin-3 (HBD-3), which activates the FGFR/JAK2/STAT3 pathway critical for healing, enhances angiogenesis, and promotes fibroblast migration, significantly expediting wound repair.¹⁰⁶ Most notably, unlike traditional antibiotics, AMPs’ unique bactericidal mechanisms make them less likely to induce resistance. This characteristic is particularly valuable for chronic wounds, which are often associated with multidrug-resistant bacteria.¹⁰⁷ For example, AMP-based wound dressings have demonstrated superior antimicrobial efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA),⁶⁴ multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA),¹⁰⁸ and extensively drug-resistant *Acinetobacter baumannii*.

Comprehensive Care for Burn Wounds

Burn wounds are highly susceptible to bacterial infections due to the compromised skin barrier, and their healing process is often complex and variable.⁵⁶ The application of AMPs in burn wound treatment has shown remarkable advantages.¹⁰⁹ In preventing infection, AMPs rapidly inhibit bacterial growth on the surface of burn wounds, effectively reducing the risk of infection. This is critical for preventing wound deterioration and protecting the wound bed from secondary injury.⁸⁶ AMPs also promote the epithelialization process in burn wounds by enhancing epithelial cell migration and coverage over the wound bed, forming a new skin barrier. This not only accelerates wound healing but also minimizes scar formation.⁶² Furthermore, AMPs enhance the expression of vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and angiogenic markers such as CD31, thereby expediting the wound healing process.⁷³ In terms of

immune modulation, AMPs inhibit the expression of pro-inflammatory cytokines, including interleukin-6 (IL-6), IL-1 β , and tumor necrosis factor- α (TNF- α), while upregulating anti-inflammatory mediators such as transforming growth factor- β 1 (TGF- β 1) and platelet endothelial cell adhesion molecule-1 (CD31). These effects not only alleviate patient discomfort but also provide robust support for successful wound healing.¹¹⁰

Challenges and Limitations

Despite substantial preclinical promise, AMP-based wound dressings face multiple translational challenges — peptide instability and proteolytic degradation, delivery and controlled-release limitations, scale-up and manufacturing costs, cytotoxicity and off-target effects, regulatory barriers, imperfect animal models, and limited clinical data — that must be addressed to enable clinical adoption. A primary limitation of many natural AMPs is poor stability in protease-rich wound environments: host and bacterial proteases rapidly degrade linear, L-amino-acid peptides, reducing local bioavailability and efficacy.⁹ Additionally, achieving therapeutic peptide concentrations at the wound site for the required duration is challenging: simple topical application often produces rapid wash-out, burst release or inactivation, limiting bactericidal exposure. Controlled-release matrices, particulate carriers and biological carriers have shown promise to sustain and localize AMP delivery while protecting peptides from proteolysis and dilution.⁹ Moreover, cost and manufacturability remain significant barriers: chemically synthesized peptides, particularly long or extensively modified sequences, are expensive to produce at scale, and formulation stability further complicates product development. Although several AMP candidates have advanced to clinical testing, the number of well-controlled human trials of AMP-based wound dressings remains small, and some clinical programs have stalled because of limited efficacy, toxicity or commercial decisions. To accelerate translation, investigators should from the outset integrate stability-enhancing chemistries, protective delivery platforms, rigorous safety and cytotoxicity testing, manufacturability assessments and cost analyses, improved and standardized animal models, and early regulatory engagement into their development pipelines. Such an integrated approach will better position AMP-based dressings for robust clinical testing and, ultimately, routine use in complex wound care.^{22,111}

Future Research Directions

Ongoing advances in AMP discovery, peptide engineering and delivery technologies are expanding the translational potential of AMP-based wound dressings for chronic wounds and burns. Key technical and translational areas likely to deliver near-term impact include: First, rational peptide engineering — using computational design, high-throughput screening, genetic/biotechnological production and chemical strategies — should produce AMPs with enhanced potency, selectivity and protease resistance.¹¹² Designed peptides should be matched to wound microenvironments or dominant pathogens to maximize efficacy while minimizing off-target cytotoxicity.¹¹³ Second, validated delivery platforms (responsive hydrogels, electrospun matrices, polymeric nanoparticles, liposomes and exosome-based vesicles) must be optimized and validated to protect peptides from proteolysis and to provide controlled, site-matched release.¹¹⁴ These carriers can shield peptides from enzymatic degradation, provide sustained or on-demand release, and localize antimicrobial activity to the wound bed—maintaining local antimicrobial pressure while reducing systemic exposure.⁶⁵ Engineering multifunctional dressings that combine antimicrobial action with anti-inflammatory, pro-angiogenic and matrix-remodeling activities (via co-delivery or multifunctional materials) is an important translational objective.¹¹⁵ More broadly, advanced chemistries and formulation strategies will expand design options to precisely control peptide presentation, stability and release kinetics appropriate to wound type and healing stage.¹¹⁶ Beyond chronic and acute infected wounds, these approaches could be adapted for surgical prophylaxis, implant coatings and other dermatological indications.^{84,89,117} Finally, adoption of standardized, higher-fidelity preclinical models (diabetic/ischemic and large-animal wounds, standardized biofilm challenges, bioluminescent and imaging readouts) will improve quantitative, longitudinal assessment of AMP activity and kinetics and better predict clinical performance.^{96,118} With coordinated progress in peptide engineering, delivery platforms, standardized preclinical models, manufacturing scale-up and regulatory alignment, AMP-based dressings may become integral components of next-generation wound care.

Conclusion

Ongoing advances in AMP discovery, peptide engineering and delivery technologies are expanding the translational potential of AMP-based wound dressings for chronic wounds, burns and other indications. AMPs combine broad-spectrum antimicrobial activity with immunomodulatory and pro-regenerative effects, making them attractive candidates for multifunctional dressings that address infection and support tissue repair. However, realizing clinical impact requires parallel progress in peptide optimization, protective and responsive delivery systems, robust preclinical models, manufacturability and regulatory pathways.

Funding

This study was supported by the Project of Yancheng Health Commission (No. YK2023072).

Disclosure

The authors declare no conflict of interest. Aoxun Zhu and Baiqi Chen contributed to the work equally and should be regarded as co-first authors.

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