EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

Review article:

PEPTIDES IN WOUND HEALING: A COMPREHENSIVE REVIEW OF THEIR ROLES, CHALLENGES, AND HYDROGEL-BASED DELIVERY SYSTEMS

Rafl M. Kamil[1], Shaik Nyamathulla[1*], Syed Mahmood[1,2,3,4*]

[1] Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
[2] Faculty of Medicine, Universiti Malaya Research Centre for Biopharmaceuticals and Advanced Therapeutics (UBAT), Universiti Malaya, 50603 Kuala Lumpur, Malaysia
[3] Centre of Advanced Materials (CAM), Faculty of Engineering, Universiti Malaya, 50603, Kuala Lumpur, Malaysia
[4] Faculty of Pharmaceutical Sciences, Chulalongkorn University, Pathum Wan, Bangkok, 10330, Thailand

* **Corresponding authors:** Shaik Nyamathulla, Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia. Phone number: +6010-529-3948; E-mail: nyamathullask@um.edu.my
Syed Mahmood, Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia. Phone number: +6018-267-9732; E-mail: syedmahmood@um.edu.my

https://dx.doi.org/10.17179/excli2025-8778

ABSTRACT

Chronic wounds are characterized by prolonged healing durations and disrupted progression through the normal phases of wound healing, hemostasis, inflammation, proliferation, re-epithelialization and remodeling. These wounds are often complicated by persistent infections and underlying conditions like diabetic mellitus, which hinders effective tissue regeneration. Traditional dressings provide limited therapeutic benefits; therefore, recent advancements in wound care have introduced peptide-based therapies that have gained considerable attention for their multifunctional roles in modulating wound repair. Peptides possess intrinsic antimicrobial, anti-inflammatory, angiogenic, and pro-regenerative properties, enabling them to regulate diverse cellular and molecular events across all stages of healing. This review highlights the mechanistic roles of therapeutic peptides in regulating and orchestrating wound healing applications. We further classify bioactive peptides derived from microbial, animal, and plant sources with documented roles in wound healing, and also address synthetic peptides engineered for wound healing. We discussed the peptide-based hydrogels, recent advancements in peptide-based hydrogels in wound healing, and also those hydrogels that are currently under investigation in clinical trials. The primary objective of this review is to provide the readers a detailed overview of the advancements in wound healing studies especially peptide incorporated hydrogels.

Keywords: Peptides, wound healing, biomaterials, hydrogels, tissue regeneration

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

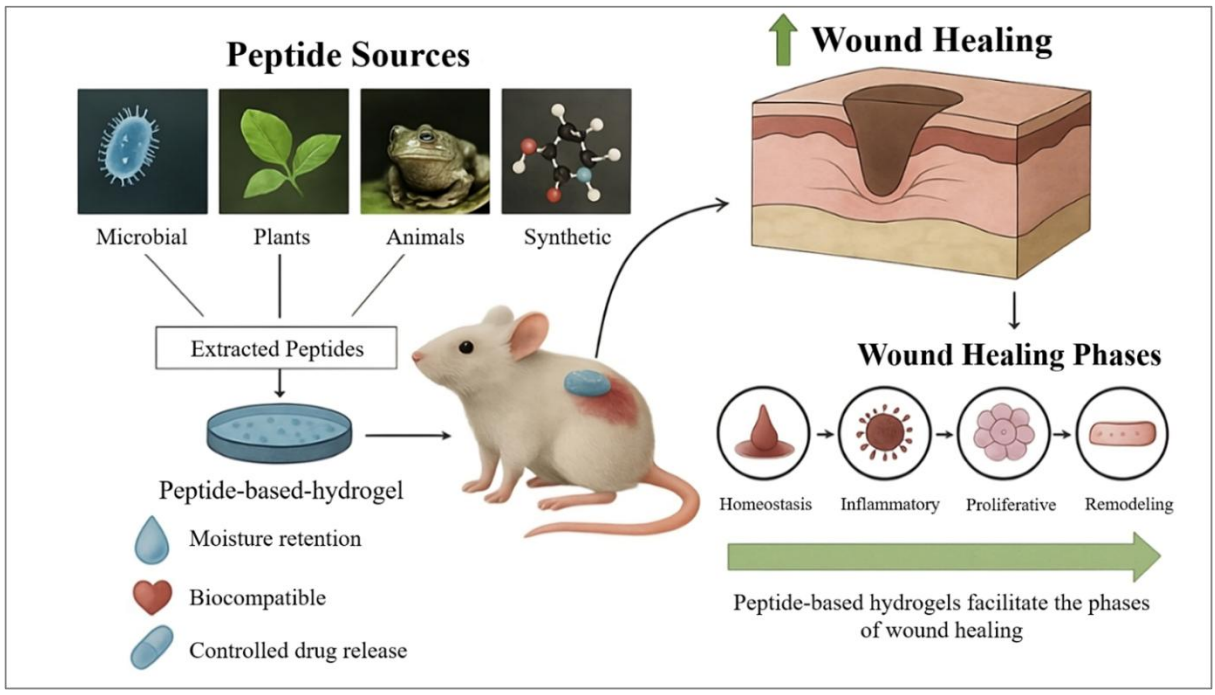

Figure 1: Graphical abstract

INTRODUCTION

The skin is the largest organ in the human body, accounting for approximately 16 % of the total body weight. It serves as the outermost barrier against environmental, microbial, and physical insults. The skin is composed of three main layers; epidermis, dermis, and hypodermis (also known as the subcutaneous layer). Each layer contributes to structural integrity, homeostasis, and immune defense (McKnight et al., 2022; Wong et al., 2016). When this barrier is compromised by injury, burns, trauma, surgery, or pathological conditions such as diabetes or peripheral vascular disease, the body initiates a complex biological process known as wound healing. This process aims to restore tissue integrity, reduce microbial load, and re-establish homeostasis through a tightly regulated cascade of cellular and molecular events (Sorg et al., 2017).

The earliest recorded wound treatments date back to ancient Egyptian script, Ebers Papyrus, they used honey and natural substances with bandages for their antimicrobial and absorbent properties to treat wounded individuals. In ancient Greece and Rome, physicians such as Galen emphasized moisture maintenance for optimal healing. Significant progress occurred in the 19th century, when Joseph Lister, guided by Pasteur's germ theory, introduced antiseptic practices using phenol, which drastically reducing surgical infections and revolutionized wound care (Ahmad et al., 2020; Michaleas et al., 2022). Today, chronic wounds significantly burden healthcare systems due to prolonged healing time and high treatment costs (Powers et al., 2016). As shown in Figure 2, the United States spends approximately $126.95 billion annually on chronic wound care, followed by substantial expenditures in Germany, Canada, China, Australia, and other countries.

Given these burdens and the urgent demand for more effective interventions peptides have attracted a significant attention for their antimicrobial, immunomodulatory, and regenerative properties. Peptides like LL-37 and β-defensins promote fibroblast and keratinocyte activity, reduce inflammation, and prevent infection (Ahmad et al., 2024). Because of their size and multifunctional activity, peptides are promising agents for chronic wound treatment, as they exert their benefits through multiple pathways that are dysregulated in chronic wounds. Some

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

of these pathways include promoting re-epithelialization by stimulating keratinocyte and fibroblast migration and proliferation, improving angiogenesis by upregulating vascular endothelial growth factor (VEGF), and accelerate extracellular matrix (ECM) remodeling by modulating the activity of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) (Gomes et al., 2017; Kumar et al., 2024). Many peptides also possess an immunomodulatory properties that shift macrophage phenotypes from a pro-inflammatory (M1) to a regenerative (M2) state, thereby resolving persistent inflammation commonly seen in chronic wounds (Nazari et al., 2025). Their high specificity, low immunogenicity, and potential for combinatorial modification make peptides highly versatile candidates for wound therapy (Guan et al., 2022). However, peptide instability remains a major limitation, which prompt their integration of peptides into delivery platforms such as hydrogels. These systems enhance peptide retention at the wound site, protect against enzymatic degradation, and sustain therapeutic activity, eventually improving healing outcomes (Kumar et al., 2024).

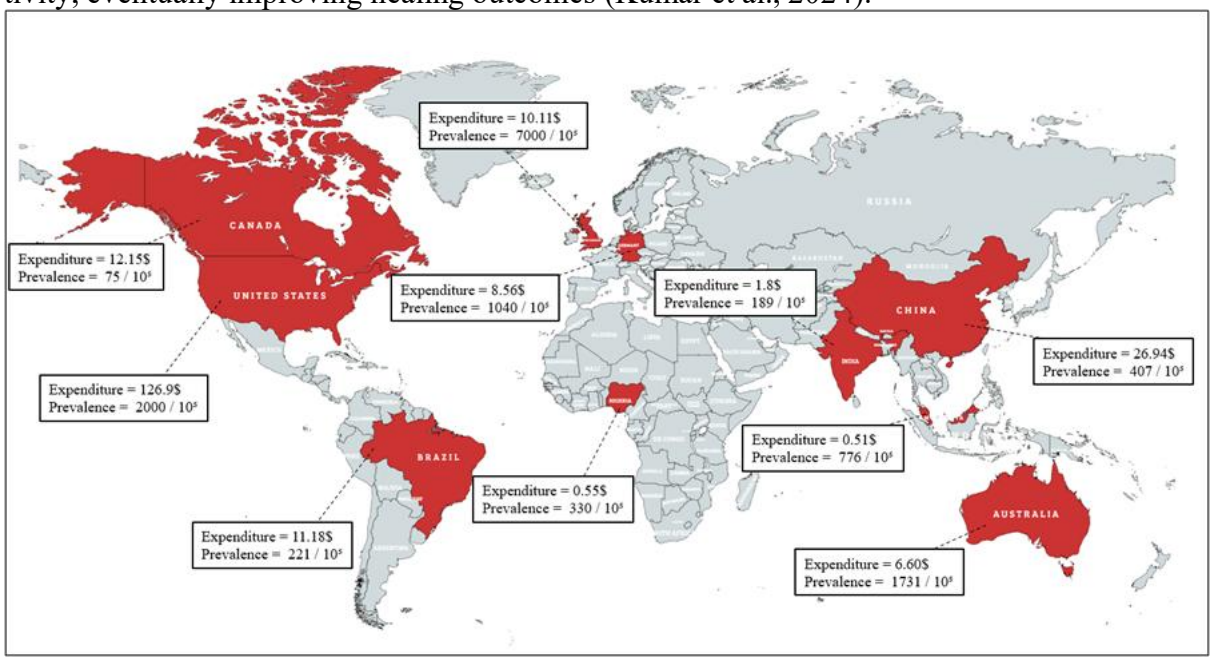

Figure 2: The illustration shows the total healthcare expenditure on wound care (in billion USD per year) and the prevalence of wounds (per 100,000 population) across selected countries (Ref: Wounds Australia, 2024; Queen and Harding, 2024; Ruiz and Lima, 2022; Queen and Botros, 2024; Hopkins et al., 2015; Queen and Harding, 2023; Jiang et al., 2020; Healthcare-in-Europe, 2008; Heyer et al., 2016; Morat and Ajemi, 2024; Iyun et al., 2024; Kharrati, 2024; Sharma et al., 2024; Sen, 2021).

This review highlights the mechanistic roles of therapeutic peptides in orchestrating wound healing, and briefly explores their integration into advanced delivery systems such as hydrogels to improve stability and bioavailability. By precisely targeting specific biological pathways, peptide-based interventions represent a promising frontier in chronic wound management. We further presented bioactive peptides derived from microbial, animal, and plant sources with documented roles in wound healing, and discussed synthetic peptides engineered for wound healing applications. We also discussed the commercial aspects of peptide-based hydrogels used in wound care, recent advancements in their application to wound healing, and their current clinical trials. Furthermore, this review also aims to provide a comprehensive guide for professionals and researchers from diverse scientific communities, including pharmaceutical sciences, clinical sciences, biomaterials, and individuals engaged in wound healing-related studies.

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

CLASSIFICATION OF WOUNDS

The classification of wounds can be made based on various parameters. An accurate classification is essential for diagnosing the severity of the wound, predicting its healing pace, and selecting the most effective treatment approach (Abazari et al., 2022). Thereby, Table 1 summarizes the key classification criteria for wounds, which are as follows: nature, etiology, depth, level of pollution, and healing process time.

Table 1: Classification of wounds based on different wound characteristics

Classification criteria	Sub-categories	Characteristics	Reference
Nature	Clean, incised wounds	Sharp injuries from surgery or sharp objects, e.g., surgical cute	Percival, 2002
	Shearing injuries	Skin separation from deeper layers due to trauma, e.g., car accidents	
	Crushing wounds	Extensive damage due to high-pressure trauma, e.g., machinery accidents	
	Burns	Injuries from thermal, chemical, electrical exposure, e.g., chemical burns	
	Contaminated wounds	Exposed to bacteria or foreign material, e.g., open traumatic wounds	
Etiology	Diabetic foot ulcers	Caused by prolonged hyperglycemia, e.g., diabetic patients with poor control	Stefanou et al., 2020; Rodrigues et al., 2019
	Venous leg ulcers	Resulting from venous hypertension, e.g., chronic venous insufficiency	
	Surgical wounds	Intentional incision healing by primary intention, e.g., postoperative scars	
	Burn wounds	Caused by heat, chemicals, or electricity, e.g., fire burns	
Depth	1st degree wounds	Affect only epidermis, cause mild erythema and pain, e.g., sunburns	Abazari et al., 2022
	2nd degree wounds	Partial-thickness injury with blistering, e.g., scald injuries	
	3rd degree wounds	Full-thickness wounds destroying all skin layers, e.g., severe burns that needs grafting	
	4th degree wounds	Extend beyond skin to muscles, fascia, or bones, e.g., electrical burns	
Contamination Level	Clean wounds	Uninfected wounds, often surgical, e.g., sterile surgical incisions	Boersema et al., 2021
	Clean-contaminated	Controlled exposure to endogenous bacteria, e.g., GI surgery wounds	
	Contaminated	Open wounds with infection risk, e.g., opened fractures	
	Dirty/infected	Infected wounds requiring aggressive management, e.g., abscesses	
Duration	Acute wounds	Heal within expected timeframe, e.g., surgical cut	Boersema et al., 2021
	Chronic wounds	Persist longer due to underlying complications, e.g., diabetic foot ulcer	
	Burn wounds	Variable healing; may involve prolonged inflammation, e.g., deep thermal burns	
	Non-healable wounds	Do not heal due to ischemia or other factors, e.g., gangrenous wounds	

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

PEPTIDES' ROLES IN ORCHESTRATING WOUND HEALING PHASES

Wound healing is a complex, multistep process characterized by a cascade of biological events that can be divided into five overlapping but distinct phases: hemostasis, inflammation, proliferation, re-epithelialization, and remodeling (Rodrigues et al., 2019). Immediately after injury, the hemostasis phase begins to prevent blood loss through rapid vasoconstriction and platelet aggregation (Golebiewska and Poole, 2015). Activated platelets release a variety of vasoactive substances and growth factors including ADP, TXA2, PDGF, TGF-β, and serotonin (5-HT), which facilitate clot formation and recruit inflammatory cells (Beura et al., 2022). Peptides such as LL-37 can further support the process of clot formation (Duan et al., 2022) as illustrated in Figure 3a.

As the hemostatic plug stabilizes, the inflammatory phase begins with neutrophil infiltration, leading to the release of reactive oxygen species, proteases, and antimicrobial peptides such as LL-37 (Adnan et al., 2025). LL-37 exerts direct antimicrobial effects and modulate immune responses by neutralizing endotoxins, recruiting immune cells, and enhancing cytokine production (Agier et al., 2015). Under normal inflammatory phase of wound healing, the monocytes differentiate from M1 to M2 macrophage phenotypes. This transition is essential for tissue debridement, secretion of tissue repair cytokines and promote wound healing. This process can be further facilitated by peptides such as Thymosin β4, which activates macrophages, thereby promoting infection control and resolution of inflammation (Yu et al., 2025) as shown in Figure 3b.

The proliferative phase then reconstructs the wound tissue through fibroblast proliferation, ECM synthesis, and angiogenesis. Endothelial cells and pericytes form new capillaries under the influence of VEGF and PDGF, while fibroblasts deposit collagen and glycoproteins (Rodrigues et al., 2019). Thymosin-β4 significantly enhances this phase by stimulating fibroblast migration, upregulating VEGF, promoting neovascularization, and exerting cytoprotective effects against oxidative stress (Srinivasan et al., 2025). As granulation tissue forms, keratinocytes at the wound edges initiate re-epithelialization by detaching from their basement membrane, extending filopodia, and migrating across the wound bed. This process is guided by growth factors such as EGF, HB-EGF, and FGF-7, and is further accelerated by peptides such as LL-37, which activates EGFR signaling to promote keratinocyte migration and proliferation (Tomic-Canic et al., 2018; Wang et al., 2016). Thymosin β4 also enhances this phase by supporting keratinocyte motility, ECM remodeling, and cytoskeletal organization, thereby facilitating rapid epithelial coverage (Yu et al., 2025) as illustrated in Figure 3c and32d.

In the final remodeling phase, the temporary granulation matrix is replaced with organized type I collagen, and myofibroblasts contract the wound before undergoing apoptosis. MMPs degrade excess ECM components, while TIMPs ensure controlled remodeling (Rodrigues et al., 2019; Xue and Jackson, 2015). Peptides like Thymosin β4 plays a critical role in scar modulation by reducing myofibroblast persistence, limiting TGF-β-driven fibrosis, and regulating MMP activity, ultimately leading to faster wound healing as shown in Figure 3e.

Wound healing peptides, structure, classification, and functional diversity

Peptides are organic molecules consisting of chains of amino acids (ranging from about 2 to more than 50) linked by peptide bond. Peptides exhibit diverse pharmacological effects, including antimicrobial, antihypertensive, anti-inflammatory, and anticancer effects (Zhou et al., 2023). A polypeptide is a longer, continuous, unbranched peptide chain, When its molecular mass reaches 10,000 Da or more, it is referred to as a protein (Feng et al., 2022). Chains of 4 – 20 amino acids are termed oligopeptides, and include dipeptides, tripeptides, and tetrapeptides (Nasadyuk, 2021). Peptides can be broadly classified according to their origin, chain length, biological role, and structural properties. Currently, peptides have attracted significant attention

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

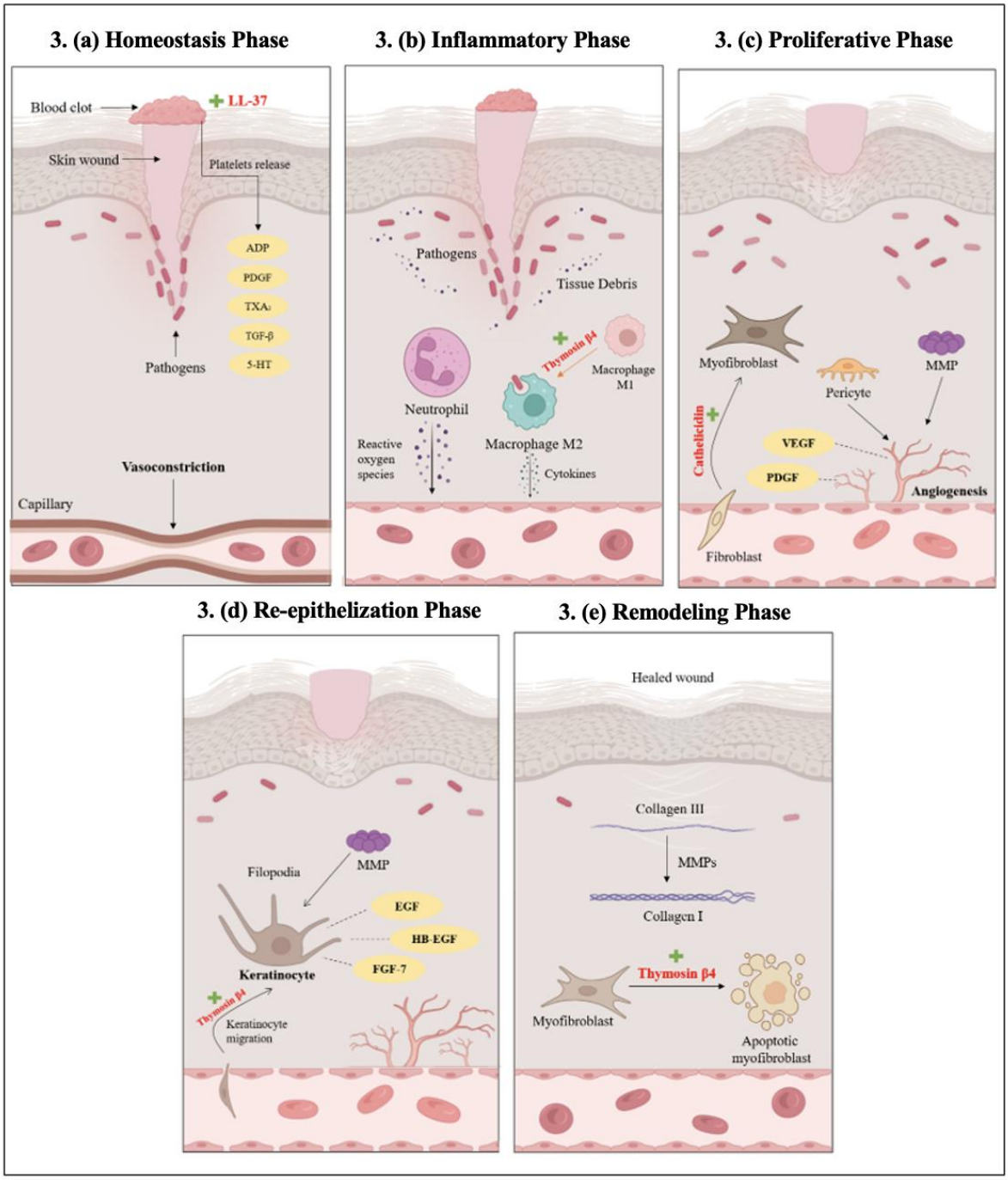

Figure 3: Schematic representation of the five sequential phases of wound healing and the associated roles of key peptides where (**a**) Hemostasis phase that is characterized by platelet aggregation and vasoconstriction mediated by secreted molecules including ADP, PDGF, TXA_2, TGF-β, and 5-HT; Here in peptides such as LL-37 can induce further clot formation. (**b**) Inflammatory phase were neutrophils and macrophages clear pathogens. Peptides such as Thymosin β4 can facilitate macrophage transition. (**c**) Proliferative phase were fibroblasts, myofibroblasts, and pericytes coordinate ECM deposition and angiogenesis. Peptides such as Cathelicidin can support this phase. (**d**) Re-epithelialization phase in which keratinocyte migration and proliferation occur, and it's driven by MMPs and growth factors (EGF, HB-EGF, FGF-7), this can be enhanced by peptides such LL-37 and Thymosin β4. Lastly, (**e**) Remodeling phase where collagen maturation and tissue contraction take place, and it's regulated by MMPs and myofibroblast apoptosis which can be facilitate by peptides such as Thymosin β4. (VEGF, Vascular Endothelial Growth Factor; TGF-β, Transforming Growth Factor-beta; MMP, Matrix Metalloproteinase; EGFR, Epidermal Growth Factor Receptor).

due to their ability to modulate diverse biological pathways and enhance cellular and molecular interactions (Gori et al., 2023).

A notable example is the Arg-Gly-Asp (RGD) peptide sequence, which enhances fibroblast recruitment and migration, thereby accelerating the inflammatory and proliferative phases of wound healing (Chen et al., 2025a). The following sections further explain different classes of peptides with wound healing properties.

Wound healing peptides from micro-organisms

Antimicrobial peptides (AMPs) are a diverse group of naturally occurring molecules found in a wide range of organisms, including humans, toad, and mice. They are generally low in molecular weight, cationic, and amphipathic. Their amphipathic nature allow them to insert into the lipid bilayers and disrupt the microbial cell membranes (Feng et al., 2022; Travkova et al., 2017). AMPs typically act through mechanisms such as pore formation, membrane disintegration, and intracellular targeting (inhibition of protein or DNA synthesis), thereby providing broad-spectrum activity against bacteria, fungi, viruses, and even cancer cells (Le et al., 2017).

AMPs contribute significantly to the wound-healing process through their antimicrobial, immunomodulatory, and regenerative properties (Nasseri and Sharifi 2022). Their immunomodulatory functions include regulating cytokine production, influencing immune cell recruitment to the wound site, suppressing excessive inflammation by downregulating TNF-α, IL-6, and other pro-inflammatory mediator, and enhancing phagocytosis by modulating macrophage activity to facilitate the clearance of necrotic tissue and pathogens (Duan et al., 2022), In addition, AMPs are highly effective against multidrug-resistant bacteria, as they target bacterial membranes, making it difficult for pathogens to develop resistance (Pervin and Hassan, 2021).

Many AMPs adopt α-helical or β-sheet conformations that enhance their stability and interaction with bacterial membranes. Also, their relatively short peptide chains enable rapid diffusion through tissue, making them particularly effective for deep wound penetration (Zhang et al., 2025). A notable example of an AMPs is Nisin, produced by *Lactococcus lactis*. It binds to lipid II on bacterial membranes, forming pores that lead to ion leakage and bacterial cell death. Its potent antimicrobial effect primarily targets Gram-positive pathogens, thereby minimizing wound infections and supporting tissue regeneration (Khan et al., 2023). Other types of AMPs are summarized in Table 2.

Wound healing peptides from animals

Animal-derived peptides have been shown to accelerate wound healing, prevent scar formation, and contribute to infection control at the wound site. As they are derived from natural animal proteins, these peptides are generally considered safe and reliable. They are sourced from a wide range of animals, including amphibians, insects, marine organisms, and mammals (Fan et al., 2024).

Structurally, animal-derived peptides are typically composed of short amino acid sequences (ranging from 12–50 residues) that may be linear or cyclic and often adopt secondary structures such as α-helices and β-sheets. They are amphipathic, containing both cationic and hydrophobic domains, which enable them to interact with microbial membranes and as well as host cells, thereby exerting antimicrobial and wound-healing effects (Sun et al., 2024; Ma et al., 2024). For example, Bovine Lactoferrin (BLF) is an iron-binding glycoprotein derived from *bovine colostrum*, with each lobe capable of binding a single Fe^{3+} ion. Its structure enables it to inhibit microbial growth by sequestering iron, which bacteria need to survive, and by disrupting microbial membranes. In wound healing, BLF modulates inflammation by downregulating key cytokines such as TNF-α and IL-6, and promotes ECM remodeling through the regulation of MMPs. It exerts positive effects across all phases of wound healing, homeostasis,

inflammatory, proliferative, re-epithelization and remodeling phase (Dyrda-Terniuk and Pomastowski, 2023; Shini et al., 2022). Other types of animal-derived peptides are summarized in Table 2.

Wound healing peptides from plants

Plant-derived peptides are typically short sequences of 2–20 amino acids with molecular weights below 3 kDa, and are generated through the enzymatic hydrolysis of plant proteins (Nicolas-Espinosa et al., 2022). Their small size and structural composition often featuring cationic and hydrophobic residues enable them to interact with and penetrate biological membranes. This facilitates various therapeutic effects, including modulation of inflammation, reduction of oxidative stress, antimicrobial activity, stimulation of cell proliferation, and remodeling of ECM, all of which are crucial to the skin repair process (Nirmal et al., 2024; Fan et al., 2022). In a burn-injury rat model, oral administration of soybean-derived peptides downregulated NF-κB pathway activation and reduced neutrophil and macrophage infiltration at wound sites. Treated animals also exhibited enhanced angiogenesis, indicated by elevated CD31 expression, and accelerated healing, achieving 67 % wound closure compared with 41 % in control animals by the eighth week (Zhao et al., 2019). Other types of plant derived peptides are summarized in Table 2.

Wound healing synthetic peptides

In addition to natural peptides, synthetic peptides have gained a considerable attention as bioactive agents for accelerating wound healing. Their small size, ease of synthesis, and high tunability make them versatile tools that can be tailored for specific biological functions. They can be rationally designed or derived from natural protein sequences to target specific pathways involved in wound repair (Guan et al., 2022; Md Fadilah et al., 2024).

A notable example is A7-1, a synthetic peptide derived from a 13-residue sequence in silk fibroin, identified for its adhesive properties and ability to support early wound regeneration. A study demonstrated that topical application of A7-1 in mice accelerated early angiogenesis and granulation tissue formation, potentially through stabilizing local growth factor gradients (Jung et al., 2024). Additional engineered peptides and their mechanisms of action are summarized in Table 3. Furthermore, to provide a concise overview of the strength of evidence, Table 4 summarizes wound healing peptides for which results have been independently reproduced across different study types.

HYDROGELS FOR THE DELIVERY OF THERAPEUTIC PEPTIDES: SHIELDING, SYNTHESIS, AND WOUND TARGETING

Hydrogels are three-dimensional networks of hydrophilic polymers that can absorb large amounts of water while retaining a semi-solid structure. With water content often exceeding 90 %, hydrogels provide a moist environment that facilitates tissue repair. They can be tuned to incorporate bioactive components (e.g., antimicrobials, growth factors, or cells) that actively promote healing (Xiang et al., 2020; Khan et al., 2016). The swollen hydrogel matrix can also absorb excess wound exudate, helping to regulate tissue fluids while maintaining hydration. Importantly, hydrogel dressings provide a degree of mechanical protection, as they are conformable and cushion the wound against external stresses. Unlike traditional dry gauze, hydrogels do not adhere tightly to the granulating wound bed, thereby minimizing pain and tissue damage during dressings (Xiang et al., 2020; Ahmed, 2015; Feng et al., 2024). These characteristics, moisture retention, non-adherence, and softness, make hydrogels particularly suitable for dry or painful wounds, including burns, necrotic wounds, and chronic ulcers.

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

Table 2: Bioactive peptides derived from microbial, animal, and plant sources with documented roles in wound healing

S. NO.	PEPTIDE	MOLECULAR WEIGHT [DA] AND ORIGIN	MECHANISM IN WOUND HEALING	TARGETED HEALING PHASE[S]	REFERENCE
WOUND HEALING PEPTIDES FROM MICRO-ORGANISMS					
1	Actinomycin X2	$C_{62}H_{86}N_{12}O_{16}$ 1255.42 Da *Streptomyces cyaneofuscatus*	Consists of a planar phenoxazinone chromophore enabling it to activate the classic NF-kB signaling pathway and down-regulate the pro-inflammatory factor IL-6.	Inflammatory, proliferative and remodeling phases	Zhou et al., 2023
2	Enterocin A	$C_{219}H_{352}N_{64}O_{66}S_5$ 4800 Da *Enterococcus faecalis*	Consist of a conserved N-terminal region and a disulfide-bonded globular C-terminal domain, which allow it to produce localized holes in cell wall causing leakage of macromolecules such as proteins and resulting in death of pathogenic organisms.	Inflammatory phase	David et al., 2016
3	Fengycin	$C_{72}H_{110}N_{12}O_{20}$ 1,463.7 Da *Bacillus subtilis* and *Bacillus velezensis*	Amphipathic cyclic lipopeptide that inhibit the growth of pathogenic fungi such as Aspergillus flavus. By disrupting membrane integrity, alter permeability, surface hydrophobicity, and causes cell lysis.	Inflammatory phase	Araujo et al., 2022
4	Iturin A	$C_{54}H_{95}N_{13}O_{15}$ 1,122.4 Da *Bacillus subtilis*	Lipopeptide containing a cyclic structure and a β -hydroxy fatty acid giving it amphipathic properties. It binds selectively to ergosterol in fungal membranes, inserting its lipophilic tail into the lipid bilayer, forming transmembrane pores, and disrupting membrane architecture.	Inflammatory phase	Zhou et al., 2021; Yang et al., 2024
5	Nisin	$C_{143}H_{230}N_{42}O_{37}S_7$ 3500 Da *Lactococcus lactis*	Encompasses five lanthionine rings that facilitate its binding to bacterial targets, and forming pores that lead to ion leakage and cell death. Additionally, it helps in reducing bacterial load in the wound site. It also increases the synthesis of TGF- and FGF-2.	Inflammatory phase	Guryanova and Ovchinnikova, 2022; Khan, 2022
6	Plantaricin A	$C_{128}H_{200}N_{32}O_{29}S$ 2847 Da *Lactobacillus plantarum*	Amphiphilic α-helical structure, enabling it to permeabilizes the inner membrane, leading to influx and efflux of various molecules across the transmembrane barrier, and altering electrical potential and pH gradients across the membrane, leading to cell death.	Inflammatory phase	Ong et al., 2020; Zhao et al., 2016

7	Subtilin	$C_{144}H_{230}N_{42}O_{39}S_6$ 3430 Da *Bacillus subtilis*	Encompasses multiple lanthionine rings. Have the ability to produce proteases enzymes which act by selectively breaking down necrotic tissue at the wound site, catalyzing the hydrolysis of peptide bonds within denatured proteins, thereby liquefying and removing barriers to tissue regeneration.	Inflammatory and proliferative phase	Shahzad, 2015
8	Surfactin	$C_{53}H_{93}N_7O_{13}$ 1036 Da *Bacillus subtilis*	Cyclic lipopeptide composed of a heptapeptide linked to a β-hydroxy fatty acid forming an amphiphilic structure, enabling it to insert into and disrupt bacterial membranes. It enhances macrophage polarization toward the M2 phenotype and boosts phagocytic activity. It also upregulates the expression of HIF-1α and VEGF.	Inflammatory, proliferative and remodeling phases	Shahzad, 2015; Yan et al., 2020
9	Tyrothricin	$C_{65}H_{85}N_{11}O_{13}$ 1228.4 Da *Brevibacillus brevis*	Rigid cyclic polypeptide composed mainly of gramicidine S and tyrocidine A. The cyclic nature confers high enzymatic stability and allows it to disrupt bacterial membranes effectively and reducing bacterial contamination.	Inflammatory and proliferative phase	Kim et al., 2015
			Wound healing peptides from animals		
10	AH90	$C_{123}H_{194}O_{28}$ 2657.2 Da *Odorrana graham*	Stimulating the release of TGF-β1 through NF-Ķb and JNK pathways. Triggers granulation formation through activation of the TGF-β/Smad pathway.	Proliferative and remodeling phases	Ahmad et al., 2024; Nasseri and Sharifi, 2022
11	Bovine Lactoferrin (BLF)	$C_{2766}H_{4290}N_{754}O_{819}S_{32}$ 80,000 Da *Bovine colostrum*	Bilobed iron-binding glycoprotein that inhibits microbial growth via iron sequestration and membrane disruption. It modulates inflammation by downregulating cytokines like TNF-α and IL-6. Also, promotes extracellular matrix remodeling by regulating MMPs.	All phases of wound healing	Dyrda-Terniuk and Pomastowski, 2023; Shini et al., 2022
12	Catestatin	$C_{107}H_{173}N_{37}O_{26}S$ 2362.8 Da Human Skin	Induces keratinocyte migration and proliferation through G-protein, PLC, EGFR, Akt/PI3K, and MAPK signaling pathways.	Proliferative phase	Nasseri and Sharifi, 2022; Hoq et al., 2011
13	Cathelicidin-OA1	$C_{134}H_{208}O_{39}$ 3,038.5 Da *Odorrana andersonii*	Amphipathic with an intramolecular disulfide bridge that allow it to accelerate re-epithelialization and stimulating fibroblast migration. Also, it upregulates TNF-α secretion during the early inflammatory phase, which facilitates macrophage recruitment to the wound site and boosts TGF-β1 secretion.	Inflammatory, proliferative, and remodeling phases.	Cao et al., 2018

14	Crotamine	$C_{204}H_{314}N_{56}O_{41}S_6$ 4,882 Da *Crotalus durissus*	Amphipathic β-sheet structure stabilized by three disulfide bonds. Exhibits membrane-disruptive activity, that leads to microbial cell death through membrane destabilization. It also possesses potent anti-inflammatory effect and downregulates pro-inflammatory mediators such as TNF-α.	Inflammatory, proliferative and remodeling phases	Yacoub et al., 2020
15	CW49	$C_{110}H_{190}O_{34}$ 2056.6 Da *Odorrana grahami*	Possess a potent pro-angiogenic ability that promotes angiogenesis. Also, it prevents excessive inflammatory response during the wound-healing process.	Inflammatory and proliferative phase	Nasseri and Sharifi, 2022; Wang et al., 2023
16	Esculentin-1a	$C_{212}H_{369}N_{59}O_{60}S$ 4800.7 Da *Rana esculenta*	Consists of 20 amino acids plus a glycinamide residue at its C-terminus which allow it to stimulates keratinocyte migration through EGFR and STAT3 pathways, and promotes re-epithelialization.	Proliferative phase	Di Grazia et al., 2015
17	Epincidin-1	$C_{114}H_{176}N_{30}O_{21}S$ 2334. 9 Da *Epinephelus coioides*	Acts as a cell proliferation inducer through an increase in S-phase and promoted vascularization in the wound site, enhances keratinocyte cell proliferation and migration, induces epithelial cell proliferation, vascularization, and collagen formation.	Proliferative and remodeling phases	Huang et al., 2017
18	Human β-defensin-3	$C_{150}H_{228}N_{44}O_{38}S_6$ 3448.1 Da Human skin, eyes, respiratory, and urogenital tract	Enhances fibroblast migration, proliferation and promotes angiogenesis through the activation of FGFR/JAK2/STAT3 pathways. It also reduces microbial burden at the wound site.	Inflammatory and proliferative phase	Nasseri and Sharifi, 2022; Takahashi et al., 2021
19	GHK-Cu	$C_{14}H_{24}N_6O_4Cu$ 403.9 Da Human plasma	Consist of histidine imidazole group and peptide backbone of GHK. It upregulates VEGF and promotes fibroblast proliferation, collagen synthesis, and keratinocyte migration. It also downregulates pro-inflammatory cytokines and ROS. Additionally, GHK-Cu facilitates ECM remodeling by regulating MMPs and TIMPs.	Inflammatory, proliferative and remodeling phases	Li et al., 2024
20	LL-37	$C_{211}H_{384}N_{64}O_{67}$ 4,492 Da Endogenously expressed in the skin and mucosal tissues in response to injury.	Cationic, amphipathic α-helical structure with a C-terminal enabling it to enhance keratinocyte and fibroblast migration, promoting re-epithelialization and granulation tissue formation. It also stimulates angiogenesis via upregulation of VEGF and modulating cytokine release (e.g. IL-6).	Inflammatory and proliferative phase	Guryanova and Ovchinnikova, 2022

21	Melittin	$C_{131}H_{229}N_{39}O_{31}$ 2844 Da Bee Venom	Cationic, amphipathic α-helical structure enables it to destroy the integrity of the bacterial outer membrane. Moreover, it exhibits anti-inflammatory properties by suppressing pro-inflammatory cytokines such as TNF-α and IL-1β.	Inflammatory and proliferative phase	Kurek-Górecka et al., 2021
22	OA-GL12	$C_{54}H_{85}N_{15}O_{16}S$ 1275.4 Da *Odorrana andersonii*	Amphipathic, and functionally rich sequence of OA-GL12 can induces the secretion of pro-inflammatory cytokines TNF-α and TGF-β1 from macrophages and activates EGFR pathway, further promoting cell migration.	Inflammatory, proliferative and re-epithelization phases.	Song et al., 2019
23	Temporins	$C_{66}H_{123}N_{17}O_{13}$ 1329 Da Granular glands in frog skin	Cationic, amphipathic α-helical conformation enables to efficiently induce HaCaT cell migration. Additionly, their antimicrobial efficacy also played an important role in the infection stage of wound healing.	Inflammatory and re-epithelization phase	Wang et al., 2023
24	Thymosin β4	$C_{212}H_{350}N_{56}O_{78}S$ 4921 Da Naturally produced in the body (in the heart, lung, brain, and liver)	Intrinsically disordered peptide under physiological conditions. It binds to G-actin, promoting cytoskeletal reorganization necessary for cell migration, particularly of keratinocytes and fibroblasts. Also, it modulates inflammation by suppressing NF-κB activation and reducing pro-inflammatory cytokines. And enhanced the switching of macrophages phenotype and myofibroblast apoptosis.	Inflammatory, re-epithelization, and remodeling phases.	Yu et al., 2025
			Wound healing peptides from plants		
25	Calotropin	$C_{30}H_{44}O_{10}$ 576.7 Da *Calotropis procera*	Steroidal backbone with a glycosidic linkage that enables strong interaction with cellular membranes and enzymatic pathways involved in tissue remodeling. It suppresses proinflammatory cytokines and inhibiting NF-κB activation. Moreover, stimulates fibroblast proliferation and collagen deposition.	Inflammation, proliferation, epithelialization, and remodeling phases.	Misra et al., 2024
26	Cecropins	$C_{176}H_{302}N_{52}O_{41}S$ Molecular weight = 3800 Da *Hyalophora cecropia*	Amphipathic basic N-terminal α-helical segment linked to a hydrophobic C-terminal that contribute to their initial electrostatic contacts with the membrane of the target microorganism. Resulting in a potent antimicrobial effect, Also, it downregulates TLR4 and inhibits pro-inflammatory cytokines (e.g., TNF-α, IL-6).	Inflammatory and proliferative phase	Wang et al., 2018
27	Cycloviolacin O2	$C_{133}H_{207}N_{37}O_{39}S_6$ 3169.5 Da *Viola odorata*	Head-to-tail cyclized backbone and a cyclic cystine knot motif that enables cyclotides to enhances bacterial clearance by both direct membrane-disrupting	Inflammatory phase	Fensterseifer et al., 2015

28	Kalata B2	$C_{67}H_{104}N_{18}O_{18}S_3$ 1515.8 Da *Oldenlandia affinis*	bactericidal action and immunomodulation, especially in wounds infected with drug-resistant Staphylococcus aureus.		
29	Soybean derived peptide	$C_{45}H_{70}N_{12}O_{12}$ 971.1 Da Soybean	Small sized peptides that can modulate the TLR4/NF-κB inflammatory signaling pathway, significantly reducing proinflammatory cytokines (e.g., TNF-α, CCL-3, CCL-11) while increasing anti-inflammatory IL-10. Furthermore, they enhance angiogenesis via upregulation of CD31, contributing to revascularization and tissue regeneration.	Inflammatory and proliferative phase	Zhao et al., 2019

Abbreviations: AMPs, Antimicrobial Peptides; BLF, Bovine Lactoferrin; ECM, Extracellular Matrix; EGFR, Epidermal Growth Factor Receptor; FGF, Fibroblast Growth Factor; FGFR, Fibroblast Growth Factor Receptor; GHK-Cu, Glycyl-L-histidyl-L-lysine–Copper[II] complex; IL, Interleukin; JAK, Janus Kinase; MAPK, Mitogen-Activated Protein Kinase; MMP, Matrix Metalloproteinase; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; PI3K, Phosphoinositide 3-kinase; STAT, Signal Transducer and Activator of Transcription; TGF-β, Transforming Growth Factor-beta; TIMP, Tissue Inhibitor of Metalloproteinases; TNF-α, Tumor Necrosis Factor-alpha; VEGF, Vascular Endothelial Growth Factor.. The chemical formulas presented were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov) and supporting databases including ChemSpider (https://www.chemspider.com), DrugBank (https://www.drugbank.ca), and ChEBI (https://www.ebi.ac.uk/chebi). Molecular weights [M.wt] were sourced from these databases or estimated using the ExPASy ProtParam tool (https://web.expasy.org/protparam) for peptides with known sequences but unlisted molecular data.

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

Table 3: Synthetic peptides engineered for wound healing applications

S. NO.	PEPTIDE	MOLECULAR WEIGHT [DA] AND ORIGIN	MECHANISM OF ACTION IN WOUND HEALING	TARGETED HEALING PHASE[S]	REFERENCE
1	A7-1	$C_{74}H_{129}N_{27}O_{15}S$ 1612 Da *Bombyx mori* fibroin heavy chain	Stimulates neovascularization, through modulation of VEGF, improves fibroblast infiltration, and act as a fibrin-like scaffold that supports cell adhesion and preserves growth factors within the wound microenvironment.	Proliferation and remodeling phases	Jung et al., 2024
2	AG30/5C	$C_{149}H_{266}N_{48}O_{40}$ 3400 Da Parent peptide AG30	Possess a potent antimicrobial activity against a range of pathogens, and enhances angiogenesis by stimulating endothelial cell proliferation and capillary formation.	Inflammation, proliferation, and remodeling phases	Nakagami et al., 2017
3	DRGN-1	$C_{71}H_{130}N_{20}O_{17}$ 1535.9 Da Komodo dragon-inspired synthetic peptide	Cationic antimicrobial peptide that possesses a partial α-helical traits in membrane which enhances its membrane-penetrating capability. Therefore, it disrupts microbial biofilms and bacterial membranes while also stimulating keratinocyte migration and proliferation via activation of the EGFR-STAT1/3 signaling cascade.	Inflammatory, proliferative and early remodeling phases	Chung et al., 2017
4	GFOGER	$C_{29}H_{44}N_9O_{10}$ 678.32 Da Collagen-mimetic peptide	Specifically binding to α2β1 integrin receptors on cells, enhancing cell adhesion, proliferation, and differentiation at the injury site, promoting tissue regeneration.	Proliferation and remodeling phases	Singh et al., 2025
5	IKVAV	$C_{25}H_{47}N_9O_7$ 555.65 Da α1 chain of laminin	Pentapeptide with an amphiphilic nature that enables sustained release and localization where it significantly suppresses fibrotic scar formation by inhibiting fibroblast migration and activation. Also, interferes with the TGF-β1 signaling pathway and downregulating TGF-β1 and α-SMA expression	Proliferation and remodeling phases	Jiang et al., 2023
6	KSL-W	$C_{64}H_{108}N_{18}O_{10}$ 1321.7 Da Synthetic decapeptide	Possesses antimicrobial effect and enhances fibroblast proliferation and migration, as evidenced by increased S and G2/M cell cycle phases and elevated F-actin production. It also upregulates the expression of MMP-1 and MMP-2 and their inhibitors TIMP-1 and TIMP-2, facilitating ECM remodeling.	Inflammation, proliferation, and remodeling phases	Gawande et al., 2014

7	LysSYL-loaded L5	$C_{53}H_{104}N_{16}O_9$ 1156.5 Da Synthetic peptide	Its amphiphilic nature allows it to accelerate wound healing by upregulating genes involved in tissue regeneration. It also causes infiltration of predominant inflammatory cells, deposition of fibroblasts and collagen.	Inflammation, proliferation, and remodeling phases	Liu et al., 2024
8	SHAP1	$C_{107}H_{205}N_{35}O_{21}$ 2316.9 Da Synthetic peptide	Induce HaCaT cell migration via the EGFR signaling pathway and transactivation of EGFR. And accelerates closure and healing of full-thickness excisional wounds in mice.	Proliferative phase	Gomes et al., 2017
9	Pep19-2.5	$C_{124}H_{206}N_{40}O_{24}S$ 2672.3 Da Synthetic peptide	Amphipathic and cationic that effectively suppresses inflammation in skin cells by inhibiting TLR2/TLR4-mediated activation of NF-κB and MAPK signaling, leading to reduced cytokine production (e.g, IL-6, IL-8, MCP-1). Also, enhances keratinocyte migration via EGFR transactivation and downstream ERK1/2 phosphorylation.	Inflammatory and proliferative phase	Pfalzgraff et al., 2016
10	RADA16-I	$C_{66}H_{113}N_{29}O_{25}$ 1712.73 Da Synthetic peptide	Possesses a direct interaction with cellular receptors to promote adhesion, proliferation, and migration of fibroblasts and keratinocytes. It also reduces inflammation and edema and accelerate wound closure	Proliferation, and remodeling phases	Dzierżyńska et al., 2023
11	RGD	$C_{13}H_{22}N_6O_6$ 346.35 Da Synthetic peptide	Mimicks cell adhesion motifs found in ECM proteins. It enhances cell adhesion, migration, and proliferation, particularly of fibroblasts and keratinocytes	Proliferation and remodeling phases	Mndlovu et al., 2023

Abbreviations: EGFR, Epidermal Growth Factor Receptor; ERK, Extracellular signal-Regulated Kinase; MMP, Matrix Metalloproteinase; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; PI3K, Phosphoinositide 3-kinase; PLC, Phospholipase C; STAT, Signal Transducer and Activator of Transcription; TGF-β, Transforming Growth Factor-beta; TLR, Toll-Like Receptor; VEGF, Vascular Endothelial Growth Factor; α-SMA, alpha-Smooth Muscle Actin. The chemical formulas presented were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov) and supporting databases including ChemSpider (https://www.chemspider.com), DrugBank (https://www.drugbank.ca) and ChEBI (https://www.ebi.ac.uk/chebi). Molecular weights (M.wt) were sourced from these databases or estimated using the ExPASy ProtParam tool (https://web.expasy.org/protparam) for peptides with known sequences but unlisted molecular data.

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

Table 4: Wound-healing peptides with details of the studies replicated by independent research groups

S.NO.	PEPTIDE	STUDY TYPE	SUMMARY OF FINDINGS	REFERENCE
1	AG30/5C	*In vitro*; preclinical; clinical	Accelerated wound closure in animal models and improved healing in severe limb ulcer patients in first-in-human clinical trial	Nakagami et al., 2017; Tomioka et al., 2014
2	AH90	*In vitro*; preclinical	Enhanced wound healing in murine models via modulation of immune and cellular responses	He et al., 2019; Liu et al., 2014b
3	BLF	*In vitro*; preclinical	Topical application accelerated wound closure and tissue repair in a rat nasal septum perforation model	Shini et al., 2022; Uşaklıoğlu and Çakan, 2023
4	Catestatin	*In vitro*; preclinical	Catestatin enhanced keratinocyte migration and proliferation *in vitro* and promoted antimicrobial, healing effects in a mouse skin injury model	Radek et al., 2008; Hoq et al., 2011
5	Cecropins	*In vitro*; preclinical	Cecropin P1 with transgenic *Kalanchoe pinnata* accelerated tissue repair *in vivo*, while Cecropin D-derived peptides enhanced fibroblast migration and demonstrated wound healing activity in insect and *in silico* models	Lebedeva et al., 2017; Rivera-Sanchez et al., 2025
6	CW49	*In vitro*; preclinical	CW49 peptide–lavender oil emulsion enhanced wound closure, regeneration, and antibacterial defense *in vivo*; in diabetic mice, it accelerated healing via re-epithelialization and granulation tissue formation	Liu et al., 2014a; Jaramillo et al., 2023
7	Esculentin-1a	*In vitro*; preclinical	Stimulated keratinocyte migration via EGFR *in vitro*; *in vivo* accelerated mouse wound closure through PI3K/AKT-mediated angiogenesis, and enhanced bronchial epithelial repair via MMP-9/EGFR signaling	Di Grazia et al., 2015; Hu et al., 2023; Cappiello et al., 2019
8	GHK-Cu	*In vitro*; preclinical	Nanoparticle formulations accelerated wound closure and antibacterial protection in rats, while *in vitro* and gene expression studies revealed regenerative, anti-inflammatory, and protective roles in tissue repair	Pickart et al., 2015; Sun et al., 2019
9	Iturin	*In vitro*; preclinical	Iturin-based chitosan–silver nanoparticles showed strong antibacterial activity and accelerated wound healing in rat excisional wounds	Yaraguppi et al., 2023; Zhou et al., 2021
10	LL-37	*In vitro*; preclinical; clinical	LL-37 promoted keratinocyte/fibroblast migration and wound closure in vitro and mice; LL-37–mimic nanofiber aerogels enhanced regeneration in diabetic mice; a multicentric clinical trial showed topical LL-37 improved healing of venous leg ulcers.	Carretero et al., 2008; John et al., 2023; Mahlapuu et al., 2021

11	Nisin	*In vitro*; preclinical	Nisin-preconditioned stem cells enhanced growth factors and cytokine balance; *in vivo*, it accelerated healing via immunomodulation, while nisin-loaded nanofiber dressings reduced infection, promoted re-epithelialization, and hastened closure without adverse effects	Karimi et al., 2021; Mouritzen et al., 2019; Heunis et al., 2013
12	RADA16-I	*In vitro*; preclinical; clinical	RADA16 hydrogels enhanced re-epithelialization and repair in mouse and rat wound models; clinically, RADA16-based formulations (PuraStat, PuraBond) have been used as safe, compatible hemostatic agents in surgery.	Dzierżyńska et al., 2023; Song et al., 2025
13	RGD	*In vitro*; preclinical	Hydrogel sheets with mesenchymal stem cells enhanced closure and soft tissue regeneration in mice, while chitosan–alginate–tannic acid scaffolds accelerated repair and skin regeneration in rats	Mndlovu et al., 2023; Ansari et al., 2021
14	Soybean derived peptide	*In vitro*; preclinical	Supplementation enhanced skin repair in rats by promoting collagen deposition and tissue regeneration, while soy bean derived small peptides attenuated burn-induced inflammation and accelerated healing through improved tissue remodeling	Zhang et al., 2020; Zhao et al., 2019
15	Temporins	*In vitro*; preclinical	Temporin A accelerated repair of MRSA-infected wounds in mice through bactericidal action, while Temporin-Ra delivered via pH-sensitive nanofibers promoted closure and tissue regeneration in rat excisional wounds.	Simonetti et al., 2008; Koohzad and Asoodeh, 2023
16	Thymosin β4	*In vitro*; preclinical	In animal models it improved re-epithelialization, collagen deposition, supported hair follicle development, and overall tissue repair. Clinically, Phase 2 studies in patients with venous stasis ulcers, pressure ulcers, and epidermolysis bullosa wounds demonstrated accelerated healing and confirmed safety and tolerability.	Raheem et al., 2024; Philp et al., 2004; Guarnera et al., 2010
17	Tyrothricin	*In vitro*; preclinical; clinical	A chitosan film-forming gel accelerated closure in rat excisional and burn wounds, while the Tyrosur® wound gel improved healing outcomes in superficial abrasive wounds in clinical settings.	Kim et al., 2015; Wigger-Alberti et al., 2012

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

Beyond passive protection, hydrogels act as an active scaffold for tissue regeneration. Their porous, hydrated structure mimics the natural ECM, allowing cells to infiltrate and proliferate within the wound site (Radulescu et al., 2022). In particular, peptide-based hydrogels rely on peptides that self-assemble into nanofibrous networks through non-covalent interactions such as β-sheet hydrogen bonding and hydrophobic forces (Dou and Feng, 2017). A hallmark of peptide hydrogels is their biomimicry of the ECM, they form nano-scale fibrous scaffolds resembling collagen fibrils and proteoglycan networks, creating a cell-friendly matrix that supports cell adhesion and migration (Wang et al., 2020). Peptides can be designed to include specific biochemical signals (e.g., the RGD cell-adhesion motif or growth factor-binding sequences), endowing these hydrogels intrinsic bioactivity not easily achieved in conventional synthetic polymer gels (Mndlovu et al., 2023). Peptide hydrogels are generally biocompatible and biodegradable *via* proteolytic enzymes because they are composed of natural and short chains of amino acid, thereby minimizing chronic foreign-body reactions (Wu et al., 2022).

The formulation of hydrogels incorporated with peptide typically begins with the selection or synthesis of short peptide sequences capable of self-assembly. These peptides are then dissolved in an appropriate solvent to initiate the process. Crosslinking agents or environmental triggers are then used to induce self-assembly into a hydrogel matrix. Therapeutic peptides such as RADA16-I may be incorporated to boost biological activity. The hydrogel is subsequently molded, sterilized, and applied to wound models (e.g., mice) for *in vivo* evaluation (Dzierżyńska et al., 2023; Stefanov et al., 2017) as illustrated in Figure 4.

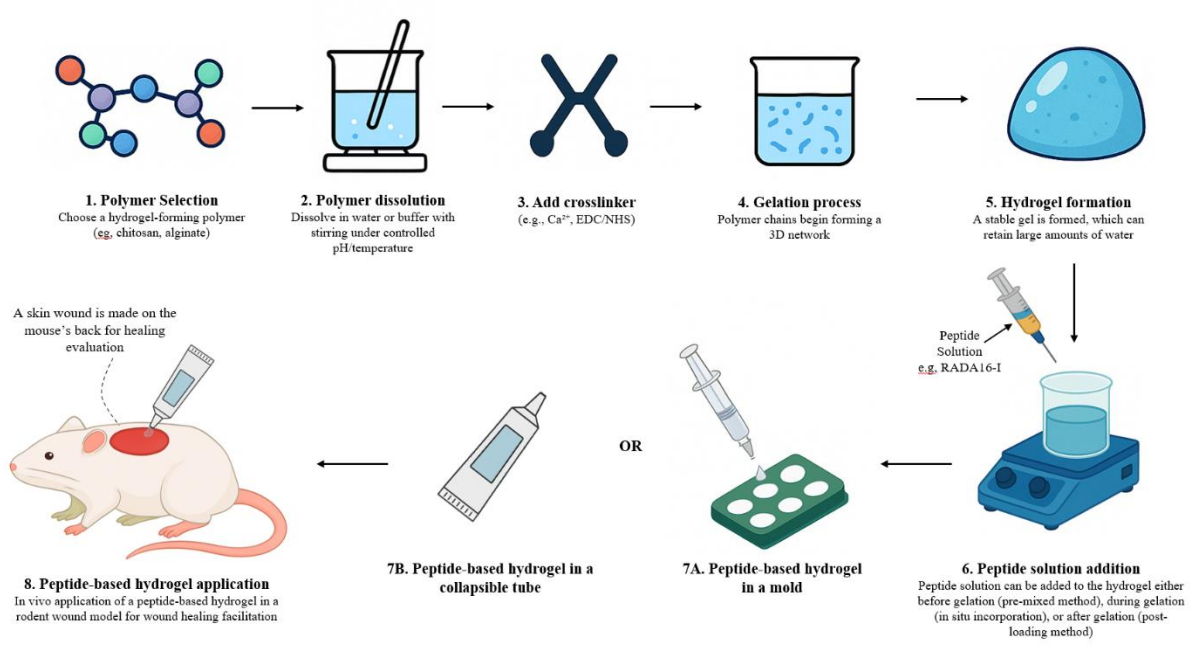

Figure 4: A schematic illustration that shows the preparation and application of peptide-based hydrogels for wound healing.

Approved and commercially available peptide-loaded hydrogels in wound care

Peptide-based hydrogels can enhance nearly all phases of wound healing. For example, during the homeostasis phase, they can aid by rapidly forming a physical barrier and promoting clot formation. In a rat bleeding model, h9e peptide solution achieved hemostasis 82 % faster than a commercial hemostatic agent (Celox™) by rapidly gelling and concentrating platelets and clotting factors at the bleeding site (Guan et al., 2022; Carter et al., 2021).

Additionally, peptide-based hydrogels can facilitate the inflammatory phase through their intrinsic antimicrobial and immunomodulatory functions (Kharaziha et al., 2021). A notable example is a hydrogel functionalized with the thrombin-derived peptide TCP-25, designed to address bacterial infection and inflammation. TCP-25 not only exhibits broad-spectrum antimicrobial activity but also binds bacterial endotoxins (e.g., lipopolysaccharide) neutralizing their inflammatory effects. In infected wound models, a TCP-25 peptide hydrogel eradicated *Staphylococcus aureus* and *Pseudomonas aeruginosa* while concurrently reducing pro-inflammatory cytokine levels in the local tissue (Dahlman et al., 2021).

Moreover, peptide hydrogels can significantly enhance the proliferative phase by serving as a bioactive scaffold for cell growth (Im et al., 2018). Because peptide matrices closely resemble native ECM, they promote keratinocyte and fibroblast migration into the wound and support their proliferation (Xiang et al., 2020). For example, in a study using a chitosan-based film-forming gel containing tyrothricin, researchers observed accelerated healing in rat wound models, including burns, abrasions, and excisions. Treated wounds showed enhanced granulation tissue formation and epithelialization compared with control groups. Additionally, histological analyses revealed increased fibroblast proliferation and angiogenesis, leading to a faster and smoother transition to tissue regeneration (Kim et al., 2015).

In the final remodeling phase, peptide hydrogels can influence remodeling and improve healing in earlier phases, eventually reducing scar formation (Song et al., 2020). For instance, a study investigating a resveratrol-loaded self-assembling peptide hydrogel, RADA-PDGF2, in a rat model demonstrated its beneficial effects on wound healing. Treated wounds displayed more organized collagen deposition and nearly normal epidermal architecture at the completion of healing, with minimal scar tissue. Furthermore, histological analyses showed that collagen fibers in treated wounds were aligned similarly to those in uninjured skin, in contrast to the disorganized bundles typically observed in scar tissue (Deptuła et al., 2023). Thus, peptide-based hydrogels not only accelerate the early stages of healing but also improve the overall quality of repair. Table 5 lists peptide-based hydrogels that are available in the current market.

Recent advancements in peptide-based hydrogels

Recent research has achieved remarkable advances in the functionalization and performance of peptide hydrogels for wound healing. For example, in 2023, Huang et al., engineered an “all-peptide” hydrogel using modified γ-polyglutamic acid and RGD-containing peptides, which could be 3D-printed with living cells. Endothelial cells overexpressing VEGF were printed within this peptide matrix, creating a living scaffold that continuously released VEGF, promoted angiogenesis. In diabetic wound models, this VEGF-eluting peptide hydrogel significantly accelerated wound closure and enhanced tissue regeneration by reducing inflammation and hypoxia (Huang et al., 2023).

In 2025, Chen et al. reported a self-healing hydrogel composed of food-derived peptides that simultaneously addresses infection, inflammation, and hemostasis. The hydrogel was formed by cross-linking egg-white proteins with oxidized polysaccharides and incorporating a copper-bound tripeptide (GHK-Cu) known for its regenerative activity. The resulting gel demonstrated broad-spectrum antibacterial and anti-inflammatory effects and rapidly stopped bleeding by adhering to tissues (Filipczak et al., 2021). In infected wound models, the GHK-Cu peptide hydrogel significantly accelerated healing, achieving ~95 % wound closure by day 12 compared with 65 % in controls, primarily by promoting neovascularization and tissue regeneration (Chen et al., 2025b).

EXCLI Journal 2025;24:1657-1689 – ISSN 1611-2156
Received: July 25, 2025, accepted: October 07, 2025, published: December 01, 2025

Table 5: List of commercial peptide-based hydrogels in the current market

PRODUCT NAME	MANU-FAC-TURER	ACTIVE COMPO-NENTS	ROUTE OF ADMIN-ISTRATION	INDICATIONS	REFER-ENCE
BIOGELX™	Biogelx Ltd.	Synthetic self-assem-bling pep-tides [e.g., IKVAV]	Injectable hy-drogel	Improve nerve re-generation through a critical nerve gap in rat model.	Guiotto et al., 2024
CORNING® PURAMA-TRIX™	Corning Inc.	RADA16-I peptide	Injectable hy-drogel	Used for tumor cell migration and inva-sion, in vivo analy-sis of tissue regen-eration, and regen-eration of brain tis-sue.	Abbasi Aval et al., 2022; Mohapatra et al., 2021
MATRISTEM®	ACell Inc.	ECM-derived peptides [porcine bladder]	Sheet or pow-der hydrogel	Burn treatment	Capella-Monsonís et al., 2020
PURASINUS™	3-D Matrix	RADA16-I peptide	Injectable hy-drogel	Hemostasis and wound healing after sinus surgery	Michaels et al., 2024
PURASTAT®	3-D Matrix	RADA16-I peptide	Injectable hy-drogel	Hemostasis in sur-gery; adjunct in chronic wound healing	Gil et al., 2022

Abbreviations: ECM, Extracellular Matrix; IKVAV, Isoleucine–Lysine–Valine–Alanine–Valine; PEG, Polyethylene Glycol; RADA16-I, Arginine–Alanine–Aspartic acid–Alanine.

Another advancement is the development of dual-action anti-infective peptide hydrogels. Puthia et al. (2020) created a hydrogel incorporating TCP-25, a peptide derived from thrombin that not only kills bacteria but also neutralizes inflammatory endotoxins (PAMPs). In mouse and pig wound models, a TCP-25 hydrogel eradicated *MRSA* and *Pseudomonas aeruginosa* infections and significantly reduced pro-inflammatory cytokines in the wound environment, thereby expediting healing (Puthia et al., 2020). This study highlights a strategy of functional-izing a polymer hydrogel with a host-defense peptide to create a dual-action dressing capable of reducing bacterial biofilm and excessive inflammation.

Peptide hydrogels are also being designed to respond to wound microenvironmental cues. For example, pH-switchable peptide assemblies have been developed to release therapeutics in infected wounds (Li et al., 2022). Many peptide hydrogels are injectable or sprayable, leverag-ing their shear-thinning behavior. A notable property of certain peptide formulations (e.g., the UD-developed peptides in G4Derm) is their ability to be applied as a liquid and rapidly gel *in situ* upon contact with tissues, conforming to irregular wound shapes (Roberts, 2024). This shear-thinning and rapid recovery behavior is particularly advantageous for filling deep or

tunneling wounds where pre-formed dressings cannot reach. Such advancements greatly enhance the applicability of peptide hydrogels in complex wound scenarios. Table 6 summarizes additional recent progress in peptide hydrogel research.

Additionally, a range of peptide-containing hydrogels is currently under investigation for skin regeneration. For example, Granexin® Gel (containing αCT1) has advanced to Phase III trial in diabetic foot ulcers, while SLI-F06, a fibromodulin-mimetic peptide hydrogel, has completed Phase I/IIa testing in post-surgical scars (Freedman et al., 2023). The emerging clinical pipeline of peptide hydrogels ranging from anti-scarring agents to antimicrobial and angiogenic dressings reflects a rapidly maturing field poised to deliver novel bioactive wound therapies. Examples of hydrogels currently in clinical trials but not yet approved by regulatory agencies are presented in Table 7.

Table 6: Recent advances on peptides as tissue regenerative wound healing agents for skin conditions

S. NO.	PEPTIDE	EXCIPIENTS SYSTEM	HYDROGEL SYSTEMS	OBSERVATIONS	REFERENCE
1	Angiopoietin-1 motif QHREDGS (Q-peptide)	Collagen-based hydrogel with peptide tethered	Chemical conjugation of peptide to hydrogel (biofunctionalization)	Q-peptide presentation in the matrix polarized macrophages to a pro-healing M2 phenotype and enhanced wound closure in diabetic models. Demonstrated a coordinated anti-inflammatory and facilitated tissue regeneration.	Mandla et al., 2019
2	Angiopoietin-1-derived QHREDGS peptide	Collagen–chitosan composite	Peptide chemically immobilized in polymer scaffold	Promoted keratinocyte survival, migration, and faster re-epithelialization in diabetic wounds. Increased granulation tissue and angiogenesis compared to diabetic wound-healing model.	Xiao et al., 2016; Hosoyama et al., 2019; Foley and Lau, 2016
3	Feruloyl-modified peptide with antioxidant motif	Glycol-chitosan	Enzymatic laccase-mediated phenolic cross-linking of peptide and polysaccharide	In a cutaneous wound model, the antioxidant peptide–chitosan hydrogel mitigated oxidative stress and significantly improved wound healing rates.	Wei et al., 2019; Robert et al., 2022
4	IKVAV–Fmoc-DD (laminin-derived IKVAV motif on Fmoc-dipeptide) + myoglobin	Hybrid: Self-assembling peptide + myoglobin protein	Co-assembly of amphiphilic peptide nanofibers with embedded protein	In a rat neural injury model, this hybrid hydrogel increased neuronal differentiation and synaptic integration of transplanted neural stem cells, leading to improved functional integration of grafts.	Roberts, 2024
5	Jelleine-1 (natural antimicrobial peptide) +	Carrier-free peptide/small-molecule	Co-assembly of peptide with small molecule	In MRSA-infected diabetic wounds, this carrier-free peptide hydrogel	Zhou et al., 2022

	8-bromoadenosine-cAMP			eradicated bacteria and promoted angiogenesis and accelerated wound closure.	
6	Thrombin-derived 25-aa peptide TCP-25	PEG-based hydrophilic hydrogel	Covalent functionalization of polymer with peptide	The antimicrobial peptide hydrogel killed *S. aureus* and *P. aeruginosa* and neutralized LPS, reducing inflammation. In mouse and porcine infection models it prevented infection and lowered pro-inflammatory cytokines.	Puthia et al., 2020
7	Ultrashort peptide	Peptide nanofibers	External stimulus-triggered assembly (formed gel upon ultrasound exposure)	In a rabbit model with bone defect, the ultrasound-triggered peptide nanofiber gel modulated macrophages toward pro-healing behavior and created an osteogenic immune microenvironment. This led to enhanced vascularized bone regeneration.	De Leon-Oliva et al., 2023; Zhang et al., 2024; Yadav et al., 2022
8	Ultrashort self-assembling peptide LK_6C	Ultrashort peptide nanofibers	Physical self-assembly into nanofibers, then oxidation crosslinking via disulfide bonds	Accelerated full-thickness skin wound closure and re-epithelialization in mice, with minimal inflammation or allergy.	Seow et al., 2016

Abbreviations: ECM, Extracellular Matrix; EGFR, Epidermal Growth Factor Receptor; Fmoc, Fluorenylmethyloxycarbonyl; HIF-1α, Hypoxia-Inducible Factor 1-alpha; MMP, Matrix Metalloproteinase; PEG, Polyethylene Glycol; TGF-β, Transforming Growth Factor-beta; VEGF, Vascular Endothelial Growth Factor.

FUTURE DIRECTIONS OF PEPTIDES IN WOUND HEALING

An innovative development in this field is the use of wound-healing peptides that selectively bind to injured tissues. One example is the cyclic peptide CAR (CARSKNKDC), which targets angiogenic vasculature and accelerates wound closure and re-epithelialization by enhancing keratinocyte migration *via* syndecan-4 signaling (Maldonado et al., 2023). Such approaches enable targeted modulation of healing pathways, making them particularly suitable for chronic or non-healing wounds.

Another promising innovation as suggested by Huang et al. is the use of 3D bioprinting to create customized peptide-based scaffolds. Where endothelial cells overexpressing VEGF were bio-printed into a peptide hydrogel scaffold, creating a bioactive matrix that substantially enhanced vascularization and wound closure in diabetic models. This demonstrates the potential of integrating peptide science with additive manufacturing to produce personalized, therapeutic wound grafts (Huang et al., 2023).

Moreover, peptides can also be incorporated into smart dressings that can monitor and respond to the wound environment. For example, wearable biosensors functionalized with peptides can be developed to detect infection-related biomarkers like *S. aureus* enzymes and

inflammation markers such as MMP-13. These dressings can wirelessly transmit diagnostic data, enabling real-time monitoring and early intervention.

Table 7: List of peptide hydrogels that are currently under investigation in clinical trials

S. NO.	PRODUCT	PEPTIDE COMPOSITION	INTENDED APPLICATION	CLINICAL TRIAL PHASE	REFERENCE
1	ADP-5 Hydrogel	Amelogenin-derived peptide (ADP-5) in gellan–xanthan hydrogel	Periodontal tissue regeneration	Phase I	Attik et al., 2023
2	CMC+PEO Dual-Polymer Gel	Carboxymethyl cellulose (CMC) and polyethylene oxide (PEO)	Prevention of postsurgical adhesions in peritoneal, intrauterine, lumbar spine, and tendon/nerve surgeries	Ongoing phase I–III trials	Ye et al., 2022
3	Granexin® Gel	ACT1 peptide (αCT1, a 25-amino-acid connexin-43 mimetic peptide)	Chronic wound healing, burns, scar reduction, and radiodermatitis	Phase I and II	Yaguchi et al., 2021
4	Novocart® Inject Plus	Fibrin/collagen gel with autologous chondrocytes	Regenerative cell therapy for articular cartilage repair in the knee	Phase III	Niemeyer et al., 2022
5	SAPB-T45K	Synthetic self-assembling peptide, short oligopeptide	Small skin wounds	Phase I	Gelain et al., 2021
6	SLI-F06	SLI-F06 peptide embedded in a cross-linked hyaluronic acid hydrogel	Surgical wound repair and scar prevention	Double blind study	Freedman et al., 2023; Banerjee et al., 2025
7	TFC-1326	Synthetic anti-freeze glycoprotein mimetic peptide (TFC-1326) – a carbohydrate–peptide hybrid compound	Anti-aging skin therapy	Pilot clinical trial	Deliencourt-Godefroy et al., 2025

Abbreviations: αCT1, Alpha Connexin C-Terminal 1; CMC, Carboxymethyl Cellulose; ECM, Extracellular Matrix; HA, Hyaluronic Acid; PEO, Polyethylene Oxide; SAP, Self-Assembling Peptide

CONCLUSION

Peptides have rapidly emerged as an effective therapy for advanced wound care due to their ability to modulate the complex biological processes that underlie tissue repair. Unlike traditional topical therapies that often target single aspects of healing, peptides offer a multifunctional approach by acting as antibacterial agents, angiogenic stimulants, immune-modulators, and regenerative inducers. Their capacity to interact with cellular receptors and modify

intracellular signaling pathways across all stages of wound healing makes them an ideal candidate for managing chronic wounds.

Therapeutic peptides, owing to their short amino acid chains, can be tailored or naturally sourced to target specific molecular pathways and regulate key mediators like VEGF, MMPs, and TGF-β in wound healing. They offer favorable pharmacokinetics including high tissue permeability, low immunogenicity, and predictable degradation, but face challenges of enzymatic breakdown and rapid clearance. To overcome these, advanced delivery systems such as hydrogel encapsulation are employed to enhance stability, efficacy, retention, and controlled release.

The future of peptide therapeutics in wound care lies in innovations at the intersection of biology, chemistry, and material science. Stimuli-responsive peptides, capable of releasing therapeutic cues in response to pH, enzymatic activity, or oxidative stress, are currently under active investigation. Integration with biosensors, wearable electronics, and 3D bioprinting technologies may enable real-time diagnostics and personalized therapeutic delivery. Furthermore, the exploration of ultrashort peptides, cyclopeptides, and peptide-mimetic analogs presents new opportunities to overcome the traditional limitations of peptide-based therapeutics.

Conflict of interest

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest in the preparation and publication of this review.

Artificial Intelligence (AI) – Assisted Technology

No AI tool was used for the writeup of this manuscript.

Author contributions

Rafl M. Kamil: Conceptualization, Methodology, Data curation, Formal analysis, Writing original draft. Shaik Nyamathulla: Conceptualization, Funding acquisition, Resources, Supervision, Review and editing. Syed Mahmood: Conceptualization, Resources, Supervision, Review and editing.

Acknowledgments

The authors would like to express their utmost gratitude and appreciation to Universiti Malaya for funding a research project (Universiti Malaya Research Excellence grant - UMREG071-2024) related to the peptide-based hydrogels for wound healing. Further, the work on peptides is supported by the Ministry of Higher Education, Malaysia by the Fundamental Research Grant Scheme (FRGS) grant (FP-048-2020) to investigate the role of peptides in chronic wounds.

REFERENCES

Abazari M, Ghaffari A, Rashidzadeh H, Badeleh SM, Maleki Y. A Systematic Review on Classification, Identification, and Healing Process of Burn Wound Healing. The International Journal of Lower Extremity Wounds. 2022;21(1):18–30. doi: 10.1177/1534734620924857.

Abbasi Aval N, Emadi R, Valiani A, Kharaziha M, Finne-Wistrand A. An aligned fibrous and thermosensitive hyaluronic acid-puramatrix interpenetrating polymer network hydrogel with mechanical properties adjusted for neural tissue. Journal of Materials Science. 2022;57(4):2883–96. doi: 10.1007/s10853-021-06733-0.

Adnan SB, Maarof M, Fauzi MB, Md Fadilah NI. Antimicrobial Peptides in Wound Healing and Skin Regeneration: Dual Roles in Immunity and Microbial Defense. International Journal of Molecular Sciences. 2025;26(13):5920.

Agier J, Efenberger M, Brzezińska-Błaszczyk E. Cathelicidin impact on inflammatory cells. Central European Journal of Immunology. 2015;40(2): 225–35. doi: 10.5114/ceji.2015.51359.

Ahmad A, Khan JM, Bandy A. A Systematic Review of the Design and Applications of Antimicrobial Peptides in Wound Healing. Cureus. 2024;16(4):e58178. doi: 10.7759/cureus.58178.

Ahmad W, Aquil Z, Alam SS. Historical Background of Wound Care. Hamdan Medical Journal. 2020;13(4): 189–95. doi: 10.4103/hmj.Hmj_37_20.

Ahmed EM. Hydrogel: Preparation, characterization, and applications: A review. Journal of Advanced Research. 2015;6(2):105–21. doi: 10.1016/j.jare.2013.07.006.

Ansari S, Pouraghaei Sevari S, Chen C, Sarrion P, Moshaverinia A. RGD-Modified Alginate–GelMA Hydrogel Sheet Containing Gingival Mesenchymal Stem Cells: A Unique Platform for Wound Healing and Soft Tissue Regeneration. ACS Biomaterials Science & Engineering. 2021;7(8):3774–82. doi: 10.1021/acsbiomaterials.0c01571.

Araujo J, Monteiro J, Silva D, Alencar A, Silva K, Coelho L, et al. Surface-Active Compounds Produced by Microorganisms: Promising Molecules for the Development of Antimicrobial, Anti-Inflammatory, and Healing Agents. Antibiotics. 2022;11(8):1106. doi: 10.3390/antibiotics11081106.

Attik N, Garric X, Bethry A, Subra G, Chevalier C, Bouzouma B, et al. Amelogenin-Derived Peptide (ADP-5) Hydrogel for Periodontal Regeneration: An In Vitro Study on Periodontal Cells Cytocompatibility, Remineralization and Inflammatory Profile. Journal of Functional Biomaterials. 2023;14(2):53. doi: 10.3390/jfb14020053.

Banerjee D, Vydiam K, Vangala V, Mukherjee S. Advancement of Nanomaterials- and Biomaterials-Based Technologies for Wound Healing and Tissue Regenerative Applications. ACS Applied Bio Materials. 2025; 8(3):1877–99. doi: 10.1021/acsabm.5c00075.

Beura SK, Panigrahi AR, Yadav P, Agrawal S, Singh SK. Role of Neurons and Glia Cells in Wound Healing as a Novel Perspective Considering Platelet as a Conventional Player. Molecular Neurobiology. 2022; 59(1):137–60. doi: 10.1007/s12035-021-02587-4.

Boersema G, Smart H, Giaquinto-Cilliers M, Mulder M, Weir G, Bruwer F, et al. Management of non-healable and maintenance wounds: a systematic integrative review and referral pathway. Wound Healing Southern Africa. 2021;14(1):8–17. doi: 10.1097/01.ASW.0000722740.93179.9f.

Cao X, Wang Y, Wu C, Li X, Fu Z, Yang M, et al. Cathelicidin-OA1, a novel antioxidant peptide identified from an amphibian, accelerates skin wound healing. Scientific Reports. 2018;8(1):943. doi: 10.1038/s41598-018-19486-9.

Capella-Monsonís H, De Pieri A, Peixoto R, Korntner S, Zeugolis DI. Extracellular matrix-based biomaterials as adipose-derived stem cell delivery vehicles in wound healing: a comparative study between a collagen scaffold and two xenografts. Stem Cell Research & Therapy. 2020;11(1):510. doi: 10.1186/s13287-020-02021-x.

Cappiello F, Ranieri D, Carnicelli V, Casciaro B, Chen H-T, Ferrera L, et al. Bronchial epithelium repair by Esculentin-1a-derived antimicrobial peptides: involvement of metalloproteinase-9 and interleukin-8, and evaluation of peptides' immunogenicity. Scientific Reports. 2019;9(1):18988. doi: 10.1038/s41598-019-55426-x.

Carretero M, Escámez MJ, García M, Duarte B, Holguín A, Retamosa L, et al. In vitro and In vivo Wound Healing-Promoting Activities of Human Cathelicidin LL-37. Journal of Investigative Dermatology. 2008;128(1):223–36. doi: 10.1038/sj.jid.5701043.

Carter T, Qi G, Wang W, Nguyen A, Cheng N, Ju YM, et al. Self-Assembling Peptide Solution Accelerates Hemostasis. Advances in Wound Care. 2021;10(4): 191–203. doi: 10.1089/wound.2019.1109.

Chen B, Liang L, Jia D, Qin M, He L, Liu S, et al. Inhibitory effect of RGD peptide hydrogel on inflammation and angiogenesis in vitro. Journal of Biomaterials Applications. 2025a;39(7):723–33. doi: 10.1177/08853282241296520.

Chen H, Yang P, Xue P, Li S, Dan X, Li Y, et al. Food-Derived Tripeptide–Copper Self-Healing Hydrogel for Infected Wound Healing. Biomaterials Research. 2025b;29:0139. doi: 10.34133/bmr.0139.

Chung EMC, Dean SN, Propst CN, Bishop BM, van Hoek ML. Komodo dragon-inspired synthetic peptide DRGN-1 promotes wound-healing of a mixed-biofilm infected wound. NPJ Biofilms and Microbiomes. 2017;3(1):9. doi: 10.1038/s41522-017-0017-2.

Dahlman A, Puthia M, Petrlova J, Schmidtchen A, Petruk G. Thrombin-Derived C-Terminal Peptide Reduces Candida Induced Inflammation and Infection In Vitro and In Vivo. Antimicrobial Agents and Chemotherapy. 2021;65(11):e0103221. doi: 10.1128/aac.01032-21.

David OM, Alese MO, Komolafe DM, Adejare IJ, Alese OO, Omonisi AE. In vitro and in vivo antimicrobial activity of partially purified enterocin produced by Enterococcus faecalis and its application in wound healing. African Journal of Clinical and Experimental Microbiology. 2016;18(1):1–10. doi: 10.4314/ajcem.v18i1.1.

De Leon-Oliva D, Boaru DL, Perez-Exposito RE, Fraile-Martinez O, García-Montero C, Diaz R, et al. Advanced Hydrogel-Based Strategies for Enhanced Bone and Cartilage Regeneration: A Comprehensive Review. Gels. 2023;9(11):885. doi: 10.3390/gels9110885.

Deliencourt-Godefroy G, Legoedec J, Bourdens M, Juin N, Nguyen L-T, Branchet M-C, et al. TFC-1326 Compound Reduces Clinical Signs of Skin Aging. Evidence From In Vitro Human Adipose and Skin Models and Pilot Clinical Trial. Journal of Cosmetic Dermatology. 2025;24(2):e16679. doi: 10.1111/jocd.16679.

Deptuła M, Sawicka J, Sass P, Sosnowski P, Karpowicz P, Zawrzykraj M, et al. Development and evaluation of RADA-PDGF2 self-assembling peptide hydrogel for enhanced skin wound healing. Frontiers in Pharmacology. 2023;14:1293647. doi: 10.3389/fphar.2023.1293647.

Di Grazia A, Cappiello F, Cohen H, Casciaro B, Luca V, Pini A, et al. d-Amino acids incorporation in the frog skin-derived peptide esculentin-1a(1-21)NH2 is beneficial for its multiple functions. Amino Acids. 2015;47(12):2505–19. doi: 10.1007/s00726-015-2041-y.

Dou X-Q, Feng C-L. Amino Acids and Peptide-Based Supramolecular Hydrogels for Three-Dimensional Cell Culture. Advanced Materials. 2017;29(16): 1604062. doi: 10.1002/adma.201604062.

Duan Z, Zhang J, Chen X, Liu M, Zhao H, Jin L, et al. Role of LL-37 in thrombotic complications in patients with COVID-19. Cellular and Molecular Life Sciences. 2022;79(6):309. doi: 10.1007/s00018-022-04309-y.

Dyrda-Terniuk T, Pomastowski P. The Multifaceted Roles of Bovine Lactoferrin: Molecular Structure, Isolation Methods, Analytical Characteristics, and Biological Properties. Journal of Agricultural and Food Chemistry. 2023;71(51):20500–31. doi: 10.1021/acs.jafc.3c06887.

Dzierżyńska M, Sawicka J, Deptuła M, Sosnowski P, Sass P, Peplińska B, et al. Release systems based on self-assembling RADA16-I hydrogels with a signal sequence which improves wound healing processes. Scientific Reports. 2023;13(1):6273. doi: 10.1038/s41598-023-33464-w.

Fan H, Liu H, Zhang Y, Zhang S, Liu T, Wang D. Review on plant-derived bioactive peptides: biological activities, mechanism of action and utilizations in food development. Journal of Future Foods. 2022;2(2):143–59. doi: 10.1016/j.jfutfo.2022.03.003.

Fan X, Ye J, Zhong W, Shen H, Li H, Liu Z, et al. The Promoting Effect of Animal Bioactive Proteins and Peptide Components on Wound Healing: A Review. Int J Mol Sci. 2024;25(23):12561. doi: 10.3390/ijms252312561.

Feng F, Zhao Z, Li J, Huang Y, Chen W. Multifunctional dressings for wound exudate management. Progress in Materials Science. 2024;146:101328. doi: 10.1016/j.pmatsci.2024.101328.

Feng L, Wang Y, Yang J, Sun Y-f, Li Y-w, Ye Z-h, et al. Overview of the preparation method, structure and function, and application of natural peptides and polypeptides. Biomedicine & Pharmacotherapy. 2022;153: 113493. doi: 10.1016/j.biopha.2022.113493.

Fensterseifer ICM, Silva ON, Malik U, Ravipati AS, Novaes NRF, Miranda PRR, et al. Effects of cyclotides against cutaneous infections caused by Staphylococcus aureus. Peptides. 2015;63:38–42. doi: 10.1016/j.peptides.2014.10.019.

Filipczak N, Yalamarty SSK, Li X, Khan MM, Parveen F, Torchilin V. Lipid-Based Drug Delivery Systems in Regenerative Medicine. Materials. 2021;14(18):5371. doi: 10.3390/ma14185371.

Foley C, Lau J. New Peptide-Modified Hydrogel Developed for Diabetic Wound Healing [PreClinical]. 2016. https://www.2minutemedicine.com/new-peptide-modified-hydrogel-developed-for-diabetic-wound-healing-preclinical/.

Freedman BR, Hwang C, Talbot S, Hibler B, Matoori S, Mooney DJ. Breakthrough treatments for accelerated wound healing. Science Advances. 2023;9(20):eade7007. doi: 10.1126/sciadv.ade7007.

Gawande PV, Leung KP, Madhyastha S. Antibiofilm and Antimicrobial Efficacy of DispersinB®-KSL-W Peptide-Based Wound Gel Against Chronic Wound Infection Associated Bacteria. Current Microbiology. 2014;68(5):635–41. doi: 10.1007/s00284-014-0519-6.

Gelain F, Luo Z, Rioult M, Zhang S. Self-assembling peptide scaffolds in the clinic. npj Regenerative Medicine. 2021;6(1):9. doi: 10.1038/s41536-020-00116-w.

Gil ES, O'Neill K, Aleksi E, Budrewicz J, Melidone R, Spirio L. Comparison of PuraStat self-assembling peptide hydrogel versus mineral-based Hemospray for endoscopic hemostasis of upper and lower gastrointestinal lesions in pigs. Frontiers in Gastroenterology. 2022;1:971353. doi: 10.3389/fgstr.2022.971353.

Golebiewska EM, Poole AW. Platelet secretion: From haemostasis to wound healing and beyond. Blood Reviews. 2015;29(3):153–62. doi: 10.1016/j.blre.2014.10.003.

Gomes A, Teixeira C, Ferraz R, Prudêncio C, Gomes P. Wound-Healing Peptides for Treatment of Chronic Diabetic Foot Ulcers and Other Infected Skin Injuries. Molecules. 2017;22(10):1743. doi: 10.3390/molecules22101743.

Gori A, Lodigiani G, Colombarolli SG, Bergamaschi G, Vitali A. Cell Penetrating Peptides: Classification, Mechanisms, Methods of Study, and Applications. ChemMedChem. 2023;18(17):e202300236. doi: 10.1002/cmdc.202300236.

Guan T, Li J, Chen C, Liu Y. Self-Assembling Peptide-Based Hydrogels for Wound Tissue Repair. Advanced Science. 2022;9(10):2104165. doi: 10.1002/advs.202104165.

Guarnera G, DeRosa A, Camerini R, on behalf of 8 European sites. The effect of thymosin treatment of venous ulcers. Annals of the New York Academy of Sciences. 2010;1194(1):207–12. doi: 10.1111/j.1749-6632.2010.05490.x.

Guiotto M, Clayton A, Morgan R, Raffoul W, Hart A, Riehle M, et al. Biogelx-IKVAV Is An Innovative Human Platelet Lysate-Adipose-Derived Stem Cells Delivery Strategy to Improve Peripheral Nerve Repair. Tissue Engineering Part A. 2024;30(21-22):681–92. doi: 10.1089/ten.tea.2023.0307.

Guryanova SV, Ovchinnikova TV. Immunomodulatory and Allergenic Properties of Antimicrobial Peptides. International Journal of Molecular Sciences. 2022;23(5):2499. doi: 10.3390/ijms23052499.

He X, Yang Y, Mu L, Zhou Y, Chen Y, Wu J, et al. A Frog-Derived Immunomodulatory Peptide Promotes Cutaneous Wound Healing by Regulating Cellular Response. Frontiers in Immunology. 2019;10:2421. doi: 10.3389/fimmu.2019.02421.

Healthcare-in-Europe. Chronic wound care today "Quality and cost effectiveness are not contradictions". https://healthcare-in-europe.com/en/news/chronic-wound-care-today.html, 2008. Accessed on October 1, 2025.

Heunis TDJ, Smith C, Dicks LMT. Evaluation of a Nisin-Eluting Nanofiber Scaffold To Treat Staphylococcus aureus-Induced Skin Infections in Mice. Antimicrobial Agents and Chemotherapy. 2013;57(8):3928–35. doi: 10.1128/aac.00622-13.

Heyer K, Herberger K, Protz K, Glaeske G, Augustin M. Epidemiology of chronic wounds in Germany: Analysis of statutory health insurance data. Wound Repair and Regeneration. 2016;24(2):434–42. doi: 10.1111/wrr.12387.

Hopkins RB, Burke N, Harlock J, Jegathisawaran J, Goeree R. Economic burden of illness associated with diabetic foot ulcers in Canada. BMC Health Services Research. 2015;15(1):13. doi: 10.1186/s12913-015-0687-5.

Hoq MI, Niyonsaba F, Ushio H, Aung G, Okumura K, Ogawa H. Human catestatin enhances migration and proliferation of normal human epidermal keratinocytes. Journal of Dermatological Science. 2011;64(2):108–18. doi: 10.1016/j.jdermsci.2011.08.001.

Hosoyama K, Lazurko C, Muñoz M, McTiernan CD, Alarcon EI. Peptide-Based Functional Biomaterials for Soft-Tissue Repair. Frontiers in Bioengineering and Biotechnology. 2019;7:205. doi: 10.3389/fbioe.2019.00205.

Hu Q, Chen C, Lin Z, Zhang L, Guan S, Zhuang X, et al. The Antimicrobial Peptide Esculentin-1a(1–21)NH2 Stimulates Wound Healing by Promoting Angiogenesis through the PI3K/AKT Pathway. Biological and Pharmaceutical Bulletin. 2023;46(3):382–93. doi: 10.1248/bpb.b22-00098.

Huang HN, Pan CY, Wu HY, Chen JY. Antimicrobial peptide Epinecidin-1 promotes complete skin regeneration of methicillin-resistant Staphylococcus aureus-infected burn wounds in a swine model. Oncotarget. 2017;8(13):21067–80. doi: 10.18632/oncotarget.15042.

Huang J, Yang R, Jiao J, Li Z, Wang P, Liu Y, et al. A click chemistry-mediated all-peptide cell printing hydrogel platform for diabetic wound healing. Nature Communications. 2023;14(1):7856. doi: 10.1038/s41467-023-43364-2.

Im H, Kim SH, Kim SH, Jung Y. Skin Regeneration with a Scaffold of Predefined Shape and Bioactive Peptide Hydrogels. Tissue Engineering Part A. 2018;24(19-20):1518–30. doi: 10.1089/ten.tea.2017.0489.

Iyun AO, Isamah CP, Ademola SA, Olawoye OA, Michael AI, Aderibigbe RO, et al. The incidence and prevalence of chronic wounds from a major plastic surgery service from a metropolitan city in south western Nigeria: A sixteen-year retrospective review. Jrnal of Tissue Viability. 2024;33(4):877–82. doi: 10.1016/j.jtv.2024.08.005.

Jaramillo V, Díaz E, Muñoz LN, González-Barrios AF, Rodríguez-Cortina J, Cruz JC, et al. Enhancing Wound Healing: A Novel Topical Emulsion Combining CW49 Peptide and Lavender Essential Oil for Accelerated Regeneration and Antibacterial Protection. Pharmaceutics. 2023;15(6):1739. doi: 10.3390/pharmaceutics15061739.

Jiang Q, Dumville JC, Cullum N, Pan J, Liu Z. Epidemiology and disease burden of complex wounds for inpatients in China: an observational study from Sichuan province. BMJ Open. 2020;10(11):e039894. doi: 10.1136/bmjopen-2020-039894.

Jiang T, Li S, Xu B, Liu K, Qiu T, Dai H. IKVAV peptide-containing hydrogel decreases fibrous scar after spinal cord injury by inhibiting fibroblast migration and activation. Behavioural Brain Research. 2023;455: 114683. doi: 10.1016/j.bbr.2023.114683.

John JV, Sharma NS, Tang G, Luo Z, Su Y, Weihs S, et al. Nanofiber Aerogels with Precision Macrochannels and LL-37-Mimic Peptides Synergistically Promote Diabetic Wound Healing. Advanced Functional Materials. 2023;33(1):2206936. doi: 10.1002/adfm.202206936.

Jung GS, Park T, Ryu J, Lee JS, Yang JD, Chung HY, et al. Wound healing induced by new synthetic peptide, A7-1, in C57BL/6 mouse model. BioMedical Engineering OnLine. 2024;23(1):75. doi: 10.1186/s12938-024-01247-7.

Karimi M, Maghsoud Z, Halabian R. Effect of Preconditioned Mesenchymal Stem Cells with Nisin Prebiotic on the Expression of Wound Healing Factors Such as TGF-β1, FGF-2, IL-1, IL-6, and IL-10. Regenerative Engineering and Translational Medicine. 2021;7(1): 30–40. doi: 10.1007/s40883-021-00194-2.

Khan F, Singh P, Joshi AS, Tabassum N, Jeong G-J, Bamunuarachchi NI, et al. Multiple potential strategies for the application of nisin and derivatives. Critical Reviews in Microbiology. 2023;49(5):628–57. doi: 10.1080/1040841X.2022.2112650.

Khan S, Ullah A, Ullah K, Rehman N-u. Insight into hydrogels. Designed Monomers and Polymers. 2016; 19(5):456–78. doi: 10.1080/15685551.2016.1169380.

Kharaziha M, Baidya A, Annabi N. Rational Design of Immunomodulatory Hydrogels for Chronic Wound Healing. Advanced Materials. 2021;33(39):2100176. doi: 10.1002/adma.202100176.

Kharrati K. India Wound Care Management Device Market Size Likely to Grow at a CAGR of 4.3 % By 2033. Custom Market Insights, 2024. https://www.custommarketinsights.com/press-releases/india-wound-care-management-device-market-size/. Accessed on May 23.

Kim J-Y, Jun J-H, Kim S-J, Hwang K-M, Choi SR, Han SD, et al. Wound healing efficacy of a chitosan-based film-forming gel containing tyrothricin in various rat wound models. Archives of Pharmacal Research. 2015;38(2):229–38. doi: 10.1007/s12272-014-0368-7.

Koohzad F, Asoodeh A. Cross-Linked Electrospun pH-Sensitive Nanofibers Adsorbed with Temporin-Ra for Promoting Wound Healing. ACS Applied Materials & Interfaces. 2023;15(12):15172–84. doi: 10.1021/acsami.2c23268.

Kumar M, Kumar D, Kumar D, Garg Y, Chopra S, Bhatia A. Therapeutic Potential of Nanocarrier Mediated Delivery of Peptides for Wound Healing: Current Status, Challenges and Future Prospective. AAPS PharmSciTech. 2024;25(5):108. doi: 10.1208/s12249-024-02827-5.

Kurek-Górecka A, Komosinska-Vassev K, Rzepecka-Stojko A, Olczyk P. Bee Venom in Wound Healing. Molecules. 2021;26(1):148. doi: 10.3390/molecules26010148.

Le C-F, Fang C-M, Sekaran SD. Intracellular Targeting Mechanisms by Antimicrobial Peptides. Antimicrobial Agents and Chemotherapy. 2017;61(4): e02340-16. doi: 10.1128/aac.02340-16.

Lebedeva AA, Zakharchenko NS, Trubnikova EV, Medvedeva OA, Kuznetsova TV, Masgutova GA, et al. Bactericide, Immunomodulating, and Wound Healing Properties of Transgenic Kalanchoe pinnata Synergize with Antimicrobial Peptide Cecropin P1 In Vivo. Journal of Immunology Research. 2017;2017(1):4645701. doi: 10.1155/2017/4645701.

Li Y, Lu Y, Zhao Y, Zhang N, Zhang Y, Fu Y. Deciphering the Wound-Healing Potential of Collagen Peptides and the Molecular Mechanisms: A Review. Journal of Agricultural and Food Chemistry. 2024;72 (47):26007–26. doi: 10.1021/acs.jafc.4c02960.

Li Z, Zhu Y, Matson JB. pH-Responsive Self-Assembling Peptide-Based Biomaterials: Designs and Applications. ACS Applied Bio Materials. 2022;5(10): 4635–51. doi: 10.1021/acsabm.2c00188.

Liu H, Duan Z, Tang J, Lv Q, Rong M, Lai R. A short peptide from frog skin accelerates diabetic wound healing. The FEBS Journal. 2014a;281(20):4633–43. doi: 10.1111/febs.12968.

Liu H, Mu L, Tang J, Shen C, Gao C, Rong M, et al. A potential wound healing-promoting peptide from frog skin. The International Journal of Biochemistry & Cell Biology. 2014b;49:32–41. doi: 10.1016/j.biocel.2014.01.010.

Liu H, Wei X, Peng H, Yang Y, Hu Z, Rao Y, et al. LysSYL-Loaded pH-Switchable Self-Assembling Peptide Hydrogels Promote Methicillin-Resistant Staphylococcus Aureus Elimination and Wound Healing. Advanced Materials. 2024;36(52):2412154. doi: 10.1002/adma.202412154.

Ma X, Wang Q, Ren K, Xu T, Zhang Z, Xu M, et al. A Review of Antimicrobial Peptides: Structure, Mechanism of Action, and Molecular Optimization Strategies. Fermentation. 2024;10(11):540. doi: 10.3390/fermentation10110540.

Mahlapuu M, Sidorowicz A, Mikosinski J, Krzyżanowski M, Orleanski J, Twardowska-Saucha K, 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 and Regeneration. 2021;29(6):938–50. doi: 10.1111/wrr.12977.

Maldonado H, Savage BD, Barker HR, May U, Vähätupa M, Badiani RK, et al. Systemically administered wound-homing peptide accelerates wound healing by modulating syndecan-4 function. Nature Communications. 2023;14(1):8069. doi: 10.1038/s41467-023-43848-1.

Mandla S, Davenport Huyer L, Wang Y, Radisic M. Macrophage Polarization with Angiopoietin-1 Peptide QHREDGS. ACS Biomaterials Science & Engineering. 2019;5(9):4542–50. doi: 10.1021/acsbiomaterials.9b00483.

McKnight G, Shah J, Hargest R. Physiology of the skin. Surgery (Oxford). 2022;40(1):8–12. doi: 10.1016/j.mpsur.2021.11.005.

Md Fadilah NI, Shahabudin NA, Mohd Razif RA, Sanyal A, Ghosh A, Baharin KI, et al. Discovery of bioactive peptides as therapeutic agents for skin wound repair. Journal of Tissue Engineering. 2024;15: 20417314241280359. doi: 10.1177/20417314241280359.

Michaels J, Kaleva AI, Bateman L, Wakelam O, Stephens J. Application of the Self-Assembling Peptide Hydrogel RADA16 for Hemostasis during Tonsillectomy: A Feasibility Study. Journal of Functional Biomaterials. 2024;15(9):271. doi: 10.3390/jfb15090271.

Michaleas SN, Laios K, Charalabopoulos A, Samonis G, Karamanou M. Joseph Lister (1827-1912): A Pioneer of Antiseptic Surgery. Cureus. 2022;14(12): e32777. doi: 10.7759/cureus.32777.

Misra D, Vyas T, Misra A, Mehta R, Singh V, Jain H. Unveiling Biological and Therapeutic Properties of Calotropis Procera: A Promising Traditional Medicine. Journal of Chemical Health Risks. 2024;14:2279–85.

Mndlovu H, du Toit LC, Kumar P, Choonara YE. Tannic acid-loaded chitosan-RGD-alginate scaffolds for wound healing and skin regeneration. Biomed Mater. 2023;18(4). doi: 10.1088/1748-605X/acce88.

Mohapatra S, Mirza MA, Hilles AR, Zakir F, Gomes AC, Ansari MJ, et al. Biomedical Application, Patent Repository, Clinical Trial and Regulatory Updates on Hydrogel: An Extensive Review. Gels. 2021;7(4):207. doi: 10.3390/gels7040207.

Morat NS, Ajemi A. Prevalence and Clinical Characteristics of Wound Care Patients in the Northernmost State Hospital of Malaysia: A Retrospective Analysis. Wounds APAC. 2024;7(2):6-9.

Mouritzen MV, Andrea A, Qvist K, Poulsen SS, Jenssen H. Immunomodulatory potential of Nisin A with application in wound healing. Wound Repair and Regeneration. 2019;27(6):650–60. doi: 10.1111/wrr.12743.

Nakagami H, Yamaoka T, Hayashi M, Tanemura A, Takeya Y, Kurinami H, et al. Physician-initiated first-in-human clinical study using a novel angiogenic peptide, AG30/5C, for patients with severe limb ulcers. Geriatrics & Gerontology International. 2017;17(11): 2150–6. doi: 10.1111/ggi.13051.

Nasadyuk CM. Short peptide sequences: current knowledge and future prospects. The Ukrainian Biochemical Journal. 2021;93(5):5–13. doi: 10.15407/ubj93.05.005.

Nasseri S, Sharifi M. Therapeutic Potential of Antimicrobial Peptides for Wound Healing. International Journal of Peptide Research and Therapeutics. 2022; 28(1):38. doi: 10.1007/s10989-021-10350-5.

Nazari M, Taremi S, Elahi R, Mostanadi P, Esmeilzadeh A. Therapeutic Properties of M2 Macrophages in Chronic Wounds: An Innovative Area of Biomaterial-Assisted M2 Macrophage Targeted Therapy. Stem Cell Reviews and Reports. 2025;21(2):390–422. doi: 10.1007/s12015-024-10806-3.

Nicolas-Espinosa J, Yepes-Molina L, Carvajal M. Bioactive peptides from broccoli stems strongly enhance regenerative keratinocytes by stimulating controlled proliferation. Pharmaceutical Biology. 2022;60(1): 235–46. doi: 10.1080/13880209.2021.2009522.

Niemeyer P, Hanus M, Belickas J, László T, Gudas R, Fiodorovas M, et al. Treatment of Large Cartilage Defects in the Knee by Hydrogel-Based Autologous Chondrocyte Implantation: Two-Year Results of a Prospective, Multicenter, Single-Arm Phase III Trial. Cartilage. 2022;13(1):19476035221085146. doi: 10.1177/19476035221085146.

Nirmal N, Khanashyam AC, Shah K, Awasti N, Sajith Babu K, Ucak İ, et al. Plant protein-derived peptides: frontiers in sustainable food system and applications. Frontiers in Sustainable Food Systems. 2024;8: 1292297. doi: 10.3389/fsufs.2024.1292297.

Ong JS, Taylor TD, Yong CC, Khoo BY, Sasidharan S, Choi SB, et al. Lactobacillus plantarum USM8613 Aids in Wound Healing and Suppresses Staphylococcus aureus Infection at Wound Sites. Probiotics and Antimicrobial Proteins. 2020;12(1):125–37. doi: 10.1007/s12602-018-9505-9.

Percival NJ. Classification of Wounds and their Management. Surgery (Oxford). 2002;20(5):114–7. doi: 10.1383/surg.20.5.114.14626.

Pervin Z, Hassan MM. Synergistic therapeutic actions of antimicrobial peptides to treat multidrug-resistant bacterial infection. Reviews and Research in Medical Microbiology. 2021;32(2):83–89. doi: 10.1097/MRM.0000000000000239.

Pfalzgraff A, Heinbockel L, Su Q, Gutsmann T, Brandenburg K, Weindl G. Synthetic antimicrobial and LPS-neutralising peptides suppress inflammatory and immune responses in skin cells and promote keratinocyte migration. Scientific Reports. 2016;6(1):31577. doi: 10.1038/srep31577.

Philp D, Goldstein AL, Kleinman HK. Thymosin β4 promotes angiogenesis, wound healing, and hair follicle development. Mechanisms of Ageing and Development. 2004;125(2):113–5. doi: 10.1016/j.mad.2003.11.005.

Pickart L, Vasquez-Soltero JM, Margolina A. GHK Peptide as a Natural Modulator of Multiple Cellular Pathways in Skin Regeneration. BioMed Research International. 2015;2015(1):648108. doi: 10.1155/2015/648108.

Powers JG, Higham C, Broussard K, Phillips TJ. Wound healing and treating wounds: Chronic wound care and management. Journal of the American Academy of Dermatology. 2016;74(4):607–25. doi: 10.1016/j.jaad.2015.08.070.

Puthia M, Butrym M, Petrlova J, Strömdahl A-C, Andersson MÅ, Kjellström S, et al. A dual-action peptide-containing hydrogel targets wound infection and inflammation. Science Translational Medicine. 2020;12(524):eaax6601. doi: 10.1126/scitranslmed.aax6601.

Queen D, Botros M. The True Cost Of Wounds For Canadians. Wound Care Canada. 2024;22(1):16-20. doi: 10.56885/nxmw2913.

Queen D, Harding K. What's the true costs of wounds faced by different healthcare systems around the world? Int Wound J. 2023;20(10):3935–8. doi: 10.1111/iwj.14491.

Queen D, Harding K. Estimating the cost of wounds both nationally and regionally within the top 10 highest spenders. Int Wound J. 2024;21(2):e14709. doi: 10.1111/iwj.14709.

Radek KA, Lopez-Garcia B, Hupe M, Niesman IR, Elias PM, Taupenot L, et al. The Neuroendocrine Peptide Catestatin Is a Cutaneous Antimicrobial and Induced in the Skin after Injury. Journal of Investigative Dermatology. 2008;128(6):1525–34. doi: 10.1038/sj.jid.5701225.

Radulescu D-M, Neacsu IA, Grumezescu A-M, Andronescu E. New Insights of Scaffolds Based on Hydrogels in Tissue Engineering. Polymers. 2022;14(4): 799. doi: 10.3390/polym14040799.

Raheem NN, Salman AS, Jawad MH. Histological evaluation of effect of thymosin beta 4 on wound healing of skin. European Journal of Dental and Oral Health. 2024;5(3):1–7.

Rivera-Sanchez SP, Ocampo-Ibáñez ID, Moncaleano MC, Liscano Y, Elvira LJF, Aristizabal Salazar YA, et al. In Vitro and In Silico Wound-Healing Activity of Two Cationic Peptides Derived from Cecropin D in Galleria mellonella. Antibiotics. 2025;14(7):651. doi: 10.3390/antibiotics14070651.

Robert B, Chenthamara D, Subramaniam S. Fabrication and biomedical applications of Arabinoxylan, Pectin, Chitosan, soy protein, and silk fibroin hydrogels via laccase - Ferulic acid redox chemistry. International Journal of Biological Macromolecules. 2022; 201:539–56. doi: 10.1016/j.ijbiomac.2021.12.103.

Roberts KB. Fresh Hope for Chronic Wounds. FDA-approved wound management products include UD-developed biomaterials. University of Delaware, 2024. https://www.udel.edu/udaily/2024/may/wound-care-patented-hydrogels-in-fda-approved-product-darrin-pochan/. Accessed on May 8.

Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound Healing: A Cellular Perspective. Physiological Reviews. 2019;99(1):665–706. doi: 10.1152/physrev.00067.2017.

Ruiz PBO, Lima AFC. Average direct costs of outpatient, hospital, and home care provided to patients with chronic wounds. Rev Esc Enferm USP. 2022;56: e20220295. doi: 10.1590/1980-220X-REEUSP-2022-0295en.

Sen CK. Human Wound and Its Burden: Updated 2020 Compendium of Estimates. Advances in Wound Care. 2021;10(5):281–92. doi: 10.1089/wound.2021.0026.

Seow WY, Salgado G, Lane EB, Hauser CAE. Transparent crosslinked ultrashort peptide hydrogel dressing with high shape-fidelity accelerates healing of full-thickness excision wounds. Scientific Reports. 2016; 6(1):32670. doi: 10.1038/srep32670.

Shahzad F. Production of Proteases by Genetically Improved Bacillus subtilis for Enhanced Skin Penetration of Antibacterial Topical Formulation. Journal of Biotechnology & Biomaterials. 2015;05(02). doi: 10.4172/2155-952x.1000186.

Sharma A, Srivastava V, Shankar R, Yadav AK, Ansari MA, Gupta SK. Epidemiological Profile of Chronic Wounds in an Indian Population: A Community-Based Cross-Sectional Observational Study. Cureus. 2024;16(9):e68684. doi: 10.7759/cureus.68684.

Shini VS, Udayarajan CT, Nisha P. A comprehensive review on lactoferrin: a natural multifunctional glycoprotein. Food & Function. 2022;13(23):11954–72. doi: 10.1039/D2FO02371G.

Simonetti O, Cirioni O, Goteri G, Ghiselli R, Kamysz W, Kamysz E, et al. Temporin A is effective in MRSA-infected wounds through bactericidal activity and acceleration of wound repair in a murine model. Peptides. 2008;29(4):520–8. doi: 10.1016/j.peptides.2007.12.011.

Singh V, Marimuthu T, Lesotho NF, Makatini MM, Ntombela T, Van Eyk A, et al. Synthesis of a retro-GFOGER Adamantane-Based Collagen Mimetic Peptide Imbibed in a Hyaluronic Acid Hydrogel for Enhanced Wound Healing. ACS Applied Bio Materials. 2025;8(6):4657–72. doi: 10.1021/acsabm.4c01895.

Song C, Li S, Zhang C, Li J, Li M, Ye L, et al. Exploring the role of two polypeptide nanofiber gels derived from RADA16-I self-assembly in accelerating burn wound healing. Scientific Reports. 2025;15(1):24476. doi: 10.1038/s41598-025-08666-z.

Song J, Li X, Li J. Emerging evidence for the roles of peptide in hypertrophic scar. Life Sciences. 2020;241: 117174. doi: 10.1016/j.lfs.2019.117174.

Song Y, Wu C, Zhang X, Bian W, Liu N, Yin S, et al. A short peptide potentially promotes the healing of skin wound. Bioscience Reports. 2019;39(3): BSR20181734. doi: 10.1042/bsr20181734.

Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin Wound Healing: An Update on the Current Knowledge and Concepts. European Surgical Research. 2016;58(1-2):81–94. doi: 10.1159/000454919.

Srinivasan K, Sureshkumar R, Nellore J, Muthaiah B, Selvan Christyraj JRS, Chandrasekaran VN. The combined impact of thymosin beta 4 and selenium on diabetic ulcers: a comprehensive review. Discover Biotechnology. 2025;2(1):11. doi: 10.1007/s44340-025-00015-0.

Stefanou A, Worden A, Kandagatla P, Reickert C, Rubinfeld I. Surgical Wound Misclassification to Clean From Clean-Contaminated in Common Abdominal Operations. Journal of Surgical Research. 2020;246: 131–8. doi: 10.1016/j.jss.2019.09.001.

Stefanov I, Pérez-Rafael S, Hoyo J, Cailloux J, Santana Pérez OO, Hinojosa-Caballero D, et al. Multifunctional Enzymatically Generated Hydrogels for Chronic Wound Application. Biomacromolecules. 2017;18(5): 1544–55. doi: 10.1021/acs.biomac.7b00111.

Sun L, Li A, Hu Y, Li Y, Shang L, Zhang L. Self-Assembled Fluorescent and Antibacterial GHK-Cu Nanoparticles for Wound Healing Applications. Particle & Particle Systems Characterization. 2019;36(4): 1800420. doi: h10.1002/ppsc.201800420.

Sun L, Liu J, He Z, Du R. Plant-Derived as Alternatives to Animal-Derived Bioactive Peptides: A Review of the Preparation, Bioactivities, Structure-Activity Relationships, and Applications in Chronic Diseases. Nutrients. 2024;16(19):3277. doi: 10.3390/nu16193277.

Takahashi M, Umehara Y, Yue H, Trujillo-Paez JV, Peng G, Nguyen HLT, et al. The Antimicrobial Peptide Human β-Defensin-3 Accelerates Wound Healing by Promoting Angiogenesis, Cell Migration, and Proliferation Through the FGFR/JAK2/STAT3 Signaling Pathway. Frontiers in Immunology. 2021;12:712781. doi: 10.3389/fimmu.2021.712781.

Tomic-Canic M, Wong LL, Smola H. The epithelialisation phase in wound healing: options to enhance wound closure. Journal of wound care. 2018;27(10): 646–58.

Tomioka H, Nakagami H, Tenma A, Saito Y, Kaga T, Kanamori T, et al. Novel Anti-Microbial Peptide SR-0379 Accelerates Wound Healing via the PI3 Kinase/Akt/mTOR Pathway. PLOS ONE. 2014;9(3): e92597. doi: 10.1371/journal.pone.0092597.

Travkova OG, Moehwald H, Brezesinski G. The interaction of antimicrobial peptides with membranes. Advances in Colloid and Interface Science. 2017;247: 521–32. doi: 10.1016/j.cis.2017.06.001.

Uşaklıoğlu S, Çakan D. The efficacy of topical lactoferrin on wound healing in an experimental animal model of nasal septum perforation. Facial Plastic Surgery. 2023;39(05):575–80.

Wang J, Ma K, Ruan M, Wang Y, Li Y, Fu YV, et al. A novel cecropin B-derived peptide with antibacterial and potential anti-inflammatory properties. PeerJ. 2018;6:e5369. doi: 10.7717/peerj.5369.

Wang W, Jia J, Li C, Duan Q, Yang J, Wang X, et al. Antimicrobial peptide LL-37 promotes the proliferation and invasion of skin squamous cell carcinoma by upregulating DNA-binding protein A. Oncol Lett. 2016;12(3):1745–52. doi: 10.3892/ol.2016.4865.

Wang X, Duan H, Li M, Xu W, Wei L. Characterization and mechanism of action of amphibian-derived wound-healing-promoting peptides. Frontiers in Cell and Developmental Biology. 2023;11:1219427. doi: 10.3389/fcell.2023.1219427.

Wang Y, Zhang W, Gong C, Liu B, Li Y, Wang L, et al. Recent advances in the fabrication, functionalization, and bioapplications of peptide hydrogels. Soft Matter. 2020;16(44):10029–45. doi: 10.1039/D0SM00966K.

Wei Q, Duan J, Ma G, Zhang W, Wang Q, Hu Z. Enzymatic crosslinking to fabricate antioxidant peptide-based supramolecular hydrogel for improving cutaneous wound healing. Journal of Materials Chemistry B. 2019;7(13):2220–5. doi: 10.1039/C8TB03147A.

Wigger-Alberti W, Stauss-Grabo M, Grigo K, Atiye S, Williams R, Korting HC. Efficacy of a Tyrothricin-Containing Wound Gel in an Abrasive Wound Model for Superficial Wounds. Skin Pharmacology and Physiology. 2012;26(1):52–6. doi: 10.1159/000343907.

Wong R, Geyer S, Weninger W, Guimberteau J-C, Wong JK. The dynamic anatomy and patterning of skin. Experimental Dermatology. 2016;25(2):92–8. doi: 10.1111/exd.12832.

Wounds Australia. A 5 Point Plan to Solve Australia's Chronic Wound Epidemic. 2024. Retrieved from: https://woundsaustralia.org/int/woundsaus/uploads/Publications/5 %20point %20plan %202024/wounds %20australia %205 %20point %20plan %202024.pdf.

Wu J, Sahoo JK, Li Y, Xu Q, Kaplan DL. Challenges in delivering therapeutic peptides and proteins: A silk-based solution. Journal of Controlled Release. 2022; 345:176–89. doi: 10.1016/j.jconrel.2022.02.011.

Xiang J, Shen L, Hong Y. Status and future scope of hydrogels in wound healing: Synthesis, materials and evaluation. European Polymer Journal. 2020;130: 109609. doi: 10.1016/j.eurpolymj.2020.109609.

Xiao Y, Reis LA, Feric N, Knee EJ, Gu J, Cao S, et al. Diabetic wound regeneration using peptide-modified hydrogels to target re-epithelialization. Proceedings of the National Academy of Sciences. 2016;113(40): E5792–E801. doi: 10.1073/pnas.1612277113.

Xue M, Jackson CJ. Extracellular Matrix Reorganization During Wound Healing and Its Impact on Abnormal Scarring. Adv Wound Care (New Rochelle). 2015; 4(3):119-136. doi: 10.1089/wound.2013.0485.

Yacoub T, Rima M, Karam M, Fajloun J. Antimicrobials from Venomous Animals: An Overview. Molecules. 2020;25(10):2402. doi: 10.3390/molecules25102402.

Yadav N, Kumar U, Roopmani P, Krishnan UM, Sethuraman S, Chauhan MK, et al. Ultrashort Peptide-Based Hydrogel for the Healing of Critical Bone Defects in Rabbits. ACS Applied Materials & Interfaces. 2022;14(48):54111–26. doi: 10.1021/acsami.2c18733.

Yaguchi A, Oshikawa M, Watanabe G, Hiramatsu H, Uchida N, Hara C, et al. Efficient protein incorporation and release by a jigsaw-shaped self-assembling peptide hydrogel for injured brain regeneration. Nature Communications. 2021;12(1):6623. doi: 10.1038/s41467-021-26896-3.

Yaraguppi DA, Bagewadi ZK, Patil NR, Mantri N. Iturin: A Promising Cyclic Lipopeptide with Diverse Applications. Biomolecules. 2023;13(10):1515. doi: 10.3390/biom13101515.

Yan L, Liu G, Zhao B, Pang B, Wu W, Ai C, et al. Novel Biomedical Functions of Surfactin A from Bacillus subtilis in Wound Healing Promotion and Scar Inhibition. Journal of Agricultural and Food Chemistry. 2020;68(26):6987–97. doi: 10.1021/acs.jafc.0c01658.

Yang S, Ji Y, Xue P, Li Z, Chen X, Shi J, et al. Insights into the antifungal mechanism of Bacillus subtilis cyclic lipopeptide iturin A mediated by potassium ion channel. International Journal of Biological Macromolecules. 2024;277:134306. doi: 10.1016/j.ijbiomac.2024.134306.

Ye W, Yang Z, Cao F, Li H, Zhao T, Zhang H, et al. Articular cartilage reconstruction with TGF-β1-simulating self-assembling peptide hydrogel-based composite scaffold. Acta Biomaterialia. 2022;146:94–106. doi: 10.1016/j.actbio.2022.05.012.

Yu H, Wang B, Li Z, Liu K, Chen W, Zhao S, et al. Tβ4-exosome-loaded hemostatic and antibacterial hydrogel to improve vascular regeneration and modulate macrophage polarization for diabetic wound treatment. Materials Today Bio. 2025;31:101585. doi: 10.1016/j.mtbio.2025.101585.

Zhang F, Lv M, Wang S, Li M, Wang Y, Hu C, et al. Ultrasound-triggered biomimetic ultrashort peptide nanofiber hydrogels promote bone regeneration by modulating macrophage and the osteogenic immune microenvironment. Bioactive Materials. 2024;31:231–46. doi: 10.1016/j.bioactmat.2023.08.008.

Zhang H, Lv J, Ma Z, Ma J, Chen J. Advances in Antimicrobial Peptides: Mechanisms, Design Innovations, and Biomedical Potential. Molecules. 2025; 30(7):1529. doi: 10.3390/molecules30071529.

Zhang J, Fu X, Li W, Li H, Ying Z, Liu X, et al. Enhancement of nutritional soy protein and peptide supplementation on skin repair in rats. Journal of Functional Foods. 2020;75:104231. doi: 10.1016/j.jff.2020.104231.

Zhao F, Liu W, Yu Y, Liu X, Yin H, Liu L, et al. Effect of small molecular weight soybean protein-derived peptide supplementation on attenuating burn injury-induced inflammation and accelerating wound healing in a rat model. RSC Adv. 2019;9(3):1247–59. doi: 10.1039/c8ra09036j.

Zhao S, Han J, Bie X, Lu Z, Zhang C, Lv F. Purification and Characterization of Plantaricin JLA-9: A Novel Bacteriocin against Bacillus spp. Produced by Lactobacillus plantarum JLA-9 from Suan-Tsai, a Traditional Chinese Fermented Cabbage. Journal of Agricultural and Food Chemistry. 2016;64(13):2754–64. doi: 10.1021/acs.jafc.5b05717.

Zhou J, Wang Z, Yang C, Zhang H, Fareed MS, He Y, et al. A carrier-free, dual-functional hydrogel constructed of antimicrobial peptide Jelleine-1 and 8Br-cAMP for MRSA infected diabetic wound healing. Acta Biomaterialia. 2022;151:223–34. doi: 10.1016/j.actbio.2022.07.066.

Zhou L, Zhao X, Li M, Yan L, Lu Y, Jiang C, et al. Antibacterial and wound healing–promoting effect of sponge-like chitosan-loaded silver nanoparticles biosynthesized by iturin. International Journal of Biological Macromolecules. 2021;181:1183–95. doi: 10.1016/j.ijbiomac.2021.04.119.

Zhou W, Xie Z, Si R, Chen Z, Javeed A, Li J, et al. Actinomycin-X2-Immobilized Silk Fibroin Film with Enhanced Antimicrobial and Wound Healing Activities. International Journal of Molecular Sciences. 2023; 24(7):6269. doi: 10.3390/ijms24076269.