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BIOACTIVE PEPTIDES IN CUTANEOUS WOUND HEALING: MOLECULAR MECHANISMS, DELIVERY STRATEGIES, AND CLINICAL PERSPECTIVES

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ABSTRACT

Chronic non-healing wounds, including diabetic foot ulcers and pressure sores, represent a growing clinical challenge due to persistent inflammation, impaired neovascularisation, and resistance to conventional therapies. Bioactive peptides have recently emerged as a versatile class of wound-healing agents capable of targeting multiple phases of cutaneous repair. This mini-review synthesises current knowledge on the molecular mechanisms, classification, delivery strategies, and translational hurdles of these molecules. Peptides derived from marine organisms, food proteins, amphibian skin, and host-defence systems, as well as those generated by rational design, exhibit remarkable multifunctionality: they suppress NF-κB-driven inflammation, promote macrophage polarisation from the pro-inflammatory M1 to the reparative M2 phenotype, stimulate angiogenesis via VEGF up-regulation, and activate PI3K/Akt/mTOR and TGF-β/Smad cascades to drive keratinocyte and fibroblast proliferation, migration, and collagen deposition. However, clinical translation is severely constrained by rapid proteolytic degradation, short plasma half-life, and lack of robust human data. Recent advances in delivery systems, including stimuli-responsive self-assembling hydrogels, nanoparticles, and molecular engineering strategies such as cyclisation and D-amino acid substitution, offer promising solutions to these pharmacokinetic limitations. Nonetheless, challenges related to manufacturing scalability, regulatory approval, and incomplete understanding of structure–activity relationships persist. Further progress will depend on integrated approaches combining rational peptide design, innovative biomaterials, and rigorous clinical evaluation to transform the considerable preclinical promise of bioactive peptides into effective, accessible wound therapeutics.

KEYWORD: Bioactive peptides; Wound healing; Chronic wounds; Angiogenesis; Inflammation; Drug delivery

1. INTRODUCTION

The skin constitutes the principal barrier against mechanical, microbial, and dehydrating insults, and its rapid restoration after injury is essential for survival. Cutaneous wound healing proceeds through four temporally overlapping phases, haemostasis, inflammation, proliferation, and remodeling, each governed by the coordinated migration, proliferation, and secretory activity of keratinocytes, fibroblasts, endothelial cells, and immune populations [1,2]. Successful repair depends on the precise spatiotemporal integration of these events; single-cell analyses of human wounds have demonstrated that inflammatory macrophages and fibroblasts sequentially support keratinocyte migration, and that disruption of this relay underlies defective re-epithelialisation in chronic ulcers [3].

When the ordered progression of healing is interrupted, wounds stall in a state of persistent inflammation and become chronic. Non-healing wounds — predominantly diabetic foot, venous, and pressure ulcers — represent a substantial and expanding area of unmet clinical need, imposing considerable costs on healthcare systems and markedly reducing patient quality of life [4]. Their prevalence is escalating in parallel with the global rise in diabetes, projected to affect more than 1.3 billion people by 2050, and with the progressive ageing of populations worldwide [5]. Infection compounds this burden, as chronic wounds are frequently colonised by antibiotic-resistant and polymicrobial biofilms that perpetuate tissue destruction [6]. Conventional interventions, debridement, moisture-retentive dressings, and recombinant growth factors, are often constrained by limited efficacy, protracted treatment periods, high cost, and the susceptibility of protein therapeutics to proteolytic degradation within the wound microenvironment [7].

Against this background, bioactive peptides have attracted growing interest as a versatile class of wound-healing agents. Defined as short amino acid sequences, typically comprising fewer than 40 residues, they can be derived from marine organisms, collagen and other food proteins, host-defence systems, or rational synthetic design [8,9]. Relative to larger biologics, peptides offer high target specificity, favourable bioavailability, low immunogenicity

and allergenicity, and ready amenability to structural optimisation [8]. Crucially, individual peptides frequently exert multifunctional activity, simultaneously attenuating excessive inflammation, promoting angiogenesis, stimulating fibroblast and keratinocyte proliferation and migration, enhancing collagen synthesis, and conferring antioxidant and antimicrobial protection [9,10]. These effects are transduced through defined molecular circuits, including the TGF-β/Smad, PI3K/Akt/mTOR, MAPK/ERK, NF-κB, and Nrf2 signalling pathways [10].

Despite a rapidly expanding body of experimental evidence, the molecular determinants that link peptide structure to specific reparative outcomes remain incompletely defined, and clinical translation is still limited. The present mini-review synthesises the current understanding of the molecular mechanisms by which bioactive peptides promote cutaneous wound healing. It first classifies these peptides according to biological origin and structure–activity relationships, then examines their mechanisms of action across the phases of repair, surveys the delivery strategies devised to overcome their pharmacokinetic limitations, and finally considers the principal challenges and prospects for clinical implementation. Priority is given to peptide classes for which mechanistic and preclinical data have been reported in the recent literature. An overview of the phases of wound healing and the corresponding sites of peptide action is presented in Figure 1.

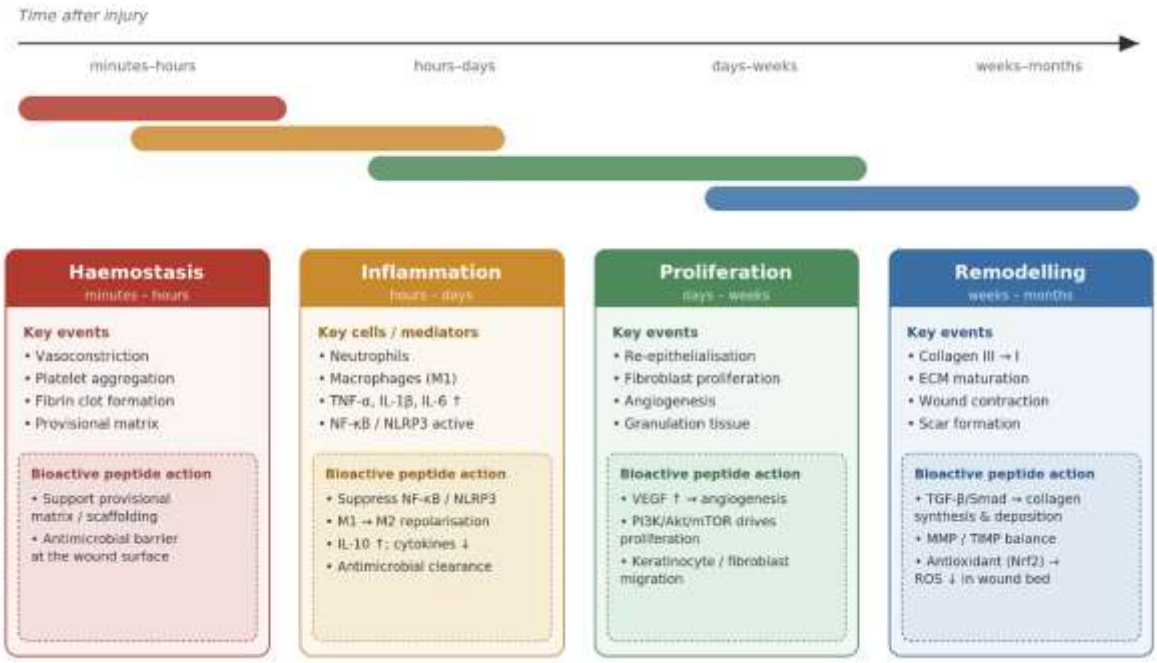

Figure 1. Wound healing phases

2. Classification and sources of bioactive peptides

Bioactive wound-healing peptides form a chemically heterogeneous group, and their most practical taxonomy is by biological origin, which broadly determines their sequence characteristics and dominant activities. Six principal source categories can be distinguished (Table 1).

Marine organisms are among the richest reservoirs of reparative peptides. Fish skin and bone, molluscs, crustaceans, algae, and marine processing by-products yield peptides, typically 2-20 amino acid residues in length, through enzymatic hydrolysis, microbial fermentation, or gastrointestinal digestion [11]. Their low molecular weight and abundance of glycine, proline, and other imino acids favour efficient absorption and confer antioxidant, antimicrobial, anti-inflammatory, and pro-migratory properties relevant to each phase of repair [9,10].

Food and mammalian proteins constitute a second major source. Collagen-derived peptides, characterised by low molecular weight and imino-acid-rich sequences, up-regulate reparative cytokines and stimulate fibroblast proliferation, collagen deposition, and re-epithelialisation [10]. Milk and bovine colostrum contribute lactoferrin-derived peptides and a high concentration of growth factors that promote cell proliferation and tissue regeneration [12], whereas bee products such as royal jelly supply peptides including royalisin, apisimin, and jelleins with antimicrobial, anti-inflammatory, and wound-promoting activity [13].

Host-defence (antimicrobial) peptides (AMPs) form a functionally central category. These short, predominantly cationic and amphipathic molecules, exemplified by the human cathelicidin LL-37 and the defensins, combine broad-spectrum antimicrobial action with potent immunomodulatory effects, and act as endogenous mediators of wound healing by controlling microbial proliferation, modulating inflammation, and promoting angiogenesis and re-epithelialisation [14,15]. More than 3,200 AMPs have been catalogued from natural and synthetic sources [16].

Their interaction with endothelial cells is biphasic and structure-dependent, influencing barrier integrity and angiogenesis through the MAPK, NF-κB, and PI3K/Akt pathways [17].

Amphibian skin represents a particularly prolific natural source of host-defence peptides. Gene-encoded peptides from frog and toad skin display broad antimicrobial activity together with immunoregulatory and pro-healing functions, and several act through less conventional mechanisms such as modulation of competing endogenous RNA networks [18]. Other invertebrate sources, including earthworm extracts and marine peanut worms (Sipuncula), similarly yield peptides with antioxidant, antimicrobial, anti-inflammatory, and wound-healing activities [19].

Finally, synthetic and rationally designed peptides extend the natural repertoire. Advances in peptide engineering permit the design of sequences with optimised stability, target specificity, and self-assembling capacity, including growth-factor-mimetic peptides and self-assembling motifs that form hydrogel scaffolds supporting cell adhesion and tissue regeneration [7,8]. Such strategies also aim to overcome the intrinsic liabilities of natural peptides, notably their proteolytic susceptibility.

Across these categories, structure–activity relationships are governed chiefly by peptide length, net charge, hydrophobicity, and amphipathicity. Cationic, amphipathic architectures underlie membrane-targeting antimicrobial action, whereas short imino-acid-rich sequences favour absorption and matrix-directed reparative signalling [10,11,13]. These structural determinants provide the mechanistic basis for the molecular actions examined in the following section.

Table 1. Classification of bioactive wound-healing peptides by biological origin.

Source category	Representative peptides / examples	Key structural features	Principal wound-relevant activities	Ref.
Marine organisms (fish, molluscs, crustaceans, algae, by-products)	Collagen-derived peptides, marine protein hydrolysates	2–20 residues; low molecular weight; Gly/Pro/imino-acid-rich	Antioxidant, antimicrobial, anti-inflammatory, pro-migratory	[10,11]
Food & mammalian proteins (collagen, milk, colostrum)	Collagen tri-/oligopeptides, lactoferrin-derived peptides, colostrum growth factors	Low molecular weight; imino-acid-rich	Fibroblast proliferation, collagen synthesis, re-epithelialisation, angiogenesis	[9,12]
Bee products	Royalisin, apisimin, jelleins (royal jelly)	Small cationic peptides	Antimicrobial, anti-inflammatory, wound-promoting	[13]
Host-defence / antimicrobial peptides	LL-37 (cathelicidin), α- and β-defensins	Cationic, amphipathic, ~12–50 residues, often α-helical	Broad-spectrum antimicrobial, immunomodulation, angiogenesis, re-epithelialisation	[14-16]
Amphibian skin peptides	Temporins, esculentins, magainins and related HDPs	Cationic, amphipathic, α-helical	Antimicrobial, immunoregulatory, pro-healing, ceRNA modulation	[17]
Other invertebrates	Earthworm-derived peptides, Sipuncula (peanut worm) peptides	Heterogeneous	Antioxidant, antimicrobial, anti-inflammatory, wound healing	[18,19]
Synthetic & rationally designed	Growth-factor-mimetic peptides, self-assembling peptides	Tailored sequences; self-assembling motifs; enhanced stability	Scaffold formation, cell adhesion, target-specific reparative signalling	[7,8]

3. Molecular mechanisms of wound-healing action

Bioactive peptides do not act on a single target but engage a network of interdependent molecular circuits that operate across all four phases of repair [1]. For clarity, their actions are organised below along five functional axes, inflammation, angiogenesis, cell proliferation and migration, matrix remodelling, and antioxidant defence, although in practice a single peptide frequently participates in several of these simultaneously. An integrated overview of the pathways involved is presented in Figure 2, and representative peptides with their defined molecular targets are summarised in Table 2.

3.1. Modulation of the inflammatory response

A self-limiting inflammatory phase is a prerequisite for orderly repair, whereas its failure to resolve is a defining feature of chronic wounds. Persistent inflammation is driven largely by sustained activation of the nuclear factor-

κB (NF-κB) and NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome pathways in wound macrophages, which maintains elevated levels of tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 [20,21]. As a master transcriptional regulator in monocytes and macrophages, NF-κB coordinates cytokine release, inflammasome activation, and the balance of macrophage phenotypes [22]. Bioactive peptides restore inflammatory homeostasis by suppressing NF-κB phosphorylation and nuclear translocation, reducing pro-inflammatory cytokine output, and promoting the transition of macrophages from the pro-inflammatory M1 to the reparative M2 phenotype. Neurotensin, a bioactive tridecapeptide, markedly lowered TNF-α in inflammation-activated macrophages while accelerating diabetic wound closure [23], and amphibian-derived peptides recruit neutrophils and macrophages to the wound and modulate their immune responses in a manner essential for timely healing [20].

3.2. Promotion of angiogenesis

Restoration of the microvasculature supplies the oxygen and nutrients required for granulation-tissue formation, and its impairment is central to the pathology of diabetic and other chronic wounds. Peptides promote neovascularisation chiefly by up-regulating vascular endothelial growth factor (VEGF) and its downstream endothelial signalling. Notably, VEGF-driven signalling also couples angiogenesis to inflammatory resolution: in diabetic foot-ulcer models, VEGF accelerated healing by simultaneously promoting M2 macrophage polarisation and fibroblast migration [24]. Host-defence peptides exert direct, structure-dependent effects on endothelial cells, modulating proliferation, migration, and barrier integrity through the MAPK, NF-κB, and PI3K/Akt pathways, with a characteristically biphasic dose response [16]. Consistent with these mechanisms, sustained delivery of neurotensin enhanced VEGF expression and vascularisation in diabetic wounds [23].

3.3. Proliferation and migration of keratinocytes and fibroblasts

Re-epithelialisation depends on the coordinated proliferation and directional migration of keratinocytes across the wound bed, while fibroblast proliferation drives granulation-tissue formation. A large family of amphibian-derived peptides, including tylotoin, RL-QN15, and tiger17, selectively stimulates the proliferation and migration of both keratinocytes and fibroblasts, accelerating closure of skin wounds in murine and rat models [20]. Collagen-derived peptides promote cell proliferation through activation of the PI3K/Akt/mTOR cascade [10], and self-assembling peptide scaffolds that mimic the extracellular matrix further enhance fibroblast adhesion, migration, and proliferation both *in vitro* and *in vivo* [25].

3.4. Collagen synthesis and extracellular-matrix remodelling

The proliferative and remodelling phases require deposition of a provisional matrix and its progressive maturation into organised collagen. The transforming growth factor-β (TGF-β)/Smad axis is the principal driver of type I and III collagen synthesis, while the balance between matrix metalloproteinases and their tissue inhibitors governs remodelling. Collagen peptides up-regulate TGF-β/Smad signalling to promote collagen synthesis, deposition, and subsequent ECM remodelling [10]. Peptide-based hydrogels likewise support organised collagen deposition and dermal bridging in acute and diabetic wounds [25], and neurotensin delivery yielded a well-organised collagen matrix accompanied by complete re-epithelialisation in diabetic rats [23,26].

3.5. Antioxidant defence

Excessive reactive oxygen species (ROS), particularly in the hyperglycaemic wound environment, damage cellular constituents and perpetuate inflammation, thereby stalling repair. Many bioactive peptides, most prominently those of marine origin, scavenge free radicals and reinforce endogenous antioxidant defences, reducing oxidative burden within the wound bed [9,11]. Because ROS accumulation and NF-κB activation are mutually reinforcing, this antioxidant activity complements the anti-inflammatory actions described above, and the two effects frequently coincide within a single multifunctional peptide [27].

Taken together, these five mechanistic axes are not independent but form a tightly integrated regulatory network. The therapeutic value of bioactive peptides lies precisely in this multifunctionality: individual sequences commonly engage inflammatory, angiogenic, proliferative, matrix-directed, and antioxidant pathways in parallel, mirroring the coordinated biology of physiological repair.

Table 2. Representative bioactive peptides, their molecular targets, and reported wound-healing effects.

Peptide / class	Molecular target(s) / pathway	Experimental model	Principal reported effect	Ref.
Amphibian peptides (tylotoin, RL-QN15, tiger17, cathelicidins)	Keratinocyte/fibroblast proliferation & migration; neutrophil/macrophage recruitment and immunomodulation	*In vitro* + murine/rat skin wounds	Accelerated closure and re-epithelialisation	[20]
Neurotensin (tridecapeptide)	↓ TNF-α (NF-κB-associated inflammation); ↑ VEGF (angiogenesis)	*In vitro* macrophages/fibroblasts + diabetic rat	Re-epithelialisation, angiogenesis, organised collagen	[23]
Collagen-derived peptides	TGF-β/Smad; PI3K/Akt/mTOR	Multiple in vitro / *in vivo* wound models	↑ Proliferation, collagen synthesis/deposition, ECM remodelling	[10]

Self-assembling (amyloid) peptide hydrogel	ECM-mimetic scaffold; fibroblast proliferation/migration	*In vitro* + normal & diabetic rats	Migration, proliferation, collagen remodelling, angiogenesis	[25]
Host-defence peptides (LL-37 and related)	MAPK, NF-κB, PI3K/Akt in endothelial cells	*In vitro* / mechanistic	Angiogenesis and barrier regulation (biphasic, structure-dependent)	[16]
Marine-derived peptides	ROS scavenging; endogenous antioxidant support	*In vitro* / *in vivo*	Antioxidant, anti-inflammatory, pro-migratory	[9,11]

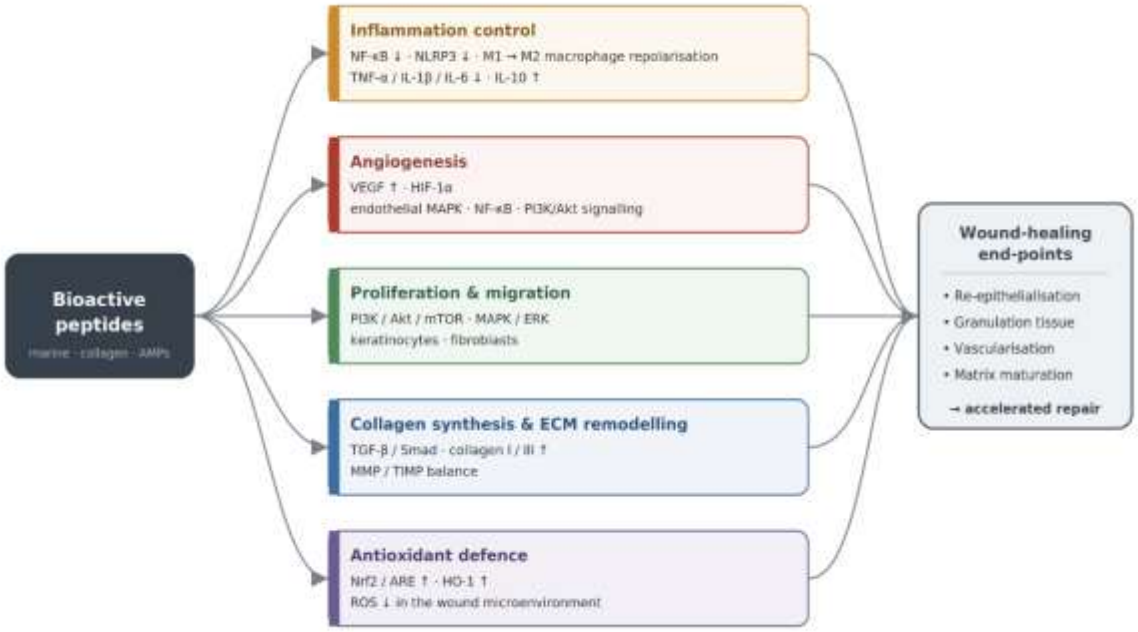

Figure 2. Molecular signalling network engaged by bioactive peptides during cutaneous wound healing. The schematic maps peptide inputs onto five interconnected axes – (i) inflammation (NF-κB/NLRP3 suppression, M1→M2 macrophage repolarisation, TNF-α/IL-1β/IL-6↓, IL-10↑); (ii) angiogenesis (VEGF↑, endothelial MAPK–NF-κB–PI3K/Akt signalling); (iii) proliferation and migration of keratinocytes and fibroblasts (PI3K/Akt/mTOR); (iv) collagen synthesis and ECM remodelling (TGF-β/Smad, MMP/TIMP balance); and (v) antioxidant defence (ROS scavenging, Nrf2/ARE-linked enzyme support) – converging on the biological end-points of re-epithelialisation, granulation, vascularisation, and matrix maturation.

4. Delivery systems and therapeutic strategies

The clinical translation of bioactive peptides is constrained less by their intrinsic activity than by their unfavourable pharmacokinetics. In the protease-rich wound environment, peptides are highly susceptible to enzymatic proteolysis and hydrolysis, and are further degraded by local changes in pH, oxidation, and photolysis [14]. Their plasma half-life is correspondingly short, that of the reparative peptide neurotensin, for example, is under two minutes, so that free peptide applied topically is rapidly inactivated before a therapeutic effect can be achieved [23]. Overcoming these limitations through appropriate delivery and structural design is therefore central to any therapeutic strategy.

Hydrogel-based carriers have emerged as the most extensively investigated platform. Peptides possess a robust capacity for supramolecular self-assembly into nanostructures and hydrogels, and stimuli-responsive peptide hydrogels can adjust their network structure in response to environmental cues to enable controlled drug release, biosensing, and scaffold construction [28]. Self-assembling peptide hydrogels act simultaneously as an extracellular-matrix-mimetic scaffold and a sustained-release reservoir; a functional amyloid peptide hydrogel of this type accelerated closure in both normal and diabetic rats while supporting fibroblast proliferation and organised collagen remodelling [25]. Functionalised polymer hydrogels extend this principle: gelatin methacryloyl (GelMA) systems incorporate cell-adhesive and matrix-metalloproteinase-responsive peptide motifs that permit cell infiltration and tunable, sustained release of therapeutic agents, and serve as bioactive wound

dressings [29]. Collagen-based formulations, hydrogels, sponges, films, and composite nanofibers, likewise provide well-established topical vehicles for peptide delivery [30].

Nanotechnology and molecular engineering address peptide instability more directly. Nanoparticulate and nanofibrous carriers improve the stability and localised delivery of antimicrobial peptides, and combinatorial nanoformulations have been developed to present these peptides effectively at the wound site [14]. At the molecular level, structural modifications, cyclisation, incorporation of D-amino acids, C-terminal amidation, and branched architectures, confer resistance to proteolysis and prolong residence time. Branched peptide biomaterials, in particular, exhibit slower degradation, greater stiffness, and self-assembling behaviour, making them suitable as drug-delivery systems and wound-healing scaffolds [31]. Conjugation and encapsulation strategies achieve the same end by physically shielding the peptide while enabling sustained release: neurotensin conjugated to polymeric porous microparticles and dispersed in a gelatin hydrogel produced sustained peptide release and markedly improved diabetic wound outcomes, including complete re-epithelialisation and a well-organised collagen matrix [23]. The choice of formulation and administration route can thus be tailored to specific wound types and clinical requirements [8].

Despite these advances, the great majority of peptide-based wound therapies remain at the in vitro or rodent-model stage, although a subset of antimicrobial peptides has progressed to clinical trials for burn and wound injuries [14,26,27]. Realising their full potential will require delivery platforms that reconcile sustained bioavailability with scalable, standardised manufacturing – challenges addressed in the following section.

5. Limitations, challenges, and future perspectives

Despite the rapidly expanding evidence base, several obstacles continue to separate bioactive peptides from routine clinical use. The most fundamental is mechanistic: although individual peptides have been shown to modulate defined signalling pathways, the structure–activity relationships that link a specific sequence to a particular reparative outcome remain incompletely defined, and a substantial part of the literature is descriptive rather than mechanistic [9,10]. This limits rational design and hinders prediction of efficacy across wound types.

Pharmacological barriers compound this problem. Even with the delivery strategies discussed above, proteolytic instability and limited bioavailability remain the principal constraints on peptide therapeutics [32]. Cationic antimicrobial peptides pose an additional concern, as their membrane-perturbing activity can become cytotoxic at higher concentrations, so that the therapeutic window must be carefully defined and potential toxicity mitigated [15,32]. Cost-effective, scalable, and standardised manufacturing represents a further bottleneck: batch-to-batch consistency, delivery efficiency, scalability, and regulatory compliance all remain unresolved for peptide- and nanoparticle-based systems [32,33]. Finally, the evidence base is heavily skewed towards in vitro and rodent studies, with a marked scarcity of well-designed randomised controlled trials in humans [11], and the long-term consequences of using antimicrobial peptides, including the theoretical emergence of resistance, require continued scrutiny [15].

Future progress is likely to follow several converging directions. Rational peptide engineering and peptidomimetic design offer the clearest route to improved proteolytic stability, target specificity, and reduced toxicity [15,32]. Combinatorial strategies, pairing peptides with optimised delivery vehicles, combining complementary peptides, or integrating them with conventional wound care, may exploit the multifunctionality of these molecules more fully, while personalised approaches tailored to specific wound types and patient profiles could enhance clinical outcomes [8,33]. In parallel, deeper mechanistic dissection using multi-omics and single-cell approaches is needed to resolve structure–activity relationships and validate molecular targets [10], and continued exploration of underexploited natural sources, such as marine organisms, will further widen the therapeutic repertoire [11].

6. CONCLUSION

Bioactive peptides act not through a single mechanism but through an integrated, multifunctional network that spans all phases of cutaneous repair — attenuating inflammation, promoting angiogenesis, driving keratinocyte and fibroblast proliferation and migration, stimulating collagen synthesis and matrix remodelling, and reinforcing antioxidant defence. This breadth of action, combined with high specificity and low immunogenicity, makes them compelling candidates for next-generation wound therapeutics. Their translation to the clinic, however, depends on resolving persistent challenges of stability, safety, manufacturing, and clinical evidence. Advances in peptide engineering, delivery technology, and mechanistic understanding, coupled with rigorous clinical evaluation, will determine whether the considerable promise of bioactive peptides is ultimately realised in wound care.

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