

MINI REVIEW



Pharmaceutical innovations in wound healing and tissue regeneration

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ABSTRACT

Wound healing is a complex, multistage biological process involving haemostasis, inflammation, proliferation, and remodelling. Chronic wounds, such as diabetic foot ulcers, pressure sores, and venous leg ulcers, often stall in this cascade due to persistent cellular dysfunction, resulting in prolonged morbidity and significant healthcare burdens. Conventional treatments largely provide symptomatic relief without addressing the underlying biological impairments. This mini-review critically evaluates recent pharmaceutical innovations designed to target specific molecular mechanisms that enhance wound repair and tissue regeneration. A focused analysis of preclinical and clinical studies highlights promising strategies including growth factors (e.g., PDGF, VEGF) that stimulate fibroblast activation and angiogenesis; bioengineered skin substitutes and stem cell-based scaffolds that support re-epithelialization and extracellular matrix remodelling; and nanocarrier systems that enable targeted, controlled drug delivery with reduced systemic toxicity. Additionally, gene and RNA-based therapies show potential in modulating wound microenvironments by restoring disrupted signalling pathways, while smart dressings incorporate responsive biomaterials to allow precise, environment-triggered drug release. These emerging approaches collectively offer targeted, effective solutions for managing complex wounds. However, their successful clinical translation necessitates interdisciplinary collaboration, regulatory oversight, and efforts to improve affordability, accessibility, and long-term safety across diverse healthcare settings.

KEY WORDS

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Introduction

Wound healing is a multifaceted biological process essential for restoring the structural and functional integrity of injured tissue. It occurs in four overlapping phases: haemostasis, inflammation, proliferation, and remodelling. Haemostasis initiates clot formation through vasoconstriction and platelet aggregation. The inflammatory phase follows, characterized by neutrophil and macrophage infiltration, which clears pathogens and debris via cytokine-mediated signalling. During the proliferative phase, fibroblasts and keratinocytes drive tissue regeneration, angiogenesis, and extracellular matrix deposition. Finally, the remodelling phase strengthens the tissue via collagen reorganization and maturation [1].

While acute wounds generally follow this cascade toward resolution, healing is often compromised in chronic wounds associated with diabetes, vascular insufficiencies, pressure ulcers, or extensive burns. Such wounds affect up to 2% of the population in developed countries and are linked to high morbidity, risk of infection, and limb amputation. Their management imposes substantial socioeconomic burdens and highlights the critical need for more effective interventions [2].

Conventional wound care practices such as dressings, debridement, and infection control often provide only symptomatic relief and fail to address the biological dysfunctions underlying impaired healing. In recent years, pharmaceutical innovations have gained attention for their potential to modulate wound repair at the cellular and molecular levels. Growth factors, bioengineered skin substitutes, and nanocarrier-based drug delivery systems have demonstrated enhanced efficacy in preclinical and early clinical settings [3].

Despite promising developments, limitations such as high cost, regulatory barriers, and variability in clinical efficacy hinder widespread adoption. Moreover, wound heterogeneity necessitates personalized approaches, complicating treatment standardization. This mini-review aims to examine key pharmaceutical advances in wound healing and tissue regeneration, highlight their mechanisms of action, and evaluate their translational potential in clinical care [4].

Mechanisms of Wound Healing and Regeneration

Wound healing is a temporally regulated, multistep biological process that restores tissue structure and function following injury. It proceeds through four interrelated phases: haemostasis, inflammation, proliferation, and remodelling. Each phase involves specific cellular responses and biochemical signalling pathways. Understanding these mechanisms is essential for identifying pharmaceutical targets aimed at improving wound outcomes, especially in impaired or chronic settings [5].

During the proliferative phase, fibroblasts are key effectors that synthesize extracellular matrix (ECM) components such as collagen types I and III, fibronectin, and hyaluronic acid are providing a scaffold for tissue repair. Myofibroblasts, differentiated from fibroblasts under the influence of transforming growth factor-beta (TGF- β), facilitate wound contraction. Concurrently, keratinocytes initiate re-epithelialization by migrating and proliferating across the wound bed through integrin-mediated interactions with the ECM. Angiogenesis, driven predominantly by endothelial cell proliferation and

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migration, ensures adequate perfusion of the regenerating tissue and is essential for granulation tissue formation [6].

This cellular interplay is tightly regulated by growth factors and cytokines. Vascular endothelial growth factor (VEGF), secreted in response to hypoxia by keratinocytes, fibroblasts, and macrophages, is a principal driver of angiogenesis and vascular permeability. Platelet-derived growth factor (PDGF), released by platelets and macrophages, promotes chemotaxis, fibroblast proliferation, and ECM deposition. TGF- β isoforms regulate inflammation, fibroblast activity, and collagen synthesis, with TGF- β 1 being pro-fibrotic and TGF- β 3 associated with scarless repair. Matrix metalloproteinases (MMPs) also play a vital role in ECM remodelling, although their overexpression can degrade structural proteins and impair healing in chronic wounds [7].

While acute wounds generally proceed through these phases efficiently, chronic wounds such as diabetic foot ulcers and pressure sores exhibit persistent inflammation, impaired angiogenesis, and disrupted growth factor signalling. These pathological deviations underscore the importance of pharmaceutical innovations that target specific molecular pathways to promote resolution and tissue regeneration [8].

Conventional Pharmacological Interventions

Topical antiseptics

Cadexomer iodine is a sustained-release antiseptic that provides broad-spectrum antimicrobial activity and aids in wound debridement by absorbing exudate and slough. Clinical studies have demonstrated its superior efficacy in reducing ulcer size compared to standard dressings. Povidone-iodine is another widely used antiseptic, though its impact on healing rates varies across different wound types. Silver-based agents include silver nitrate, primarily used to cauterize over granulation tissue, and silver-impregnated dressings that release silver ions to target a wide range of pathogens. Despite their popularity, silver dressings have not consistently demonstrated superior healing outcomes over conventional dressings [9].

Systemic antibiotics

Systemic beta-lactam antibiotics, such as penicillin and cephalosporin, remain standard for treating wounds with clinical signs of infection. These agents are especially effective against common wound pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa*. However, they are not indicated for colonized but non-infected wounds [10].

Anti-inflammatory drugs

NSAIDs are commonly used to manage pain and inflammation by inhibiting cyclooxygenase enzymes. While effective symptomatically, some studies suggest they may delay healing. Corticosteroids are typically reserved for specific ulcerative conditions with an autoimmune or inflammatory component, where modulation of excessive immune activity is necessary for tissue preservation [11].

Pharmaceutical Innovations

Growth factors and cytokine-based therapies

Growth factors such as platelet-derived growth factor (PDGF-BB), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF-A), and fibroblast growth factor (FGF) play critical roles in wound repair. These

molecules activate cellular processes, including fibroblast proliferation, keratinocyte migration, angiogenesis, and extracellular matrix (ECM) synthesis by binding to specific receptor tyrosine kinases [12].

Recombinant PDGF-BB, formulated as a topical gel, is the only FDA-approved growth factor for chronic wounds and is used in diabetic foot ulcers. Clinical trials have demonstrated their ability to significantly accelerate healing timelines and improve complete wound closure rates. Novel delivery approaches such as supramolecular hydrogels and ECM-affinitive constructs co-delivering PDGF and VEGF are under exploration for enhancing neovascularization and epidermal regeneration [13].

Although EGF and FGF are biologically active in promoting proliferation and tissue repair, they currently lack regulatory approval for wound applications. The integration of these cytokines into bioactive delivery platforms continues to be investigated for enhanced therapeutic efficacy [14].

Bioengineered skin substitutes and cellular therapies

Bioengineered skin substitutes combine structural support with regenerative capacity, mimicking the architecture and function of human skin. Products such as bilayered constructs embedded with neonatal keratinocytes and fibroblasts stimulate ECM remodelling, reepithelialization, and cytokine production. These substitutes are used for managing diabetic foot ulcers and venous leg ulcers, demonstrating shorter healing durations and improved closure rates compared to standard wound care [15]. Additional strategies incorporate platelet-rich plasma (PRP) to enhance the concentration of autologous growth factors. Stem cell-embedded scaffolds also show promise by delivering multipotent cells capable of differentiating into skin-relevant lineages, facilitating both dermal and epidermal regeneration. These advances are moving toward more bioactive, patient-specific wound solutions [16].

Nanotechnology in wound healing

Nanotechnology has revolutionized wound management by enabling controlled drug release and antimicrobial action at the nanoscale. Metallic nanoparticles such as silver and gold disrupt bacterial membranes and prevent biofilm formation, making them effective in infection control. These nanoparticles are often embedded in hydrogel matrices or applied as part of dressings for localized, sustained antimicrobial delivery [17].

Drug-encapsulating nanocarriers like liposomes, nanoemulsions, and nanogels offer prolonged release of cytokines, antibiotics, or antioxidants. Nanofiber scaffolds engineered to mimic ECM structures enhance cellular adhesion and support tissue remodelling. These systems provide enhanced bioavailability, reduced systemic toxicity, and spatiotemporal control of therapeutic agents, offering significant advantages over traditional formulations [18].

Gene therapy and rna-based interventions

Gene and RNA-based therapies introduce a paradigm shift in precision wound modulation. These approaches aim to alter gene expression directly within the wound environment using small interfering RNAs (siRNAs), messenger RNAs (mRNAs), or gene-editing tools like CRISPR/Cas9. By silencing pro-inflammatory cytokines or upregulating angiogenic factors, these tools can address the molecular dysfunctions characteristic of chronic wounds [19].

Topical delivery systems are being optimized for safety and efficiency, including lipid nanoparticles, viral vectors, and non-viral methods like tissue nanotransfection. Gene therapy products have begun to gain regulatory approval for certain skin disorders, marking a key step toward broader application in wound healing. Although most gene-based strategies remain in the preclinical phase for wounds, early data show promise in accelerating healing and reducing scar formation [20].

Smart dressings and drug-releasing biomaterials

Smart dressings represent an advanced class of wound care materials that respond dynamically to the wound microenvironment. These systems are engineered to release therapeutic agents such as antibiotics, growth factors, or anti-inflammatory molecules in response to environmental cues like pH, temperature, or oxidative stress [21].

pH-responsive hydrogels, for example, release their drug payload when exposed to the acidic conditions of infected wounds, ensuring targeted antimicrobial action. Temperature-sensitive polymer foams alter their porosity to modulate drug diffusion and moisture retention based on wound temperature. Composite dressings that combine multiple layers and materials provide both barrier function and controlled release [22].

Diagnostic-integrated dressings are being developed to monitor wound parameters such as pH and moisture in real-time. These systems hold potential for personalized wound care by adjusting therapy based on continuous feedback, ultimately improving outcomes while minimizing drug overuse [23].

Comparative Analysis of Innovations vs Traditional Therapies

Innovative wound care modalities such as negative-pressure wound therapy (NPWT), platelet-rich plasma (PRP), and antimicrobial photodynamic therapy (aPDT) have demonstrated superior outcomes compared to traditional topical dressings and antibiotics across multiple clinical parameters [24].

NPWT has consistently shown enhanced wound healing and significant reduction in postoperative infections. Clinical evidence supports its utility in various surgical domains, including orthopaedic and spinal procedures, where it substantially decreases infection rates and shortens hospital stay durations. Additionally, in high-risk populations such as obese patients undergoing cesarean sections, NPWT has lowered the incidence of surgical site infections without increasing complication rates [25].

PRP therapy, particularly in the management of chronic diabetic foot ulcers, offers both clinical and economic advantages. It facilitates angiogenesis, accelerates granulation tissue formation, and reduces recurrence rates. Cost-effectiveness analyses suggest that PRP contributes to increased quality-adjusted life years while maintaining acceptable or reduced treatment costs when compared to conventional dressings [26]. Similarly, antimicrobial photodynamic therapy has emerged as a targeted approach for infection control. Its use in surgical patients has led to significant reductions in infection

rates and overall healthcare expenditures, with minimal adverse effects [27].

These innovations also contribute to improved pain and scar management by promoting optimal tissue regeneration and minimizing inflammation. Compared to traditional therapies, the advanced modalities deliver faster healing, better infection containment, and greater cost-effectiveness. Particularly in patients with complex or chronic wounds, such as those associated with diabetes, obesity, and burns. Further long-term studies are warranted to validate scalability and sustained outcomes in diverse clinical settings [28].

Challenges and Limitations

Cost and accessibility

Advanced wound care interventions often face limited accessibility due to infrastructure constraints and unequal distribution across healthcare systems. Availability in rural and resource-limited settings remains inconsistent [29].

Regulatory and clinical trial hurdles

Gene and cellular therapies encounter complex regulatory requirements. In jurisdictions like the U.S., autologous cell-based products are classified as biologics, demanding rigorous clinical trials to demonstrate safety and consistency, which can delay clinical translation [30].

Long-term safety and efficacy

Data on long-term effects are limited. Concerns include immune responses, transient expression of therapeutic agents, and theoretical risks such as graft rejection or neoplastic transformation. Ongoing surveillance is critical to ensure sustained outcomes [31].

Ethical concerns in genetic/cellular therapies

Key ethical challenges involve informed consent in early-phase studies, transparency in patient communication, and debate over stem cell sources. Genome editing raises theoretical concerns about unintended heritable effects, highlighting the need for robust ethical governance in translational research [32].

Conclusions

Recent advances in Nano-biotechnology, particularly through the development of liposomal, polymeric, and dendrimer-based nanocarriers which have significantly enhanced targeted drug delivery by improving solubility, bioavailability, and minimizing systemic toxicity. Simultaneously, nanostructured scaffolds such as nanogels have facilitated tissue regeneration by modulating cellular microenvironments and promoting stem cell differentiation. Looking ahead, AI-driven nanoparticle engineering and CRISPR-based gene editing are expected to transform precision medicine through intelligent, patient-specific theranostic applications. However, the successful clinical translation of these innovations relies on robust multidisciplinary collaboration across nanoscience, bioengineering, and clinical research to ensure safety, scalability, and broad patient accessibility.

Disclosure Statement

No potential conflict of interest was reported by the author.

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