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Toward precision wound healing: Integrating regenerative therapies and smart technologies

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Abstract

Wound healing is a complex and multi-stage process that involves four key phases: haemostasis, inflammation, proliferation, and tissue remodeling. This sequence can often be disrupted in chronic conditions such as diabetes, severe burns, and persistent infections, leading to delayed healing and abnormal scarring. Conventional treatments, including dressings, antiseptics, and topical antimicrobials, are important but often do not achieve complete healing. As a result, research has increasingly focused on complementary and advanced interventions that target specific cellular and molecular pathways. This review discusses advancements in cell-based therapies, gene delivery systems, and growth factor treatments, as well as the use of bioactive compounds and drug delivery methods driven by nanotechnology. Biomaterials such as chitosan, silk fibroin, and casein fibers have shown promise as scaffolds for tissue regeneration, while injectable hydrogels and bioadhesives offer less invasive solutions for complex wounds. Emerging strategies include AI-enabled smart bandages, bioengineered skin grafts, 3D bioprinting, and RNA-based therapeutics, which enhance precision and personalize the healing process. Evidence from preclinical and clinical studies highlights the therapeutic benefits of stem cell therapy, growth factor modulation, and non-invasive techniques like shock wave or microcurrent stimulation. The combination of traditional wound care with innovative biological and technological approaches offers transformative potential for personalized, rapid, and scar-free recovery. However, challenges such as high costs, safety concerns, and the absence of standardized clinical protocols remain substantial obstacles. Future research should focus on optimizing biocompatibility, scalability, and cost-effectiveness to facilitate broader clinical adoption.

Keywords: Wound Healing; Regenerative Therapy; Biomaterials; Gene Therapy; Advanced Technologies; Clinical Translation

1. Introduction

Wound healing is a critical physiological process that repairs damaged skin and tissues through four main stages: haemostasis, inflammation, proliferation, and extracellular matrix (ECM) remodeling [1]. Each stage is essential for effective wound closure and tissue regeneration. Disruptions can lead to chronic wounds, such as diabetic foot ulcers, venous leg ulcers, and pressure sores, which are significant global health challenges [2]. These wounds affect millions, complicate treatment, and may result in serious consequences like amputation or infection. They also negatively impact quality of life, especially as diabetes, vascular diseases, and aging populations rise. Traditional wound care methods include dressings, antiseptics, antibiotics, and compression therapy. While essential, these methods often fail for complex wounds. They protect against infection, but do not sufficiently promote cell regeneration or address underlying issues such as inflammation and impaired growth factor signaling. The overuse of antibiotics can lead to resistance, and

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conventional dressings might not foster healing in chronic conditions. Economic constraints, like frequent changes, also limit access to effective care, particularly in low-resource areas [3], [4], [5].

To address these challenges, researchers are developing innovative strategies that include biological, chemical, and technological approaches. Stem cell therapy, gene therapy, and growth factor delivery target healing at the molecular level, focusing on repair and tissue integrity. Biomaterials like bioengineered scaffolds and hydrogels mimic natural skin properties to enhance cell growth and vascularization. Natural and chemical agents such as curcumin and aloe vera provide anti-inflammatory and healing benefits [6]. Nanotechnology improves these treatments by protecting active compounds and ensuring accurate delivery. Additionally, advanced technologies, including smart bandages with biosensors, offer real-time monitoring of wound conditions. Customizable grafts from 3D bioprinting and RNA-based therapies are also being explored to improve healing and personalize treatment.

Given the complexity of wound healing and the multifaceted nature of chronic wound management, this review aims to provide a comprehensive overview of emerging complementary and advanced therapeutic approaches. Unlike earlier studies that primarily focus on a single method, this paper integrates insights from cellular therapies, biomaterials, bioactive compounds, and advanced technologies to present a holistic perspective on modern wound care. By analyzing findings from preclinical studies, clinical trials, and technological innovations, the review highlights both the promise and challenges of these novel strategies.

The objectives of this review are threefold:

- To examine the current limitations of conventional wound care and emphasize the clinical need for more effective interventions.
- To evaluate complementary therapies, such as cell therapy, gene therapy, growth factors, and bioactive agents, that directly influence cellular and molecular healing processes.
- To explore advanced technologies, including smart dressings, bioengineered skin substitutes, nanomaterials, and RNA-based therapeutics, with a focus on their translational potential in clinical practice.

By consolidating these diverse approaches, the review aims to highlight the interdisciplinary nature of modern wound healing research and identify pathways for future development. Ultimately, integrating traditional methods with innovative biological and technological strategies has the potential to transform wound care into a patient-centered, cost-effective, and globally accessible practice.

2. Traditional and Emerging Therapeutic Approaches

2.1. Conventional Wound Care

This review discusses new strategies to enhance traditional wound care, which relies mainly on dressings, antiseptics, and antibiotics. These methods often struggle with chronic wounds due to problems like inadequate blood flow and bacterial overgrowth. In contrast, emerging therapies such as cell and gene interventions and growth factor applications address the biological factors of healing. Innovations in biomaterials, nanotechnology, and drug delivery have led to more active, technology-driven wound management. For example, stem cell therapies with mesenchymal and adipose-derived cells have shown promise for diabetic ulcers, while negative pressure wound therapy is now common for chronic wounds. However, experimental therapies, such as RNA-based and gene therapies, struggle with inconsistent results and safety concerns, highlighting the need for standard protocols and larger trials.

Integrating biomaterials like chitosan and silk fibroin with bioactive compounds in wound dressings can actively promote healing. Nanomaterials enhance drug stability and localized delivery, which reduces side effects. Smart bandages and biosensors enable continuous monitoring, allowing timely medical intervention and fewer hospital visits. These advancements could significantly lower the financial and healthcare burdens of chronic wounds, particularly for diabetics. However, challenges persist. Safety issues surrounding stem cell and gene therapies, high production costs of bioengineered products, and differences in wound biology hinder accessibility. Future research should focus on these challenges through collaboration. Improvements in biomaterials and nanotechnology could lead to safer, more affordable options for growth factor and RNA delivery. Standardizing cell preparation and refining dosing could enhance the consistency of therapies, and expanding clinical trial designs with larger samples and consistent outcomes is crucial for validating efficacy. Digital health tools, such as AI monitoring and personalized treatment plans, will also enhance precision medicine in wound care.

2.2. Complementary Therapies

Conventional therapies alone are often insufficient for treating chronic or non-healing wounds. This limitation has led to the development of complementary strategies that promote regeneration, angiogenesis, and tissue repair at the cellular and molecular levels. Among these, cell therapy, gene therapy, and growth factor-based treatments are considered some of the most promising approaches. Table 1 provides a summary of preclinical studies on cell therapy, gene therapy, and growth factor delivery approaches in various wound models, highlighting their sources, mechanisms of action, and therapeutic outcomes.

Table 1 Preclinical investigations of cell-based, gene, and growth factor therapies for wound healing across different animal models.

Therapy	Source	Wound Model	Animal Model	Delivery Route	Therapeutic Mechanism	Ref.
Cell therapy	Bone marrow-derived cells	Excisional wounds	C57BLKS/J-m 1/1 Leprdb/db mice	Injection	Stimulated neovascularization, enhanced granulation, and accelerated re-epithelialization	[7]
	Umbilical cord stem cells	Excisional wounds	db/db mice	Subcutaneous injection	Promoted angiogenesis; upregulated VEGF, PDGF, and KGF expression	[8]
	Bone morphogenetic protein-2 with mesenchymal stromal cells	Chronic wounds	Sprague Dawley rats	Injection	Induced tissue structure redevelopment; normalized epidermis, sebaceous glands, collagen, and blood vessels	[9]
	Adipose-derived stem cells (inguinal tissue)	Pressure ulcers	C57BL/6 mice	Injection	Reduced inflammation; promoted epidermal hypertrophy, collagen synthesis, and vascular barrier restoration	[10]
Gene therapy	Human TGF- β 1 cDNA (pcDNA3.1/GS)	Excisional wounds	C57BKS Cg-m+/+Leprdb mice	Intradermal injection	Improved re-epithelialization, angiogenesis, and collagen tissue remodeling	[11]
	VEGF165 plasmid DNA	Incisional wounds	Sprague Dawley rats	Intradermal injection	Increased VEGF expression, eNOS activity, and angiogenesis	[12]
	pGWIZ-CA5 plasmid	Excisional wounds	BKS Cg-m+/+ Leprdb/J mice	Intradermal injection	Enhanced wound healing; reduced distal necrosis	[13]
	RGD-K-lipopeptide-rhPDGF-B gene	Incisional wounds	Sprague Dawley rats	Subcutaneous injection	Improved epithelialization, keratinization, fibroblast migration, and vascularization	[14]

Growth factor delivery	VEGF + bFGF (plasma-derived)	Diabetic/open wounds	BKS Cg-m+/+ Leprdb/db mice	Scaffold implantation	Accelerated wound closure; enhanced tissue granulation and re-epithelialization	[15]
	IGF-1 (ligament and connective tissue)	Incisional wounds	Sprague Dawley rats	Injection	Improved collagen organization and tensile strength	[16]
	bFGF (fibroblast-derived)	Excisional wounds	Balb/c mice	Injection	Enhanced fibroblast proliferation, angiogenesis, and wound contraction	[17]
	EGF + bFGF	Diabetic wounds	Male ICR mice	Intraperitoneal injection	Sustained growth factor release; improved re-epithelialization, angiogenesis, and collagen deposition	[18]

2.2.1 Cell Therapy

Cell therapy utilizes living cells to enhance wound healing by releasing bioactive molecules, modulating inflammation, and regenerating damaged tissue. Stem cells are particularly valuable due to their ability to differentiate into various cell types and secrete factors that support immune responses and tissue repair. Mesenchymal stem cells (MSCs) from bone marrow increase angiogenesis and granulation tissue formation, while adipose-derived stem cells (ADSCs) are abundant and promote fibroblast activity and reduce inflammation. Umbilical cord-derived stem cells are also promising due to their high growth potential and low immunogenicity. In addition to whole cells, exosomes and secretomes released by stem cells are gaining attention as therapeutic agents. Exosomes carry proteins, growth factors, and microRNAs that enhance angiogenesis and re-epithelialization without the risks of cell transplantation, like immune rejection or tumor formation. Secretomes contain a mix of signaling molecules that help modulate inflammation and speed up tissue repair. These cell-free products offer a safer and potentially more scalable alternative to cell transplantation in regenerative medicine.

2.2.2 Gene Therapy

Gene therapy is another advanced complementary strategy that aims to modify or introduce genetic material to promote wound healing. This approach employs viral or non-viral vectors to deliver genes that encode proteins such as growth factors, cytokines, or components of the extracellular matrix. Plasmid-based gene therapy has been explored for administering vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β), both vital for angiogenesis and collagen deposition [19], [20]. Figure 1 summarizes the major complementary and advanced approaches in wound healing, including cell therapy, gene therapy, growth factor administration, biomaterial-based strategies, and bioactive therapeutics.



Figure 1 Advanced wound healing strategies should be inserted in the Complementary Therapies section

While viral vectors, such as adenoviruses and lentiviruses, offer high efficiency in gene transfer, they raise safety concerns related to immunogenicity and insertional mutagenesis. Non-viral vectors, including nanoparticles, hydrogels,

and liposomes, present safer alternatives but may have limitations regarding stability and lower transfection efficiency. Clinical outcomes with gene therapy have been mixed. Some studies report enhanced vascularization and faster wound closure with VEGF plasmid delivery, whereas others show inconsistent results due to variations in dosage, vector design, and patient-specific factors. Despite these challenges, gene therapy continues to be a promising avenue, particularly when integrated with biomaterial carriers or combined with other regenerative approaches [21].

2.2.3 Growth Factor-Based Treatments

Growth factors are natural proteins that regulate cell proliferation, migration, and angiogenesis, making them essential mediators of wound healing. The therapeutic administration of exogenous growth factors has demonstrated considerable potential in managing chronic wounds. Platelet-derived growth factor (PDGF), for instance, has been extensively studied for its ability to stimulate fibroblast proliferation and vascularization. Similarly, VEGF and basic fibroblast growth factor (bFGF) are crucial for the formation of new blood vessels and extracellular matrix remodeling, while epidermal growth factor (EGF) promotes keratinocyte migration and re-epithelialization. Insulin-like growth factor-1 (IGF-1) also contributes to improved collagen deposition and tensile strength in healing tissue. However, a substantial limitation of growth factor therapy is the short half-life and rapid degradation of these proteins in wound environments, which diminishes their therapeutic efficacy. To address this issue, researchers are developing controlled-release delivery systems, such as hydrogels, nanocarriers, and scaffolds, that can provide sustained release and localized activity. These innovations improve bioavailability while minimizing systemic side effects, making growth factor delivery an increasingly viable option for clinical applications.

3. Bioactive and Natural Therapeutics in Wound Repair

3.1. Natural Compounds

Natural products are extensively studied for wound care due to their anti-inflammatory, antioxidant, and antimicrobial properties. Curcumin, a polyphenol derived from turmeric, promotes fibroblast proliferation, collagen deposition, and angiogenesis while downregulating TNF- α and IL-6. Formulations of curcumin using nanocarriers address its instability and significantly enhance wound closure [22], [23]. Aloe vera gel, which is rich in polysaccharides and glycoproteins, improves fibroblast migration, collagen synthesis, and angiogenesis, while also reducing inflammation and scar formation. Naringin and naringenin, flavonoids found in citrus fruits, help lower oxidative stress and cytokine release, thereby enhancing fibroblast activity, collagen alignment, and tensile strength [24], [25]. Despite promising results, variability in source materials and a lack of standardized dosing present challenges to clinical translation. Utilizing nanodelivery and bioengineered formulations may enhance stability and efficacy.

3.2. Chemical Agents

Various pharmacological agents have been repurposed for wound healing. Erythropoietin (EPO), traditionally used for treating anemia, stimulates endothelial proliferation and angiogenesis, thereby improving oxygenation and tissue repair in ischemic and diabetic wounds. Simvastatin, known for its cholesterol-lowering effects, accelerates wound closure by promoting angiogenesis, lymphangiogenesis, and collagen remodeling while reducing inflammation and oxidative stress. Melatonin, recognized for its role in regulating circadian rhythms, enhances epithelialization, collagen synthesis, and angiogenesis by modulating NF- κ B and MAPK pathways, which also helps minimize scar formation. Other agents, such as neomycin-silver nanoformulations, further improve antimicrobial activity and tissue regeneration. While these compounds demonstrate significant preclinical potential, concerns regarding systemic side effects, appropriate dosage, and long-term safety limit their clinical application.

3.3. Mechanistic Insights

The therapeutic benefits of both natural and chemical agents stem from their ability to regulate three essential processes: inflammation, angiogenesis, and ECM remodeling. Anti-inflammatory activity is crucial in chronic wounds, which are characterized by prolonged immune responses. Curcumin, naringin, melatonin, and simvastatin suppress pro-inflammatory cytokines (TNF- α , IL-1 β , NF- κ B), help to restore a balanced wound environment. Pro-angiogenic effects are vital for ensuring an adequate supply of nutrients and oxygen, which are essential for healing. EPO and simvastatin stimulate endothelial migration and the formation of blood vessels, while curcumin and aloe vera increase VEGF expression. ECM remodeling is important for maintaining structural integrity and preventing scars. Aloe vera and curcumin enhance collagen deposition and fibroblast proliferation, whereas melatonin and simvastatin regulate matrix turnover enzymes, improving tensile strength and reducing fibrosis.

4. Biomaterials and Nanotechnology-Based Strategies

4.1. Biomaterials for Scaffolds and Dressings

Biomaterials offer physical support and bioactive functions that enhance wound healing. Chitosan, which is derived from chitin, is valued for its antimicrobial, hemostatic, and film-forming properties. It promotes fibroblast proliferation, accelerates wound closure, and can be functionalized for drug delivery. Silk fibroin, sourced from silkworm cocoons, provides tensile strength and a porous structure that mimics the ECM. This supports cell adhesion and vascularization while reducing scarring. Casein fibers, derived from milk proteins, release bioactive peptides that promote angiogenesis and collagen deposition while also offering antimicrobial protection. These biomaterials outperform conventional gauze by actively stimulating tissue repair in addition to providing coverage [26]. Table 2 summarizes key biomaterial-based interventions for wound healing, outlining their biological targets, therapeutic outcomes, and supporting evidence.

4.2. Nanomaterials and Smart Delivery

Nanotechnology introduces advanced systems that enhance therapeutic delivery and infection control. Nanogels can encapsulate drugs, growth factors, or natural compounds, releasing them in response to pH changes, enzymes, or temperature, ensuring localized and sustained action [24]. Both metallic and polymeric nanoparticles provide multifunctional benefits. Silver and zinc oxide nanoparticles exhibit strong antimicrobial activity and stimulate keratinocyte migration, while gold nanoparticles help modulate inflammation and promote angiogenesis. Polymeric nanoparticles enable the targeted and controlled release of biomolecules. Antimicrobial composites, which integrate nanomaterials with biopolymers like chitosan or silk fibroin, combine infection control with regenerative support, thereby reducing healing times for chronic and infected wounds [25]. Collectively, these platforms effectively address two major challenges in wound care: persistent infection and the instability of bioactive agents.

Table 2 Representative biomaterial-based strategies for wound healing, their biological targets, and therapeutic outcomes.

Biomaterial	Therapeutic Target	Observed Outcome	Ref.
Oxidized bacterial cellulose, chitosan, and collagen nanocomposites	Rapid hemostasis and wound closure	Enhanced blood clotting capacity and improved hemostatic efficiency, accelerating healing	[27]
Silk fibroin	Hemostasis, low inflammatory potential, and barrier function	Faster healing with improved re-epithelialization, dermis formation, collagen synthesis, and epidermal differentiation	[28]
Casein fibers	Immunomodulation and tissue regeneration	Stimulated macrophages, endothelial cells, and fibroblasts; promoted angiogenesis; reduced chronic inflammation	[29]
Chitosan–guar–peppermint gel	Full thickness burn treatment	90% wound contraction by day 22; enhanced angiogenesis, collagen fiber deposition, and fibroblast proliferation	[30]
Multilayered electrospun nanocomposite membrane	Burn wound management	High antibacterial activity, excellent water absorption, and accelerated tissue repair	[31]
Titanium dioxide nanoparticles/gelatin composite	Infected wound repair	Promoted fibroblast proliferation and antibacterial protection	[32]

4.3. 3D Bioprinting and Tissue Engineering Scaffolds

3D bioprinting and engineered scaffolds represent advanced approaches in regenerative medicine. Bioprinting allows for the creation of patient-specific constructs using bioinks made of hydrogels, polymers, and living cells. This technique enables the precise deposition of fibroblasts, keratinocytes, and vascular structures, accelerating integration, reducing scarring, and promoting organized tissue formation. Tissue engineering scaffolds, which can be fabricated from natural

(such as collagen and alginate) or synthetic (like PLGA and PCL) polymers, mimic the ECM and provide cues for angiogenesis and cell differentiation. Smart scaffolds that incorporate nanoparticles, growth factors, or biosensors enhance healing by offering controlled delivery and real-time monitoring. These innovative strategies represent a shift from traditional wound management to functional tissue replacement; however, scalability and regulatory approval continue to pose significant challenges.

5. Advanced Technologies Transforming Wound Care

5.1. Injectable Hydrogels and Bioadhesives

Injectable hydrogels and bioadhesives represent key innovations in wound care, offering a minimally invasive method that adapts to various wound shapes. Made from natural polymers like chitosan, alginate, and gelatin, or synthetic ones such as PEG and PVA, these hydrogels create a moist environment that fosters cell growth and nutrient flow. They can be infused with antibiotics, growth factors, or stem cells for targeted, sustained release [33]. Bioadhesive products improve tissue adhesion, lower infection risks, and can replace sutures or staples in surgeries. Recent research demonstrates their effectiveness in promoting new blood vessel formation and granulation tissue development, especially in diabetic ulcers and burn injuries.

5.2. AI-Enabled Smart Bandages and Biosensors

Artificial intelligence (AI) has enabled the creation of smart bandages and biosensors that monitor wound health in real-time. These devices use microelectronic sensors to track pH, oxygen levels, temperature, and bacterial load, which provide insights into healing progress [34], [35], [36], [37], [38]. The data can be sent wirelessly to healthcare providers, allowing for early intervention if complications arise. AI algorithms further analyze this information to predict issues and recommend treatment changes. Some prototypes even deliver therapy by releasing medication or applying electrical stimulation based on sensor readings [39]. This continuous monitoring is particularly beneficial for chronic wounds, reducing the need for hospital visits and enhancing patient outcomes. A comparative timeline of these therapeutic modalities is presented in Figure 2, summarizing the onset of their effects, peak healing phases, and representative examples. This visual comparison highlights the diverse kinetics of wound repair across biological, chemical, and material-based strategies.

Modality	Onset of effect	Peak efficacy	Peak efficacy
 Stem cell therapy	3–7 days	2–3 weeks	Bone marrow, Adipose-derived, Placental
 Gene delivery	2–4 weeks	Months to years	Cones spermid, Blacental : ediver
 Exsipient growth factor delivery	Hours to a days	1 to 4 weeks	C = 4 weeks
 Hydrogel matrices	Seconds to a day	1 to 4 week	Gelatin methacryloyl-box copolymer nanocomposite
 Bioengineered sca-folds	1–2 weeks	Half-week to 3 weeks	Gelatin methacryloyl box copolymer nanocomposites

Figure 2 Comparative timeline of wound healing modalities, illustrating their onset of action, peak therapeutic efficacy, and representative examples.

5.3. Bioengineered Skin Substitutes

Bioengineered skin substitutes are designed to mimic the structure and function of natural skin, providing alternatives to autografts and allografts. They fall into three categories: cellular constructs, acellular matrices, and composite substitutes. Cellular substitutes include keratinocytes, fibroblasts, or stem cells within scaffolds to aid re-epithelialization and vascularization. Acellular matrices, made from decellularized dermis or synthetic materials, offer structural support for host cell infiltration. Composite substitutes blend biological and synthetic materials to improve integration and durability. Clinical trials have shown success in treating large burns and chronic ulcers, speeding up healing and reducing scarring. However, high production costs and limited scalability hinder their widespread use.

5.4. RNA-Based Therapies (siRNA/miRNA)

RNA-based therapies are emerging as a promising approach in molecular wound care. They target gene expression pathways involved in inflammation, angiogenesis, and tissue regeneration. Small interfering RNAs (siRNAs) can silence genes that lead to excessive inflammation or fibrosis, while microRNAs (miRNAs) help regulate various signaling networks to promote balanced healing. For instance, siRNAs aimed at matrix metalloproteinases have shown success in reducing excessive degradation of the extracellular matrix in chronic wounds, and specific miRNAs can boost angiogenic factor expression. A key challenge is the delivery of these therapies, as free RNAs are unstable and easily degraded. Researchers are working on nanoparticles, liposomes, and hydrogel carriers to protect RNA and ensure targeted delivery to wound sites. While still in early stages, RNA-based therapies offer significant potential for precision medicine in wound care.

Figure 3 illustrates representative advanced technology-based strategies, including 3D bioprinting, injectable hydrogels, bioengineered grafts, and AI-enabled sensors that are currently being explored to enhance wound healing.

6. Preclinical Models in Wound Healing Research

Preclinical models play a crucial role in advancing wound care research, offering valuable insights into the biological mechanisms of repair and allowing for the evaluation of novel therapies before they enter clinical trials. Among these models, animal studies are particularly important as they enable controlled wound induction, replication of disease conditions, and systematic assessment of therapeutic efficacy. The most commonly used preclinical wound models include excisional wounds, incisional wounds, burn wounds, diabetic wounds, and infected wounds. Each model offers a unique perspective on healing processes and therapeutic outcomes.

6.1. Excisional and Incisional Wound Models

Excisional and incisional wound models are fundamental and widely utilized approaches in studying wound repair. Excisional wounds are created by removing full-thickness skin, typically in circular or square shapes, to simulate tissue loss. These models are valuable for studying re-epithelialization, granulation tissue formation, and scar development, making them particularly useful for testing dressings, biomaterials, and topical agents. In contrast, incisional wounds consist of linear cuts made with surgical instruments. These models are designed to evaluate tensile strength, collagen alignment, and the effects of sutures or adhesives. They are commonly used to assess various surgical wound closure methods and interventions that influence scar quality. Together, excisional and incisional models provide key insights into the dynamics of tissue regeneration and repair.



Figure 3 Advanced wound healing technologies: 3D bioprinting, injectable hydrogels, bioengineered grafts, and AI-enabled sensors.

6.2. Burn and Diabetic Wound Models

Burn wound models are essential for studying thermal injuries, which often result in deep tissue damage and impaired healing. Burns are induced using heated instruments or scalding water, with the severity controlled to simulate partial- or full-thickness burns. These models are particularly relevant for testing advanced dressings, bioengineered skin substitutes, and therapies that address extensive tissue loss and a heightened risk of infection.

Diabetic wound models replicate the impaired healing commonly seen in patients with diabetes, where hyperglycemia disrupts blood vessel formation, immune responses, and collagen synthesis. Diabetes in rodents is usually induced through streptozotocin (STZ) injections or genetic modifications. The wounds created in these diabetic animals heal slowly, making these models valuable for testing regenerative therapies such as stem cells, growth factors, and nanomaterials. Given that diabetic ulcers pose a significant global health challenge, these models are critical for translational research.

6.3. Infected Wound Models

Infected wound models simulate one of the most prevalent complications in clinical wound care: microbial colonization and biofilm formation. Researchers inoculate wounds with pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or polymicrobial mixtures to investigate infection dynamics. These models are vital for evaluating antimicrobial dressings, nanomaterials, and systemic or topical antibiotics. They also provide insights into host-pathogen interactions and the role of immune modulation in the healing process. Infected wound models are especially important for studying chronic wounds, where persistent infections often delay healing and lead to complications.

6.4. Assessment Methods

To evaluate healing in preclinical models, researchers utilize a range of histological, imaging, and biochemical methods. Histological analyses, including hematoxylin and eosin (H&E) staining and Masson's trichrome staining, are employed to assess epithelialization, collagen deposition, angiogenesis, and inflammatory cell infiltration. Imaging techniques, such as digital planimetry, along with advanced modalities like optical coherence tomography and confocal microscopy, enable non-invasive monitoring of wound closure and tissue architecture over time. Biochemical markers offer quantitative insights into molecular changes, including levels of cytokines, growth factors, oxidative stress markers, and matrix metalloproteinases (MMPs). Collectively, these assessments provide a comprehensive evaluation of therapeutic effects and correlate structural changes with functional recovery.

7. Clinical Advances and Trials

Translating preclinical findings into clinical practice is crucial for improving patient outcomes in wound care. Over the past two decades, significant progress has been made in applying regenerative and technology-driven strategies, particularly for chronic and hard-to-heal wounds. Clinical trials have explored the potential of stem cell and gene therapies, as well as non-invasive physical interventions, to accelerate healing and reduce complications. Despite promising results, several challenges still hinder widespread clinical adoption. Table 3 summarizes recent clinical trials investigating diverse wound healing interventions, highlighting study designs, treatment outcomes, and therapeutic effectiveness.

Table 3 Summary of clinical studies evaluating advanced wound healing interventions.

Intervention	Target Wound	Participants	Study Duration	Dose	Study Design & Location	Clinical Outcome	Ref.
Noncontact Normothermic Wound Therapy	Chronic full-thickness wounds	22 vs 21	3 months	–	Randomized, USA	Improved wound healing rate; minor adverse events (infection, pain, irritation) observed	[40]
Timolol maleate ophthalmic gel	Pressure ulcers, diabetic foot ulcers	24 vs 24	8 months	–	Prospective, randomized, double-blind, controlled, USA	Study ongoing; results not disclosed	[41]
ON101 cream	Diabetic foot ulcers	114 vs 122	7 months	Twice daily	Randomized, USA/China/Taiwan	Enhanced wound closure; improved ulcer duration, size, and HbA1c; consistent efficacy	[42]

Extracorporeal shock wave therapy	Acute and chronic wounds	25 vs 10	3 months	–	Prospective, monocentric clinical trial, Germany	Faster re-epithelialization; reduced infection risk; no major adverse effects	[43]
Wireless Microcurrent Stimulation (WMCS)	Partial-thickness burns	31 vs 29	6 days (mean)	3 sessions/week	Prospective randomized trial, Singapore	Healing in 6 days with WMCS vs 8 days with traditional dressings; mild side effects (pain, itching)	[1]

7.1. Stem Cell Therapy for Diabetic Ulcers

Stem cell therapy has emerged as one of the most extensively studied regenerative strategies for chronic wounds, especially diabetic foot ulcers (DFUs). Clinical trials using autologous bone marrow-derived MSCs have shown improved wound closure rates, enhanced angiogenesis, and a reduced risk of amputation. Additionally, ADSCs are being investigated, with early studies reporting increased granulation tissue formation and faster re-epithelialization. Umbilical cord-derived MSCs are also gaining interest due to their high proliferative capacity and reduced immunogenicity for allogeneic applications. Importantly, most stem cell-based interventions have demonstrated favorable safety profiles, although challenges such as standardization of cell preparation, delivery methods, and long-term efficacy are still being evaluated.

7.2. Gene Therapy Applications

Gene therapy trials have primarily focused on delivering growth factors to stimulate angiogenesis and tissue repair. Plasmid-based VEGF therapies have been tested in ischemic and diabetic wounds, with some studies reporting quicker closure and improved blood flow. The clinical application of fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) gene delivery has also been explored, although results have varied due to differences in vector design, dosing, and wound characteristics. While viral vectors provide high transfection efficiency, they raise safety concerns. In contrast, non-viral carriers are safer but may be less effective. Although no gene therapy has yet received regulatory approval for wound healing, ongoing trials continue to refine delivery systems and optimize therapeutic outcomes.

7.3. Non-Invasive Strategies

Several non-invasive technologies have been integrated into clinical practice, offering supplementary options for managing chronic wounds. Shock wave therapy delivers acoustic waves to the wound area, stimulating angiogenesis and improving blood flow. Clinical studies on diabetic and ischemic ulcers have reported faster healing times and reduced pain. Microcurrent stimulation, which applies low-level electrical currents, enhances keratinocyte migration, fibroblast activity, and collagen synthesis. Trials suggest that it can decrease healing time and improve tissue organization in chronic ulcers. Negative pressure wound therapy (NPWT) is one of the most widely used non-invasive approaches; it utilizes controlled suction to remove exudates, decrease edema, and enhance perfusion. NPWT has been shown to significantly improve closure rates in diabetic, traumatic, and surgical wounds, making it a standard adjunct in many clinical settings.

7.4. Challenges in Translation

Despite encouraging advancements, several barriers hinder the transition of advanced therapies from trials to routine practice. Safety is a major concern, particularly for gene and stem cell therapies, where risks of immune reactions, tumorigenicity, or off-target effects must be carefully managed. Cost is another significant challenge; cell-based therapies and bioengineered products are expensive to manufacture, which limits accessibility in low-resource settings. Scalability and standardization pose critical hurdles, such as large-scale production of stem cells, viral vectors, or complex biomaterials that require rigorous quality control and regulatory approval. Furthermore, variability in trial design, patient selection, and outcome measures complicates the comparison of results across studies, slowing the path to clinical adoption.

8. Discussion

This review highlights the growing strategies to improve traditional wound care, which relies heavily on supportive methods like dressings, antiseptics, and antibiotics. These conventional approaches often struggle with chronic wounds due to issues like poor blood flow, immune dysfunction, and bacterial overgrowth. In contrast, newer therapies, including cell and gene interventions and growth factor applications, focus on the biological aspects of healing. Innovations in biomaterials, nanotechnology, and drug delivery have shifted wound management toward more active, technology-driven solutions. This approach combines natural compounds, biomaterials, and digital advancements with regenerative medicine. For instance, stem cell therapies using mesenchymal and adipose-derived cells have shown promise for healing diabetic ulcers, and negative pressure wound therapy is now a standard treatment for chronic wounds. However, experimental therapies, like RNA-based and gene therapies, face challenges related to inconsistent results and safety, emphasizing the need for standardized protocols and larger trials. The implications of these findings are substantial. By integrating biomaterials such as chitosan or silk fibroin with bioactive compounds, wound dressings can actively promote healing. Nanomaterials improve drug stability and localized delivery, reducing side effects. Smart bandages and biosensors enable continuous monitoring, allowing for timely medical intervention and reducing unnecessary hospital visits. These innovations could significantly decrease the financial and healthcare burdens associated with chronic wounds, especially in diabetic individuals.

Despite these advancements, challenges remain. Safety concerns related to stem cell and gene therapies, high production costs of bioengineered products, and the complexities of scaling up these innovations hinder accessibility. Furthermore, preclinical successes often do not translate into clinical benefits because of differences in wound biology between species. Future research should aim to address these challenges through interdisciplinary collaboration. Advances in biomaterials and nanotechnology could provide safer, more affordable options for growth factors and RNA delivery. Standardizing cell preparation and refining dosing can improve the consistency of stem cell and gene therapies. Additionally, expanding clinical trial designs with larger sample sizes and consistent outcome measures is essential to validate therapeutic efficacy. Integrating digital health tools, such as AI monitoring and personalized treatment plans, will further enhance precision medicine in wound care.

9. Conclusion

Wound healing remains a significant clinical challenge, especially in chronic conditions such as diabetes, burns, and infections, where traditional therapies often fall short. This review highlights a shift from conventional symptomatic management to integrative approaches that actively promote regeneration. Complementary strategies—including stem cell therapy, gene delivery, and growth factor administration—target biological pathways directly. Additionally, biomaterials and nanotechnology improve drug stability, controlled release, and antimicrobial action. Advanced innovations such as injectable hydrogels, AI-enabled smart bandages, bioengineered skin substitutes, and RNA-based therapeutics showcase how technology can transform wound care into a personalized and precision-driven field. This synthesis offers a novel perspective by integrating biological, material-based, and digital innovations within a single framework. By connecting these diverse approaches, it outlines a roadmap for future research and clinical applications in wound care. However, challenges related to safety, cost, scalability, and regulatory approval must be addressed for widespread adoption. Looking ahead, interdisciplinary collaboration among clinicians, bioengineers, molecular biologists, and data scientists will be essential. With ongoing innovation and clinical validation, next-generation wound therapies have the potential to decrease healthcare burdens, enhance quality of life, and provide accessible, patient-centered solutions globally.

Compliance with ethical standards

Disclosure of conflict of interest

There is not conflict of interests.

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