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REVIEW

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Cutting edge strategies for diabetic wound care: Nanotechnology, bioengineering, and beyond

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Abstract

Diabetic wounds affect millions of people globally, posing significant clinical and socioeconomic challenges due to their prolonged healing times and risk of complications. This review provides a comprehensive examination of the pathophysiology underlying delayed wound healing in patients with diabetes, focusing on key mechanisms such as hyperglycemia, oxidative stress, vascular insufficiency, and chronic inflammation. Impairments in angiogenesis, growth factor signaling, and tissue regeneration create a complex therapeutic landscape that demands multifaceted approaches. Accordingly, this review critically examines current clinical interventions such as topical growth factors, antioxidant therapies, and hyperbaric oxygen. Furthermore, it explores innovative solutions, such as advanced wound dressings, bioengineered materials, and stem cell therapy, which offer enhanced wound healing outcomes. We provided a comprehensive analysis of innovative platforms, such as nanoparticle-loaded hydrogels and 3D printing, shedding light on their transformative potential to revolutionize wound care through personalized multifunctional therapies. This review concludes by identifying critical gaps and proposing a roadmap for future research and clinical innovations to enhance diabetic wound management and improve patient outcomes.

KEYWORDS

3D printing, diabetic wound healing, hydrogels, nanotechnology, regenerative medicine, stem cell therapy

1 | INTRODUCTION

Diabetic wounds are a diverse group of chronic wounds that arise due to the complex metabolic and vascular complications of diabetes.[1,2] They include diabetic foot ulcers (DFUs), non-healing post-surgical wounds, trauma-induced chronic wounds, venous and arterial ulcers, and pressure injuries.[3–5] These wounds are often slow to heal and highly prone to infection, frequently leading to hospitalization, amputation, and increased mortality.[6–9] DFUs affect 6.4% of people with diabetes globally, with 19%–34% developing one in their lifetime.[10] The 5-year mortality rate reaches 70% after major amputations, and 25% of diabetes patients suffer from poor wound recovery.[11] About 25.5% of diabetic chronic wounds are trauma-related and become non-healing due to neuropathy. Peripheral arterial disease occurs in over 40% of DFU cases, with arterial ulcers in 2.1% of diabetics.[12] Their complex treatment and recurrent nature lead to frequent outpatient visits and high infection risk, escalating healthcare costs. Diabetic wounds account for 25%–50% of diabetes treatment costs and are the leading cause of non-traumatic amputations in the United States.[13] Direct costs for diabetic foot care are $8659 per patient, with annual expenses ranging from $9 to $13 billion.[14] With global diabetes prevalence projected to reach 642 million by 2040, effective management strategies are urgently needed.[15]

Diabetic wound management faces significant barriers. Neuropathy, poor circulation, and immune dysfunction impair healing by reducing blood flow, oxygen delivery, and immune response at wound sites.[16,17] This environment promotes chronic inflammation and infection. Diabetes compromises immune cells such as neutrophils and macrophages, which are crucial for fighting infections and clearing wound debris.[18] Successful diabetic wound management requires collaboration between endocrinology, surgery, podiatry, and infectious disease specialists. This model strains healthcare resources, particularly in areas with limited access to wound care. Addressing these challenges requires innovative strategies combining nanotechnology with targeted drug delivery, immune modulation, and regenerative techniques to improve patient outcomes.[19,20]

Nanotechnology offers precision in drug delivery, improving the therapeutic index through targeted delivery mechanisms.[21–23] Various nanoparticles (NPs) such as lipid-based systems (e.g., liposomes),[24] polymeric NPs (PNPs),[25] metallic NPs (MNPs) (silver, gold, etc.),[26] and biopolymer-based carriers (e.g., chitosan)[27] have shown significant potential in diabetic wound care. These NPs enhance drug efficacy by allowing targeting of wound sites, facilitating better retention, penetration, and sustained release of therapeutic agents. LNPs improve wound healing by enhancing skin permeability, while MNPs exhibit antibacterial and pro-angiogenic properties crucial for treating chronic wounds.[28,29] Recent innovations in bioengineered scaffolds, hydrogels, and wound dressings further demonstrate the integration of nanotechnology with regenerative medicine.[30] These scaffolds, often infused with growth factors or stem cells, promote cellular proliferation, angiogenesis, and collagen deposition, crucial steps in diabetic wound healing. Biopolymer-based nanofibrous scaffolds, which can be functionalized with bioactive molecules, have emerged as powerful tools for enhancing wound closure and tissue regeneration. Additionally, 3D-printed hydrogel scaffolds offer tailored solutions by providing structural support and incorporating bioactive compounds that target inflammation and promote healing.[31]

Despite these advances, significant challenges remain in translating these therapies from the laboratory to the clinic. Issues such as biocompatibility, the precise regulation of drug release, and the scalability of manufacturing processes pose hurdles to their widespread clinical use. This review provides a comprehensive examination of the latest advancements in nanotechnology-driven drug delivery and bioengineered regenerative strategies for diabetic wound management. We explore cutting-edge approaches such as innovative hydrogels, PNPs, bioengineered scaffolds, and stem cell-based therapies, highlighting both their therapeutic potential in diabetic wound care. Furthermore, we discuss the integration of 3D/4D printing and artificial intelligence (AI) with various clinical interventions, emphasizing the need for continued research to optimize these treatments and improve patient outcomes.

2 | PATHOPHYSIOLOGICAL INSIGHTS INTO DIABETIC WOUND HEALING

Diabetic wound healing is a complex and multifactorial process, deeply affected by the underlying pathophysiological conditions associated with diabetes. Unlike normal wound healing, which follows a predictable sequence of tissue repair, diabetic wounds are characterized by delayed healing and an increased risk of complications such as chronic infections and amputations.[32]

With this framework in mind, it becomes essential to compare the structured process of normal wound healing with the pathological alterations in diabetic wounds, as illustrated in Figure 1. In normal wound healing (Figure 1a), the process unfolds through four well-coordinated stages: hemostasis, inflammation, proliferation, and remodeling. In hemostasis, platelets form fibrin clots to halt bleeding and provide scaffolds for cellular

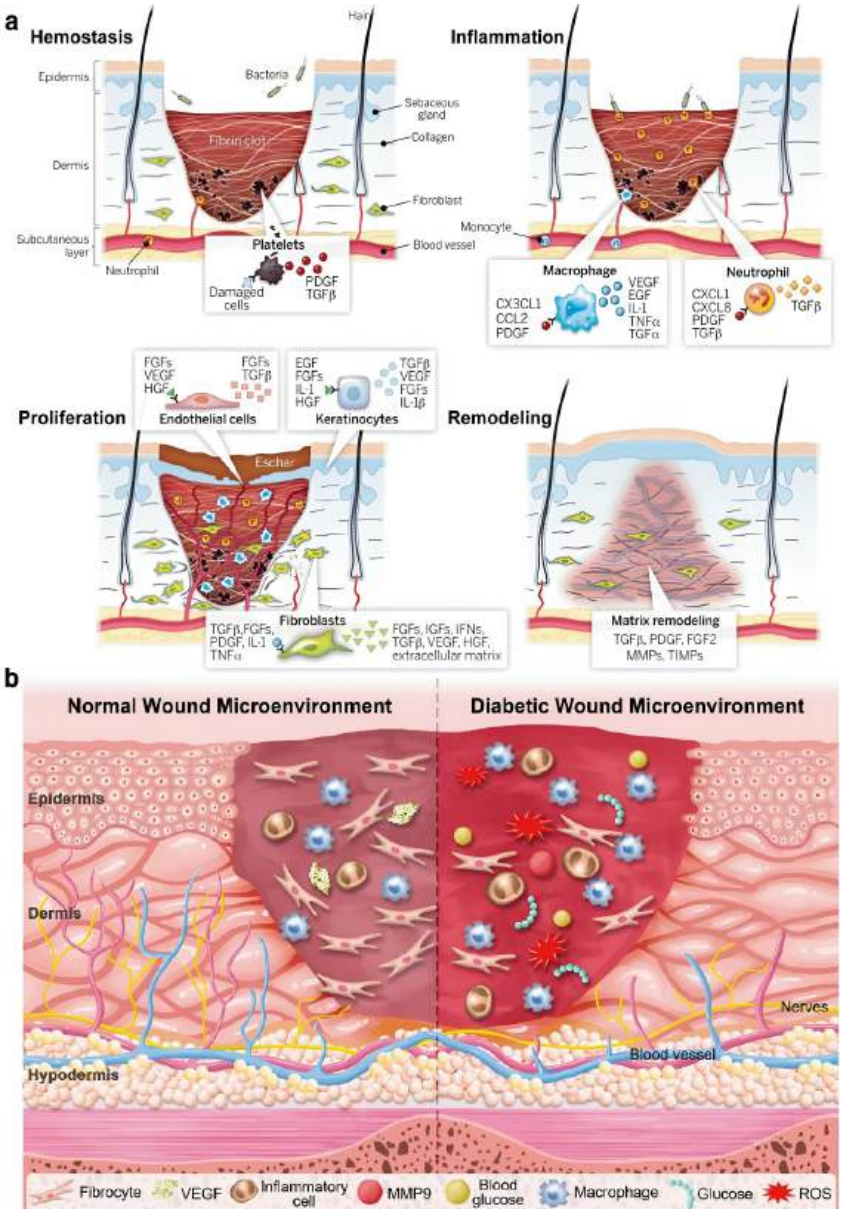

FIGURE 1 Comparison of normal and diabetic wound healing processes and microenvironments. (a) Schematic overview of healing processes, including (i) hemostasis and coagulation, (ii) inflammation, (iii) proliferation, and (iv) remodeling, in a normal wound. Reproduced under the term of the CC-BY license with permission from ref.[33] Copyright 2023, The Authors. (b) Differences between the normal wound microenvironment and the diabetic wound microenvironment, highlighting impaired angiogenesis, inflammation, and altered ECM composition in diabetic wounds. Reproduced under the term of the CC-BY license with permission from ref.[34] Copyright 2022, The Authors.

migration. During inflammation, neutrophils and macrophages release cytokines and growth factors (VEGF, PDGF, TGF-β) to activate immune cells and initiate repair. The proliferative phase involves fibroblasts and endothelial cells generating ECM components and stimulating angiogenesis. In remodeling, MMPs and TIMPs restructure the ECM to form mature scar tissue, enabling effective wound repair.[33]

In contrast, Figure 1b shows pathological disruptions in diabetic wounds. Hyperglycemia impairs healing phases, prolongs inflammation, and delays proliferation and remodeling. Reduced VEGF and PDGF levels impair angiogenesis, limiting oxygen and nutrient supply. Chronic inflammation persists due to pro-inflammatory cytokines, with macrophages favoring the M1 phenotype over the tissue-repairing M2 state. Elevated reactive oxygen species (ROS) and AGEs increase oxidative stress, damaging cellular components. Diabetic wounds show ECM dysregulation through excessive MMP activity and insufficient TIMP control, leading to tissue degradation.

This environment disrupts fibroblast function and collagen synthesis, highlighting the need for targeted therapies.[34] Further summarizing these disruptions, Figure 2 provides an overview of how hyperglycemia initiates multiple harmful pathways that impair diabetic wound healing (discussed in following subsections). Hyperglycemia disrupts wound healing and impairs cellular function and immune responses.[35] Vascular insufficiency in diabetic patients results in poor blood flow, limiting oxygen and nutrient delivery for tissue regeneration.[36] Additionally, the diabetic wound environment exhibits prolonged inflammation that hinders healing phases, while deficiencies in growth factors delay tissue regeneration.[37] Understanding these pathophysiological mechanisms is essential for developing targeted therapeutic strategies to improve wound healing outcomes in diabetic patients and hence discussed in the following subsections.

2.1 | Hyperglycemia and impaired wound healing

Hyperglycemia impairs wound healing in diabetic patients through harmful biochemical processes. A key mechanism is protein glycation, forming AGEs that accumulate in tissues and blood vessels.[38] In diabetic wounds, AGEs cause ECM and blood vessel stiffening, reducing elasticity and nutrient delivery.[39] AGEs also promote oxidative stress by stimulating ROS production and damaging cells and tissues. This activates pathways leading to nerve dysfunction and ischemia, which delay healing.[40] Another major factor impairing diabetic wound healing is the inhibition of neovascularization, where new blood vessels form to supply nutrients to damaged tissue.[41] Hyperglycemia impairs endothelial cell function, which is essential for blood vessel formation. High glucose levels cause excessive cell death in endothelial cells, disrupting angiogenesis and reducing vascularization.[42] Without adequate blood supply, the wound remains in a prolonged inflammatory state, unable to progress to the proliferative phase of healing, where tissue regeneration and repair occur.[15]

The diabetic environment shows dysregulation of growth factors such as VEGF and EGF, crucial for wound repair. Low levels of these factors delay wound closure.[43] Hyperglycemia alters immune and inflammatory responses, increasing pro-inflammatory cytokines TNF-α and IL-6 while reducing antioxidants. This imbalance leads to chronic inflammation in diabetic wounds, preventing healthy granulation tissue formation and promoting tissue degradation.[44] Chronic inflammation and oxidative stress form a feedback loop impeding diabetic wound healing, often leading to ulcers and increasing risks of infection, gangrene, and amputation.[45] The interplay of abnormal glycation, impaired angiogenesis, and inflammation creates significant challenges in managing diabetic wounds, where minor injuries can become serious threats.[46]

2.2 | Oxidative stress and tissue damage

Oxidative stress plays a critical role in diabetic wound pathophysiology, causing tissue damage and impaired healing.[45] Hyperglycemia leads to ROS overproduction, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, which damage cellular components.[47] The body's normal pro-oxidant/antioxidant balance is disrupted in diabetic patients due to high blood glucose, creating oxidative stress that impairs antioxidant defenses and leads to inflammation and delayed wound healing.[15,48]

In diabetic wounds, oxidative stress impairs fibroblasts, keratinocytes, and endothelial cells involved in healing.[49] Fibroblasts, which produce ECM and collagen for wound closure, are vulnerable to ROS, limiting tissue formation through reduced proliferation and migration.[50] Similarly, Oxidative stress causes endothelial cell apoptosis, compromising blood flow and delaying recovery. These cellular impairments maintain the wound in a chronic inflammatory state, preventing proper closure and regeneration.[51] Furthermore, oxidative stress contributes to AGE formation when proteins or lipids become glycated due to high glucose levels.[52] AGEs accumulate in diabetic tissues, causing vascular dysfunction and endothelial damage while activating inflammatory pathways.[53] This creates a cycle where oxidative stress and AGEs impair wound healing through reduced blood flow and persistent inflammation.[15,48]

Given the role of oxidative stress in diabetic wound pathology, managing it is crucial for healing. Strategies include antioxidant therapies to balance ROS production and antioxidant defenses, and treatments targeting oxidative damage. Reducing oxidative stress preserves fibroblast and endothelial cell function, promotes angiogenesis, and reduces inflammation, improving healing and lowering complication risks.[54]

2.3 | Vascular dysfunction and angiogenesis deficits

Vascular insufficiency significantly impairs diabetic wound healing by disrupting angiogenesis, the formation of new blood vessels that supply oxygen and nutrients.[55]

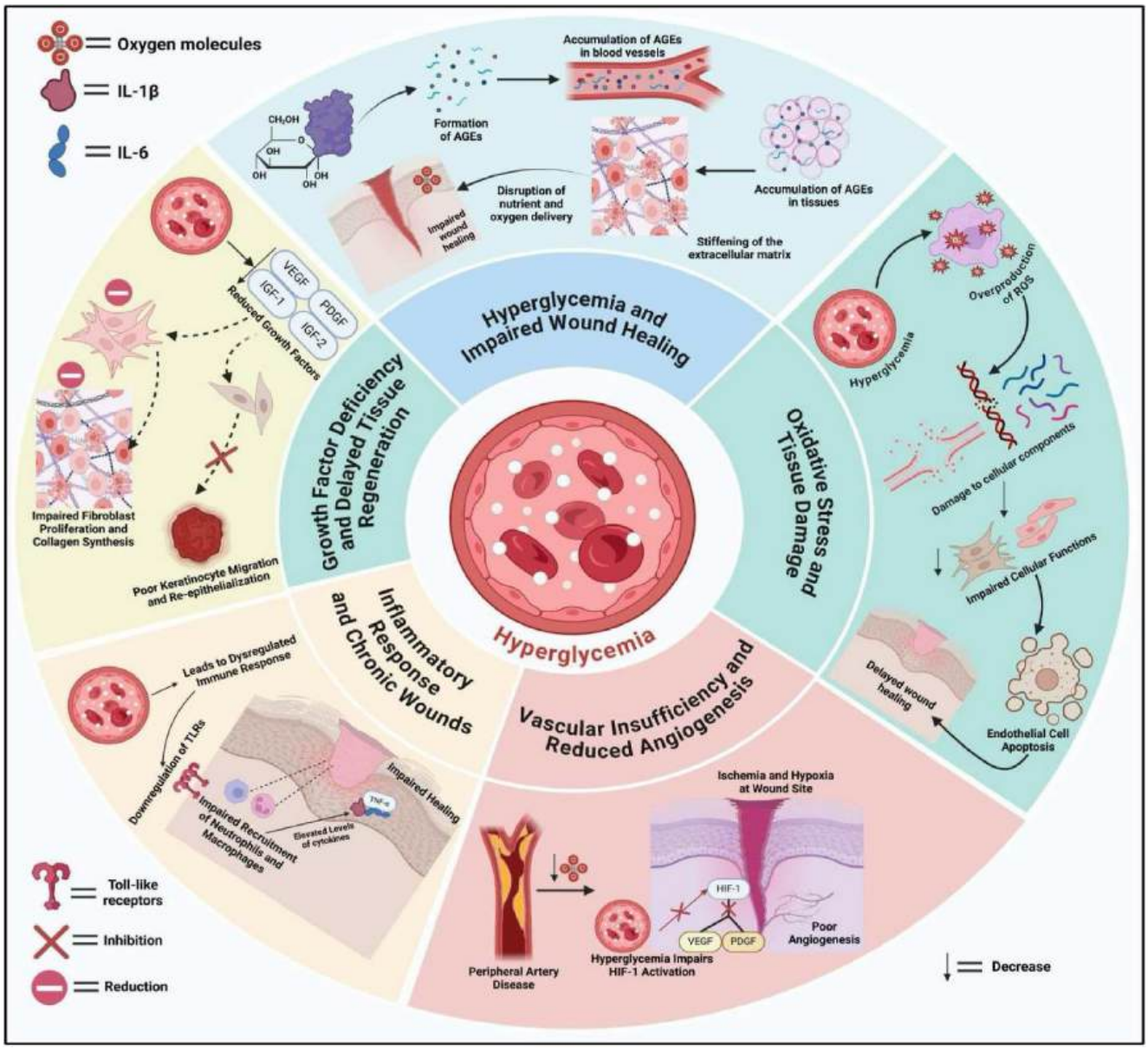

FIGURE 2 Figure demonstrates the pathophysiological mechanisms impairing diabetic wound healing. Chronic hyperglycemia leads to the formation of AGEs, inducing oxidative stress and endothelial dysfunction. Oxidative stress damages key cellular components, impairing fibroblast and endothelial cell function. Vascular insufficiency due to peripheral artery disease results in reduced angiogenesis and hypoxia at the wound site. A dysregulated inflammatory response and elevated pro-inflammatory cytokines prevent progression to the healing phase. Growth factor deficiencies further delay tissue regeneration and wound closure (created with Biorender).

In diabetic patients, peripheral artery disease disrupts blood flow to the extremities, causing ischemia and insufficient oxygen supply essential for healing. This hypoxic environment typically activates hypoxia-inducible factor-1 (HIF-1), a transcription factor that promotes angiogenesis by upregulating genes such as VEGF.[56]

However, in the context of diabetes, hyperglycemia disrupts HIF-1 function by inhibiting its stabilization and activity, preventing pro-angiogenic signals during hypoxia.[40] This impairs wound healing by reducing new blood vessel formation needed for oxygen and nutrient supply.[46] Diabetic wounds show decreased levels of angiogenic factors VEGF and PDGF, which are vital for angiogenesis.[57] VEGF promotes blood vessel growth, while PDGF aids cell recruitment for tissue repair.[57,58] This reduction in angiogenic factors impairs vascular development, leaving wounds ischemic and unable to heal properly.[13] Vascular damage and deficient angiogenic responses lead to chronic non-healing wounds in diabetic patients. These wounds remain inflammatory and fail to progress into healing phases.[59] Reduced blood flow and impaired angiogenesis delay healing and

increase the risks of infection, necrosis, and amputation. Addressing vascular insufficiency and enhancing angiogenesis are critical for diabetic wound care, with therapies focused on restoring blood flow.[15]

2.4 | Chronic inflammation and immune dysregulation

The inflammatory response in diabetic wounds shows excessive, prolonged inflammation that impairs healing.[60] While healthy wound healing involves brief inflammation followed by tissue repair,[61] diabetic wounds exhibit dysregulation. Downregulation of Toll-like receptors (TLRs) impairs pathogen recognition and immune responses.[60] This reduced TLR activity weakens inflammatory cell recruitment and immune defense, making diabetic wounds more prone to bacterial infections.[40]

Chronic diabetic wounds predominantly show M1 macrophages, which secrete pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β.[62] Although these cytokines initiate the immune response, their persistence leads to prolonged inflammation that impairs wound repair by hindering keratinocyte and fibroblast activity.[15,63] Moreover, the presence of elevated levels of AGEs in diabetic patients further exacerbates the inflammatory response.[64] Formed through non-enzymatic glycation during hyperglycemia,[65] AGEs interact with immune cells to maintain inflammation and disrupt collagen production.[46] The collagen that is produced in the presence of AGEs is often of poor quality, leading to fragile and dysfunctional scar tissue. Another critical issue in diabetic wounds is immune cell dysfunction. Neutrophils, the first responders in wound healing, show impaired function in diabetic patients, leading to inefficient bacterial clearance.[59] Macrophages fail to transition from pro-inflammatory M1 to anti-inflammatory M2 phenotype, preventing inflammation resolution and tissue repair. This traps the wound in chronic inflammation, halting the progression to healing phases.[15,66]

2.5 | Growth factor depletion and delayed regeneration

Growth factor deficiency significantly impairs healing in diabetic wounds.[67] In diabetic patients, essential growth factors for wound healing, including VEGF, PDGF, and insulin-like growth factors (IGF-1 and IGF-2), are reduced.[68] These factors are vital for angiogenesis, fibroblast proliferation, and ECM production.[69] VEGF stimulates angiogenesis to supply oxygen and nutrients, while PDGF and IGF-1/2 promote fibroblast activity for collagen and ECM production.[40,46]

Poor angiogenesis results in inadequate vascularization, depriving wounds of nutrients and oxygen needed for regeneration. The lack of PDGF and IGF reduces fibroblast proliferation and collagen synthesis, leading to weak granulation tissue formation.[70] Granulation tissue provides essential scaffolding for epithelial cell migration during re-epithelialization. Down-regulated growth factor receptors and rapid growth factor degradation further limit cellular response and bioavailability.[40] Diabetic wounds show an imbalance in ECM components and remodeling.[71] Excessive MMP activity, which degrades ECM proteins, is problematic in diabetic wounds. While MMPs normally break down damaged tissue, their overactivity hinders stable matrix formation for tissue regeneration. This imbalance and insufficient growth factor signaling impair normal wound healing.[40]

The combination of growth factor deficiency, poor ECM remodeling, and excessive MMP activity creates an environment where wounds remain chronically inflamed. This results in non-healing wounds in diabetic patients that resist conventional treatments. Understanding these mechanisms is crucial for developing targeted therapies like growth factor supplementation or ECM remodeling modulators to improve healing outcomes.[66]

A thorough understanding of the cellular and molecular disruptions in diabetic wounds, including impaired angiogenesis, persistent inflammation, and oxidative stress, lay the groundwork for identifying effective therapeutic strategies. With this foundation, the next section explores how current clinical interventions attempt to counteract these pathologies and promote wound resolution.

3 | CONTEMPORARY CLINICAL INTERVENTIONS IN DIABETIC WOUND HEALING

Current clinical interventions for diabetic wound healing focus on stimulating cellular proliferation and angiogenesis, along with antioxidant and anti-inflammatory therapies designed to mitigate oxidative damage and chronic inflammation. Additionally, hyperbaric oxygen therapy (HBOT) has shown promise in improving the oxygenation of ischemic tissues, thereby promoting wound healing. Advanced wound dressings and bioengineered materials offer improved moisture control, protection against infection, and enhanced tissue regeneration. Finally, regenerative approaches, including stem cell therapy, aim to restore functional

tissue by harnessing the body's inherent repair mechanisms.

3.1 | Topical growth factors and bioactive agents

Growth factors and bioactive compounds are crucial in resolving poor healing mechanisms in diabetic wounds. Growth factors such as EGF, VEGF, and PDGF promote wound healing by stimulating ECM production, angiogenesis, and fibroblasts.[40,46] In addition to these traditional growth factors, TGF-β and IGF-I show promise in modulating inflammation and promoting tissue remodeling.[58] While direct topical application delivers concentrated doses of growth factors, conventional delivery methods face challenges. The bioactivity of growth factors may be limited by rapid proteolysis and lack of structural support, reducing their effectiveness in chronic wounds.[72] However, conventional topical applications of growth factors often face challenges, including rapid degradation and limited bioavailability at the wound site, which can reduce their therapeutic impact.

Bioactive substances such as proteins, peptides, and hyaluronic acid (HA) oligomers in wound dressings enhance growth factor activity and support wound healing through increased blood flow and tissue formation. Hyaluronic acid oligomers promote granulation tissue production and re-epithelialization in diabetic wounds.[13,66] Innovative bioactive dressings are especially relevant for diabetic wounds, as they address delayed healing caused by oxidative stress, neuropathy, and poor vascularization. Biomaterial-based delivery systems like hydrogels and scaffolds provide structural support while protecting growth factors from degradation. These platforms counter impaired healing in diabetic patients through sustained growth factor release at wound sites. Gene-mediated delivery enables host cells to produce growth factors over time, offering a potential solution for chronic wounds.[40,72] Research shows nerve growth factors key role in wound healing by enhancing keratinocyte proliferation and angiogenesis, which are impaired in diabetic pathophysiology, accelerating diabetic wound healing. Advanced delivery systems with NGF and bioactive molecules provide effective diabetic wound care options.[46]

Integrating growth factors and bioactive compounds modulates diabetic wound healing by accelerating cellular processes while addressing oxidative stress and inflammation.[73,74] Despite their therapeutic potential, challenges such as growth factor instability, cost, and safety concerns persist, necessitating further research into optimized cost-effective delivery methods.

3.2 | Antioxidant and anti-inflammatory therapies

Given the complex relationship between oxidative stress and chronic inflammation in diabetic wounds, a multimodal approach incorporating antioxidant and anti-inflammatory therapies presents a promising pathway for treatment. Elevated oxidative stress leads to cellular dysfunction, prolonging healing and increasing infection risk.[40] In diabetic wounds, excess ROS production causes oxidative damage, impairing ECM protein synthesis critical for wound healing.[58] Novel therapies like nitric oxide-releasing NPs enhance antioxidant defenses and reduce ROS levels.[13] Additionally, natural products such as *Syzygium aromaticum* and *Moringa oleifera* promote healing by strengthening antioxidant defenses while alleviating inflammation.[58]

The inflammatory response influences wound healing through macrophage polarization. In diabetic wounds, pro-inflammatory M1 macrophages release cytokines like TNF-α and IL-1β, contributing to chronic inflammation that impairs healing.[75] Growth factors regulate inflammatory pathways and cellular responses, acting as key modulators in diabetic wound management.[46] Clinical studies show antioxidant and anti-inflammatory therapies enhance wound healing. Tejada et al. found that these treatments improved healing rates in diabetic patients.[44] The enhancement occurs through increased fibroblast and keratinocyte migration for collagen synthesis. Anti-inflammatory interventions reduce inflammatory response duration, helping prevent chronic ulcers.[76]

Despite the benefits of antioxidant and anti-inflammatory therapies, several considerations remain important. Individual response variability necessitates personalized treatment approaches. Treatment efficacy depends on diabetes severity, metabolic responses, and coexisting conditions. While antioxidant supplements are generally safe, monitoring for adverse effects and drug interactions is essential. Anti-inflammatory and antioxidant therapies in diabetic wound healing represent a promising approach to improve outcomes by reducing oxidative stress and modulating inflammation. However, additional research is needed to establish protocols and validate these therapies across patient populations.[58]

3.3 | Hyperbaric oxygen therapy

In the management of chronic DFUs, HBOT is gaining prominence as a viable clinical intervention. This therapeutic modality effectively targets tissue hypoxia, which

is a critical barrier in wound healing and a factor in preventing amputation by delivering 100% oxygen at pressures exceeding 1 atm. HBOT's therapeutic mechanisms center on enhancing oxygen availability in the wound microenvironment, which is indispensable for driving cellular processes involved in tissue repair and regeneration.

HBOT stimulates angiogenesis to restore blood flow to hypoxic tissues and enhances leukocyte activity for combating infections. Capo et al.[77] provided a HBOT treatment timeline showing biomarkers and wound closure evidence. The study showed reduced inflammatory cytokines TNF-α and IL-1β, demonstrating HBOT's anti-inflammatory effects in diabetic patients. Elevated growth factors TGF-β, PDGF, and HIF-1α promote angiogenesis and collagen synthesis. These findings highlight HBOT's benefits in wound healing by reducing inflammation and supporting tissue regeneration.[44,77] However, systematic reviews indicate uncertainty in HBOT's efficacy for accelerating wound healing or reducing amputation rates, particularly in patients without peripheral arterial occlusive disease.[78] While studies suggest 20 treatment sessions may be necessary for benefits, many trials show no significant differences between HBOT-treated and control groups, leading to cautious clinical application.

HBOT's clinical use faces challenges including high costs and specialized facility requirements, limiting accessibility in resource-limited settings. Potential adverse effects such as barotrauma, oxygen toxicity, and claustrophobia must be considered in risk-benefit analyses.[46,78] Therefore, optimal patient selection criteria and treatment protocols remain areas of active investigation. While HBOT offers value for diabetic wound healing, current evidence does not support its routine clinical use. Research continues to refine protocols, determine suitable patient populations, and clarify HBOT's role in healing outcomes. Ongoing studies will enhance our understanding of HBOT's efficacy and applications in chronic wound management.[79]

3.4 | Wound dressings and bioengineered materials

Advanced wound dressings maintain optimal moisture for effective wound healing by preventing desiccation and promoting cellular migration. Different dressing types address specific wound conditions. Hydrocolloid dressings create a moisture barrier effective for superficial wounds with minimal exudate.[58] Hydrogels benefit dry wounds by providing hydration and facilitating tissue repair, while foam dressings manage moderate to heavy exudates and offer protection for diabetic wounds.[40,46]

Bioengineered materials, including skin substitutes and scaffolds, serve as transformative solutions in diabetic wound care by mimicking natural skin's characteristics. Decellularized ECM-based scaffolds provide a supportive environment that enhances growth factors and improves nutrient delivery.[80] Collagen-based products promote cell adhesion and accelerate wound healing,[81] while biopolymers like chitosan and alginate offer antimicrobial properties and support tissue regeneration.[40] An investigation focused on using biopolymers (silk and gelatin (S/G)), modified with polyethylene glycol (PEG), to create a film combining mechanical stability with controlled drug release.[82] Varying silk-to-gelatin ratios in S/G films produced surfaces with different smoothness, affecting cell adhesion. PEG modification enhanced fluid uptake, essential for wound hydration. Wounds treated with PEG-modified ciprofloxacin-loaded S/G films showed rapid closure and collagen deposition by day 7, demonstrating the effectiveness of this bioengineered approach. The findings highlighted the potential of bioengineered polymeric materials to accelerate wound closure through a combination of mechanical support, antimicrobial action, and sustained drug release.

Growth factors incorporated into bioengineered materials represent a key advance in wound healing therapies. These materials deliver growth factors to wound sites, providing sustained release that stimulates angiogenesis and collagen synthesis. This targeted delivery maintains growth factor bioactivity and supports critical cellular processes.[46] The clinical efficacy of these advanced wound dressings and bioengineered materials is increasingly supported by the ongoing research and development. Research increasingly supports the efficacy of these advanced wound dressings. Novel technologies like NPs enhance material properties for growth factor delivery and antimicrobial action. Although initially costly, these treatments could reduce healing times and complications, leading to long-term cost savings in diabetic wound management.[83]

3.5 | Stem cell and regenerative therapies

Stem cell therapy represents a promising clinical intervention for diabetic wound healing by leveraging cells' regenerative potential. Mesenchymal stem cells (MSCs) are particularly effective due to their anti-inflammatory, immunomodulatory, and pro-angiogenic properties that improve the wound microenvironment.[84,85] MSCs and

other stem cells support wound healing through cellular proliferation and enhanced angiogenesis, while also improving islet engraftment and function in diabetic conditions.

Recent bioengineering advances have explored techniques to optimize MSC therapeutic efficacy. Encapsulating pancreatic islets within hydrogel polymers protects transplanted cells from immune rejection while enabling nutrient exchange and supporting wound healing in diabetic patients.[85] The integration of MSCs with decellularized pancreatic ECM has enhanced islet cell growth and insulin expression, addressing pathophysiological barriers in diabetic wound healing.[84] These bioengineered constructs improve cell viability within diabetic wounds. Stem cell-derived exosomes show promise as paracrine mediators of healing. Studies demonstrate that these exosomes stimulate macrophage autophagy, accelerating wound healing through enhanced tissue repair and reduced inflammation.[15,86,87] As a cell-free alternative to stem cell implantation, exosomes offer fewer safety concerns while maintaining regenerative effects. This approach allows easier scaling and standardization than whole-cell therapies, simplifying regulatory approval. Platelet-rich plasma and cell-based products show promise by providing growth factors that support angiogenesis and tissue regeneration.[86,88] Patient-specific factors such as vascular impairment and immune health may lead to inconsistent treatment outcomes.

Multiple stem cell sources including bone marrow-derived MSCs (BM-MSCs), adipose-derived stem cells (ADSCs), and human amniotic MSCs are under investigation. BM-MSCs have improved ulcer healing in diabetic patients, though adverse events necessitate careful monitoring.[56] ADSCs offer practical advantages due to their abundance and have shown efficacy in wound healing. Human amniotic MSCs may outperform autologous ADSCs in certain diabetic wound models.[58,89] Overall, stem cell therapy and regenerative approaches represent a significant advancement in the treatment of diabetic wounds. These therapies hold immense promise in improving healing outcomes by addressing the multifaceted challenges associated with impaired wound healing in diabetic patients.

Taken together, contemporary clinical interventions for diabetic wound healing span a broad spectrum, from conventional topical agent to advanced bioengineered constructs and regenerative therapies. Among them, topical growth factors and bioactive dressings offer a biologically targeted yet relatively accessible option, though challenges with degradation and delivery persist. Antioxidant and anti-inflammatory therapies, particularly those involving natural compounds and nano-enabled systems, are promising due to their ability to address the oxidative and inflammatory milieu but still require standardization in dosing and protocols. HBOT offers physiological benefits for oxygen-deprived tissues and supports angiogenesis, but its high cost and inconsistent evidence across patient subtypes limit its widespread use. In contrast, bioengineered dressings and scaffolds, especially those incorporating smart polymers and sustained drug delivery, provide structural and biochemical advantages, making them suitable for moderate to severe wounds with infection risk. Finally, stem cell-based approaches, including exosome therapy, are at the forefront of regenerative medicine with strong preclinical support for wound healing and immune modulation; however, scalability, cost, and long-term safety remain barriers to clinical integration. Overall, hybrid strategies that combine biophysical support (e.g., scaffolds or hydrogels) with bioactive or regenerative payloads (e.g., growth factors or stem cells) currently show the greatest potential for translation into personalized and effective diabetic wound therapies.

Despite their clinical utility, conventional therapies often fall short in providing sustained, targeted, and multifactorial healing support in diabetic wounds. This therapeutic gap has spurred the development of smart biomaterials and nanotechnology-based platforms, which are explored in the next section as next-generation solutions for improving wound healing outcomes.

4 | SMART BIOMATERIALS AND NANOTECHNOLOGY-DRIVEN STRATEGIES FOR DIABETIC WOUND HEALING

4.1 | Hydrogels: A classic choice with cutting-edge impact

Hydrogels, characterized by their three-dimensional cross-linked networks of water and polymers, have also gained substantial attention in diabetic wound management.[90] Their high-water content, adhesion, and mechanical strength make them ideal for mimicking the extracellular matrix. Hydrogels provide breathability and biocompatibility, maintaining optimal conditions for wound healing.[25] Moreover, their ability to act as drug delivery systems (DDSs) enhances therapeutic efficacy by encapsulating hydrophobic drugs and ensuring sustained localized release. Hydrogels can also be engineered to encapsulate NPs, combining the benefits of hydrogels with the targeted delivery and enhanced efficacy of NPs.[91] These NP-loaded hydrogels enable the sustained localized release of therapeutic agents such as

antimicrobial NPs or growth factors, which significantly improve healing outcomes. This integration of nanotechnology enhances the controlled release of drugs, reduces the need for frequent reapplication, and provides multifunctional effects, such as antibacterial, antioxidant, and anti-inflammatory properties, which are crucial for diabetic wound care. As a result, NP-infused hydrogels represent a versatile and powerful approach, offering both structural support and active therapeutic potential to treat chronic wounds.[92]

In an innovative investigation, the authors developed SMPAAM hydrogel, a sponge-like macro-porous poly AA co MADA material, for diabetic wound care.[81] The SMPAAM hydrogel demonstrated a synergistic combination of antibacterial and antioxidative effects, along with mechanical robustness, to support wound healing (Figure 3a). Synthesized via a redox reaction between Ti_3C_2 MXene and ammonium persulfate, this porous sponge-like hydrogel utilizes a copolymerization of acrylic acid and methacrylic acid derivative monomers. MXenes are versatile 2D materials widely used to create hydrogels with advanced functional properties.[93] The SMPAAM hydrogel demonstrated significantly enhanced healing over 14 days compared to other hydrogels and controls. Sequential wound images (Figure 3b) and histological analysis (Figure 3c) revealed accelerated wound closure, increased re-epithelialization, and reduced wound thickness, underscoring engineered hydrogels like SMPAAM's potential to address the specific healing challenges of diabetic wounds. An important advancement in these dressings is the incorporation of antimicrobial properties to address the high infection susceptibility in diabetic wounds. Embedded antimicrobial agents reduce bacterial load and infection risk, allowing unimpeded healing. This approach integrates moisture balance, infection control, and tissue regeneration for optimal healing.[94]

Researchers have recently developed an innovative hydrogel composite for diabetic wound management, demonstrating its potential through rigorous in vitro and in vivo evaluations. This novel composite, termed DSPVA, integrates silk fibroin and ROS-scavenging dendrimers into a PVA matrix. Their design leverages the unique benefits of each component: silk fibroin for mechanical resilience, dendrimers for antioxidative properties, and PVA for its structural integrity. Fabricated via gamma radiation, DSPVA hydrogels exhibit enhanced surface porosity and stability, crucial for cellular interaction and tissue regeneration. In vitro testing confirmed DSPVA's antioxidative efficacy (Figure 4a), where DSPVA-treated L929 cells demonstrated significantly reduced ROS levels, marked by decreased green fluorescence compared to controls. This reduction indicates the hydrogel's effectiveness in neutralizing oxidative stress, a common impediment in diabetic wound healing. In vivo studies using diabetic mice further validated DSPVA's wound-healing capabilities (Figure 4b–d). Over a 16-day period, DSPVA-treated wounds exhibited accelerated healing, with marked reductions in wound area relative to PVA-only and control groups. Quantitative analysis on day 10 showed a reduction in wound area to 30% in DSPVA-treated wounds versus 56.5% in controls (Figure 4c). Histological assessments (Figure 4d) highlighted enhanced re-epithelialization and collagen deposition, underscoring the hydrogel's ability to modulate the wound environment favorably. The findings position DSPVA hydrogels as promising candidates for advanced diabetic wound care by providing antioxidative protection and supporting cellular repair mechanisms.[95]

The safety and biocompatibility of advanced hydrogel systems are critical for their clinical translation, particularly in diabetic wound settings where tissue regeneration is often compromised. Recent in vivo studies have shown that hydrogels incorporating MXene nanosheets, such as Ti_3C_2-based formulations, exhibit favorable integration within polymer networks and maintain mechanical integrity during wound healing without producing toxic degradation products. These hydrogels are injectable, adhesive, and self-healing, making them suitable for chronic wound environments. Notably, MXene hydrogels have been shown to promote macrophage polarization toward the M2 phenotype, supporting anti-inflammatory responses and tissue regeneration, without inducing chronic inflammation or systemic toxicity.[96,97]

Similarly, dendrimer- and nanoenzyme-reinforced hydrogels, such as those incorporating MnO_2 nanosheets or ROS-scavenging dendrimers, exhibit excellent in vitro and in vivo biocompatibility. These materials support cell viability and promote fibroblast and keratinocyte proliferation without generating harmful byproducts. They effectively modulate the wound microenvironment by reducing oxidative stress and inflammation, with no evidence of adverse immune reactions or systemic toxicity in diabetic models.[98]

Hydrogels with photopolymerizable or photothermal agents such as polydopamine, ferric ion/polyphenol chelates, and niobium carbide offer additional therapeutic advantages through on-demand activation and localized heating. These platforms demonstrate robust hemostatic activity and antimicrobial effects while maintaining good tissue compatibility. Toxicological evaluations in animal models revealed no significant local irritation, inflammatory response, or systemic toxicity. In particular, niobium carbide-containing hydrogels have demonstrated hemocompatibility and

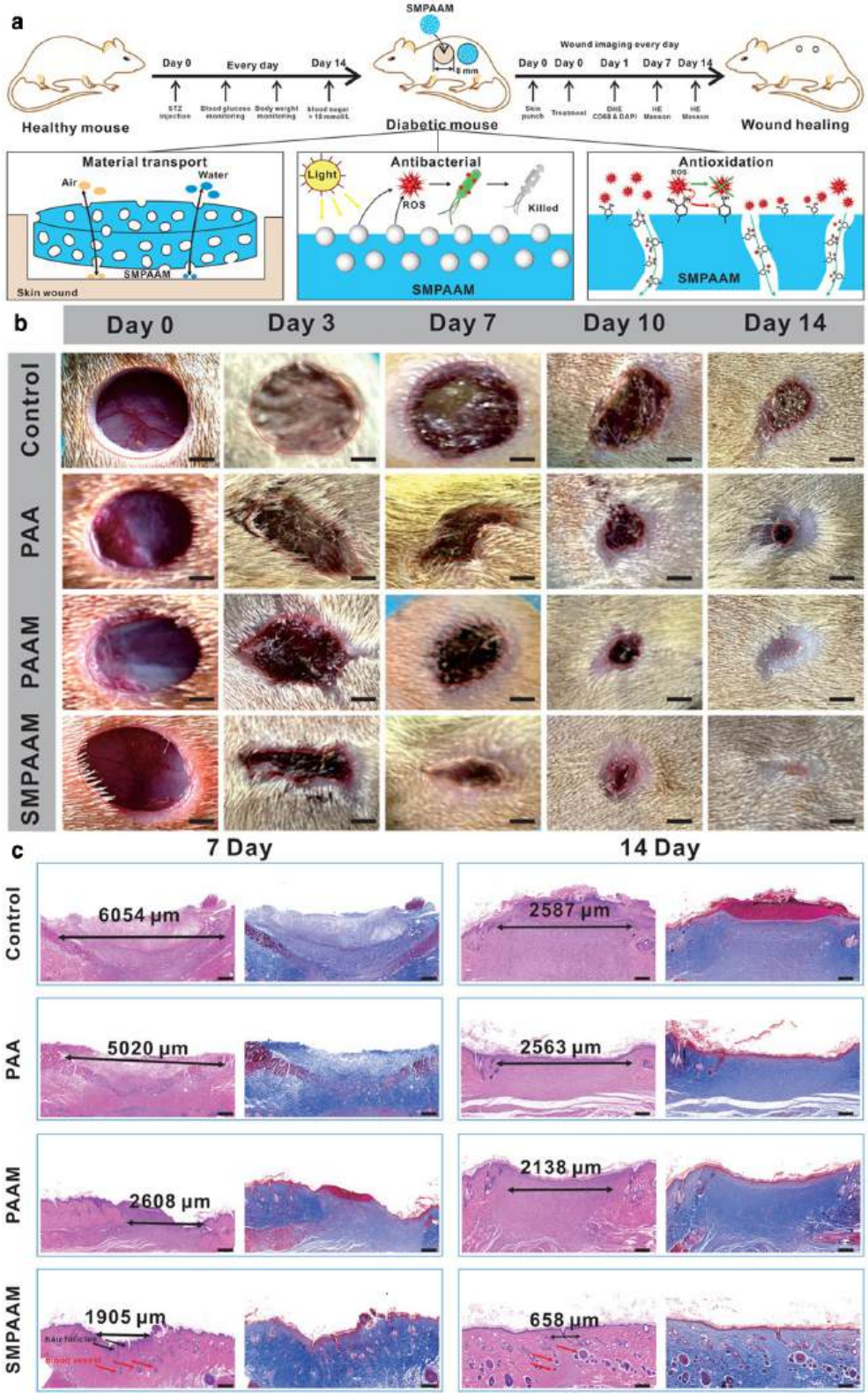

FIGURE 3 Enhanced wound healing with SMPAAM hydrogel in a diabetic mouse model. (a) Schematic of SMPAAM application and therapeutic mechanisms. (b) Sequential wound images over 14 days, showing accelerated closure in SMPAAM-treated wounds. Scale bar: 2 mm. (c) Histological analysis (hematoxylin and eosin or H&E and Masson's trichrome or MT staining) on days 7 and 14, indicating improved re-epithelialization and dermal remodeling with SMPAAM treatment. Scale bar: 500 μm. Reproduced with permission from ref.[81] Copyright 2022, WILEY-VCH.

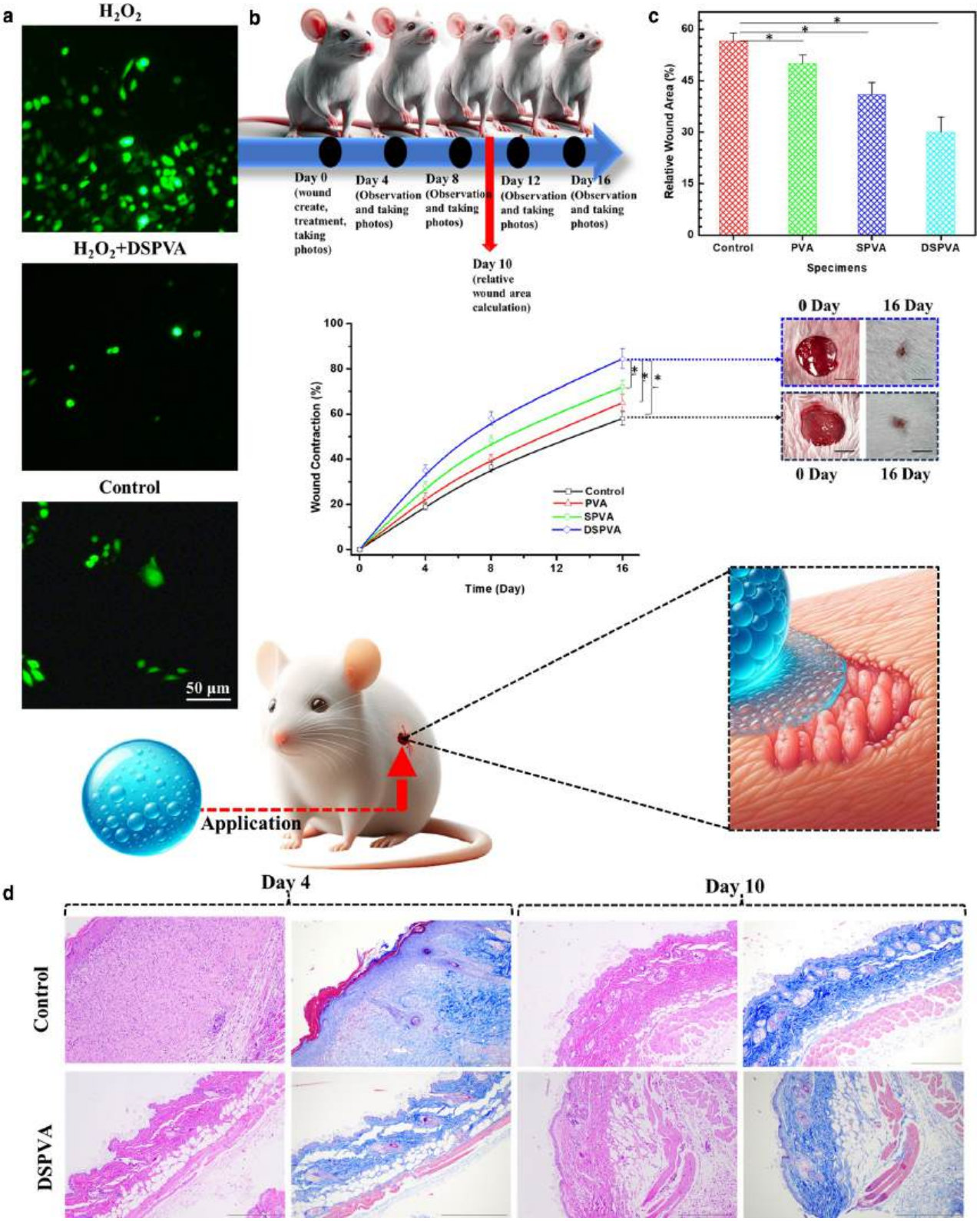

FIGURE 4 In vitro and in vivo antioxidant and wound healing performance of DSPVA hydrogels. (a) Fluorescence micrographs depicting the scavenging of intracellular reactive oxygen species in L929 cells challenged with H_2O_2, demonstrating the efficacy of DSPVA hydrogels in reducing oxidative stress. (b) Timeline and wound closure progression in DSPVA-treated diabetic mice (scale bar: 5 mm). (c) Quantitative wound area analysis on day 10. (d) Histological comparison on days 4 and 10 highlights accelerated healing in DSPVA-treated wounds (first and third column for H&E; second and fourth column for MT) (scale bar: 200 μm). Reproduced with permission from ref.[95] Copyright 2024, Elsevier.

biosafety, supporting their use in diabetic wound applications.[96,97,99]

4.2 | Nanoparticles: Lipidic, metallic, and polymeric carriers

Traditional diabetic wound treatments face significant challenges. While therapies like topical growth factors and HBOT show potential, they are limited by delivery, cost, and accessibility.[90] Stem cell therapy, though promising, faces complexity barriers.[100] In response to these limitations, novel approaches using advanced technologies are being investigated to improve targeted delivery and therapeutic efficacy.

Figure 5 outlines emerging diabetic wound care modalities, including nanotechnology solutions, biomolecular approaches, and regenerative cell therapies. Nanotechnology is particularly effective for precise drug delivery and tissue regeneration in diabetic wounds. The following sections examine how NP-based therapies are advancing wound management by addressing conventional treatment limitations. In diabetic wound healing, targeted drug delivery maximizes therapeutic efficacy while reducing systemic effects. Nanotechnology enables precise delivery of therapeutic agents to wounds. NPs penetrate tissue layers, control drug release, and protect bioactive molecules from degradation. This approach addresses challenges in diabetic wounds, including poor vascularization, inflammation, and microbial colonization. Various NPs (gold, silver, polymeric, lipid-based) provide multiple therapeutic functions such as angiogenesis, re-epithelialization, and antibacterial effects. Different NPs support each wound healing phase (hemostasis, inflammation, proliferation, remodeling), demonstrating nanotechnology's versatility in delivering stage-specific treatments. The following subsections explore lipid, metallic, and PNPs in diabetic wound care.

4.2.1 | Lipid nanoparticles

Lipid nanoparticles (LNPs) have emerged as a promising tool for targeting diabetic wound healing. They offer advantages like improved drug stability, targeted delivery, and controlled release to enhance healing in diabetic wounds.[101] LNPs can modulate cellular processes, reduce inflammation, and promote angiogenesis to accelerate wound healing. For instance, ionizable LNPs have been employed to deliver VEGF-A mRNA, which enhances endothelial cell proliferation and accelerates wound healing by promoting vascular regeneration.[102] Such approaches highlight the role of LNPs in directly addressing the impaired vascularization that often hampers diabetic wound healing.

Researchers developed a trisulfide-derived LNP (TS LNP) to encapsulate IL4 mRNA to reprogram the wound microenvironment by targeting ROS and modulating immune responses.[103] This nanoformulation enables ROS scavenging and immune modulation (Figure 6a). IL4 mRNA delivery promotes macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 type, supporting wound repair. Fibroblasts treated with TS2-IL4 LNP showed enhanced viability under oxidative stress (Figure 6b) and reduced intracellular ROS (Figure 6c). In diabetic mice, TS2-IL4 LNP treatment resulted in faster wound closure compared to controls (Figure 6d,e), suggesting a safe and effective strategy for treating diabetic wounds through ROS scavenging and immune modulation. LNPs have been used to enhance ASCs' regenerative capacity for tissue repair. A study using isomannide-derived LNPs (DIM1T LNPs) reprogrammed ASCs by delivering saRNA and E3 mRNA, modulating immune responses and extending protein expression.[104] The engineered ASCs (DS-ASCs) showed sustained production of HGF and CXCL12, crucial for wound healing. In a diabetic wound model, DS-ASCs outperformed wild-type ASCs in promoting wound closure and tissue repair, demonstrating LNPs' effectiveness for engineering ASCs and improving their therapeutic potential.

Nanostructured lipid carriers (NLCs) offer a promising approach for delivering drugs in diabetic wound treatment due to their ability to provide sustained release, improve drug stability, and minimize systemic exposure. In one study, NLCs were used to encapsulate recombinant human thrombomodulin (rhTM), enhancing its therapeutic effect on chronic wounds.[105] The incorporation of carbopol created a stable rhTM NLC-gel, maintaining stability and prolonged release over 12 weeks while improving cell migration in human epidermal keratinocytes. With 92% encapsulation efficiency and sustained release for 72 h, the system promoted wound healing while reducing systemic exposure. Another study showed that NLCs loaded with 20(S)-Protopanaxadiol promoted wound closure and vascular regeneration in chronic diabetic wounds.[106] These findings demonstrate NLCs as an effective platform for delivering therapeutic agents in diabetic wound management.

Hou et al. developed hypahorine (HYP) encapsulated in liposome NPs (HYP-INPS) to enhance diabetic wound healing by modulating inflammation.[107] In diabetic wounds, excess pro-inflammatory M1 macrophages impede healing. Encapsulating HYP, an anti-inflammatory compound, within liposomes enabled

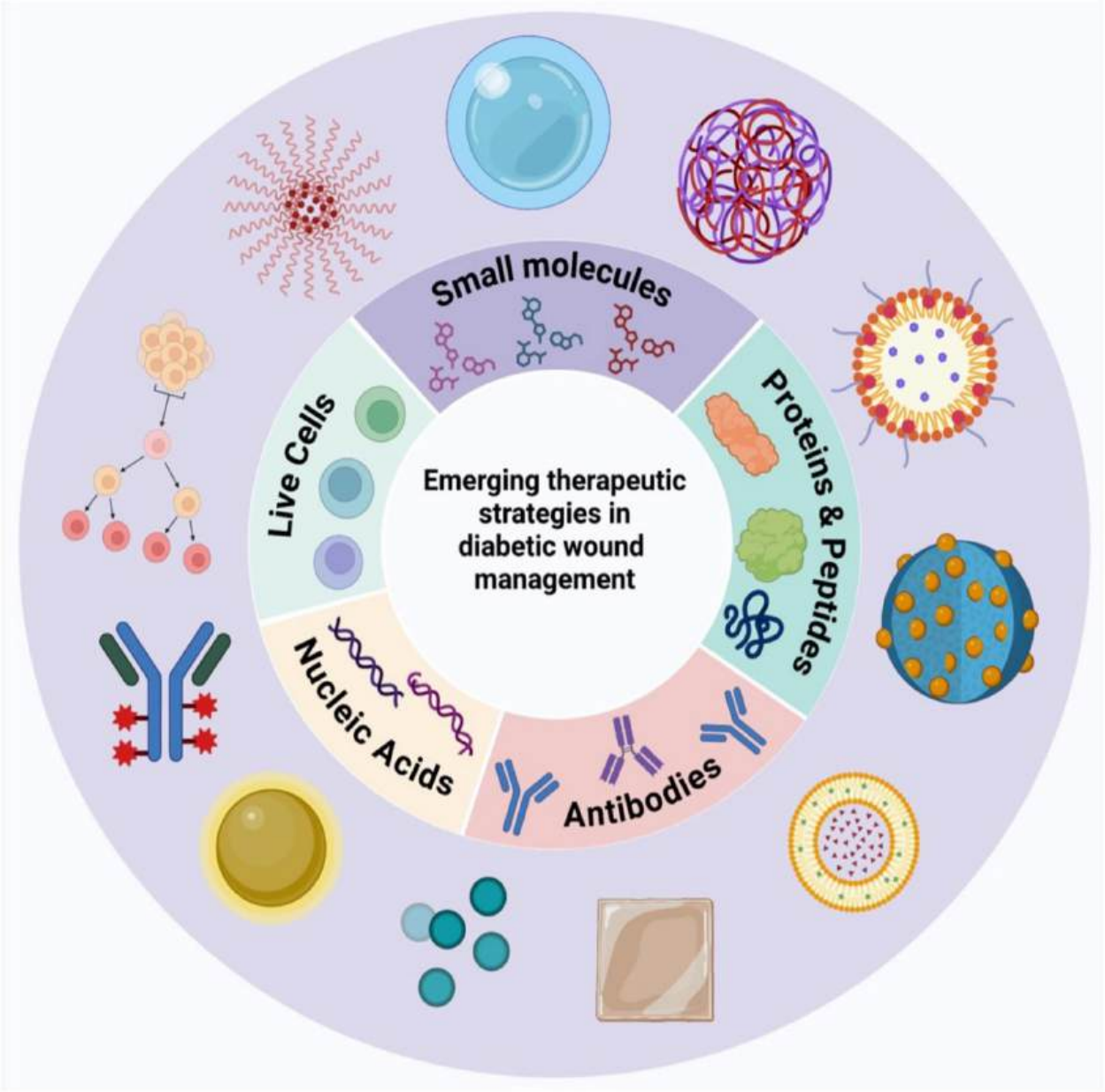

FIGURE 5 Emerging therapeutic strategies in diabetic wound management (created with Biorender).

selective suppression of M1 macrophages while promoting the anti-inflammatory M2 phenotype, as shown in Figure 7a. Studies on bone marrow-derived macrophages showed that HYP-INPS reduced M1 activity, enhanced cell migration, and increased M2 macrophage presence, with ASB10 identified as a key regulator in the M1 to M2 transition. In diabetic rats, HYP-INPS accelerated wound closure and reduced inflammation. The sustained release from liposomes prolonged therapeutic effects, demonstrating HYP-INPS's potential for treating chronic diabetic wounds.[107] Excessive inflammatory response is a major challenge for diabetic wound healing, hindering recovery. Bacterial toxins like α-hemolysin (Hlα) exacerbate inflammation and delay healing. Tang et al. developed red blood cell membrane-mimicking liposomes (RC-Lips) loaded with curcumin to address this issue.[108] These liposomes adsorb Hlα, reducing its damaging effects on keratinocytes (Figure 7b). In diabetic mice with infected wounds, RC-Lips enhanced wound healing and re-epithelialization, decreased IL-1β levels, and increased IL-10, indicating successful inflammatory response modulation and M2 macrophage polarization. The results demonstrate the potential of liposomes for managing diabetic wounds.

In recent years, nanoemulsions have shown significant promise as an advanced therapeutic strategy for diabetic wound healing, offering advantages in skin permeation, controlled release, and fibroblast cell

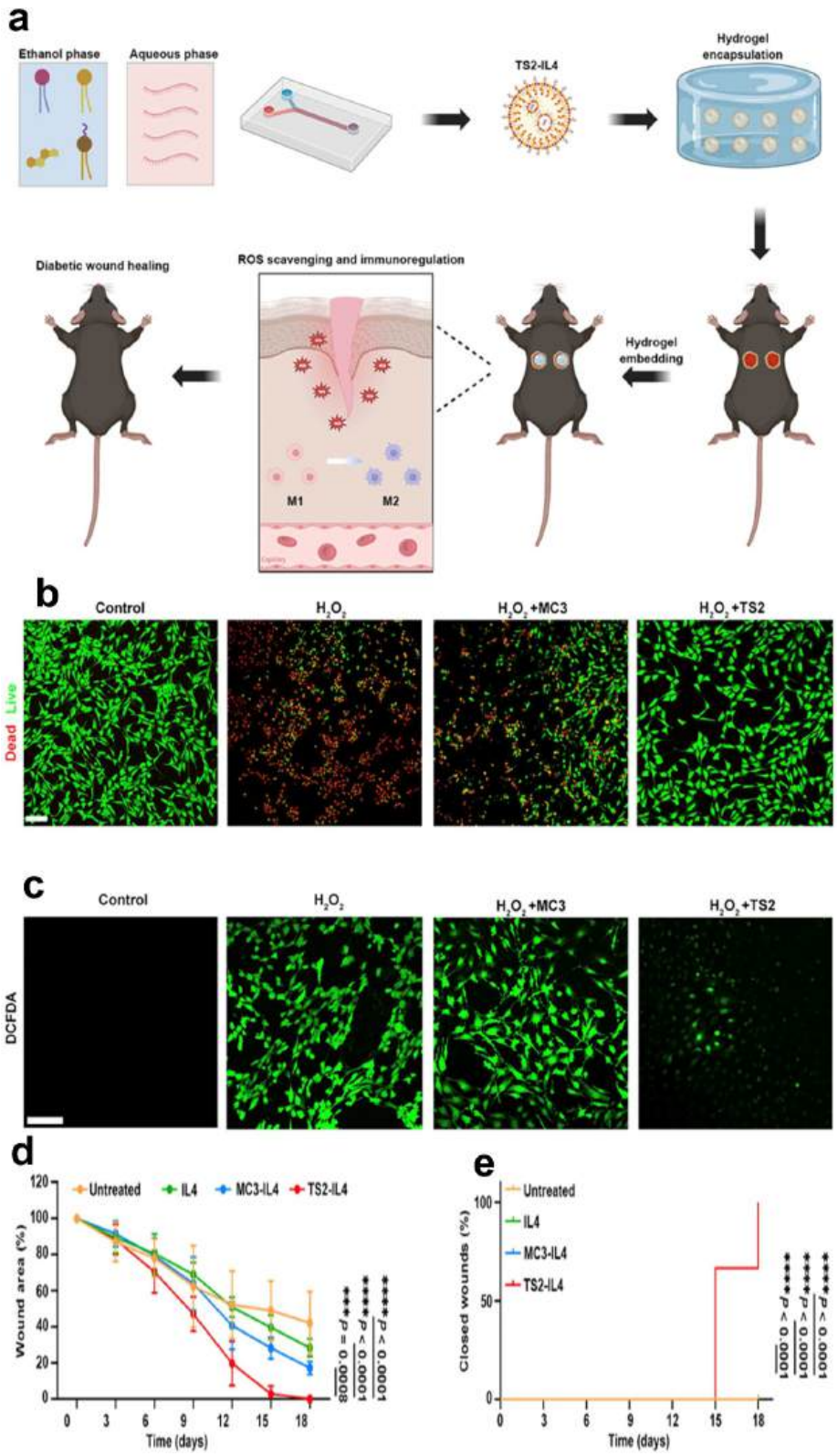

FIGURE 6 (a) Synthesis and therapeutic action of TS2-IL4 LNP-mRNA in a hydrogel for diabetic wound healing, promoting ROS scavenging and M2 macrophage polarization. (b) Fibroblast viability under oxidative stress with TS2-IL4 LNP treatment, showing increased live cells (green) and reduced dead cells (red) (scale bar: 100 μm). (c) Reduced intracellular ROS in fibroblasts treated with TS2-IL4 LNP (scale bar: 100 μm). (d) Wound area reduction over time, with TS2-IL4 LNP treatment accelerating closure. (e) Complete wound closure timeline for each treatment group, with TS2-IL4 LNP showing the fastest closure. Reproduced under the term of the CC-BY license with permission from ref.[103] Copyright 2024, The Authors. LNP, lipid nanoparticles; ROS, reactive oxygen species.

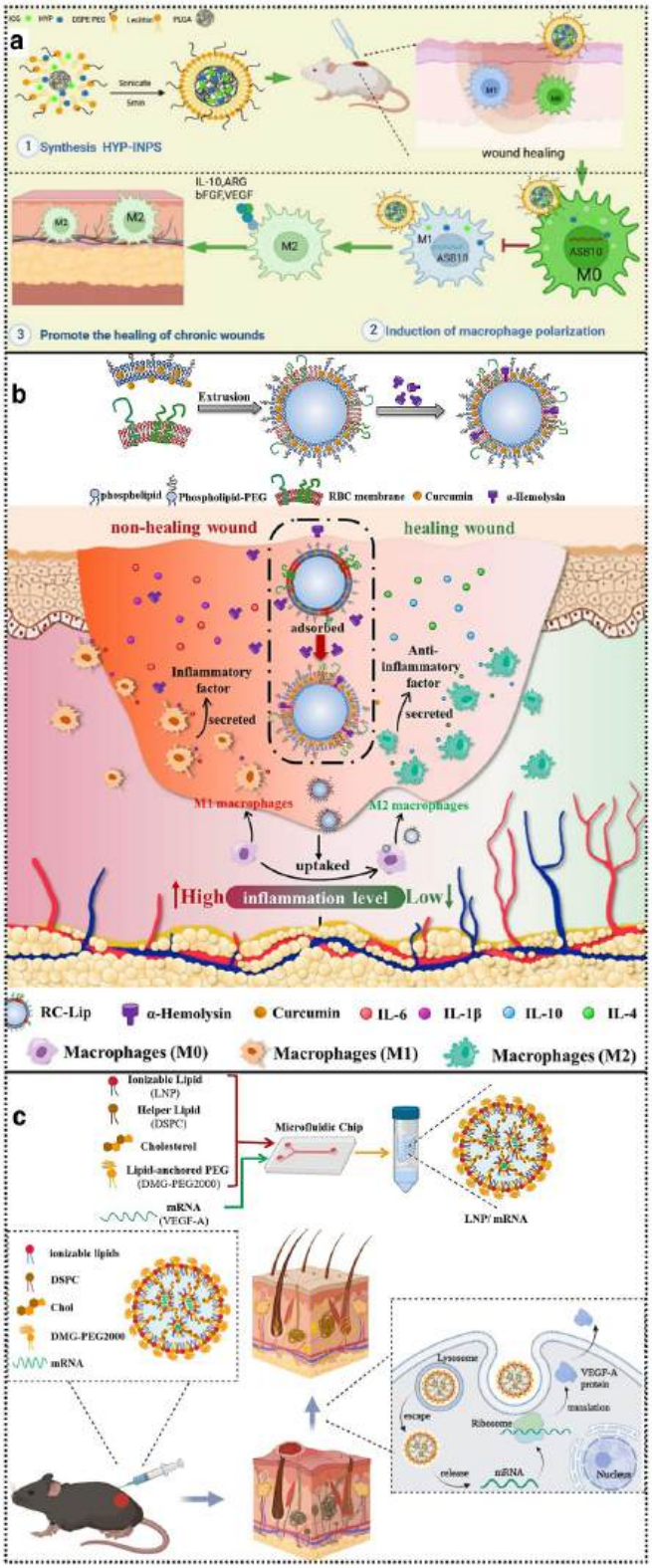

FIGURE 7 Legend on next page.

proliferation, crucial for wound healing processes.[109,110] The need for improved therapies has driven innovation in multifunctional lipid nanoemulsions. A nanoemulsion containing quercetin, chlorine e6, and rosemary oil (QCRLNEs) demonstrated effective anti-inflammatory and antibacterial properties under NIR irradiation, showing significant wound closure and antimicrobial effects while minimizing cytotoxicity. In vivo zebrafish studies revealed QCRLNEs' biocompatibility and enhanced wound healing capabilities for infectious diabetic wounds.[111] Research on nanoemulsions using collagen peptides from sturgeon fish skin evaluated antidiabetic and wound-healing effects in mice.[112] The low-MW and high-dose nanoemulsion enhanced diabetic wound healing by 95.53% and reduced fasting blood glucose levels by 46.75%. These results indicate that nanoemulsions from sturgeon fish skin collagen peptides show potential for diabetic wound healing applications.

LNPs are also used to deliver growth factors to wound sites. In an innovative approach, Zha et al.[102] developed LNPs encapsulating VEGF-A mRNA to promote angiogenesis and accelerate wound healing in diabetic wounds (Figure 7c). The LNPs, made via microfluidic chip, showed spherical morphology with 101 nm size and negative zeta potential. Studies in diabetic mice showed that LNP/VEGF-A mRNA treatment led to almost complete wound closure by day 14 compared with controls. The NPs enabled mRNA release within cells, producing VEGF-A protein that enhanced endothelial cell function and vessel formation (Figure 7c). Histological analysis showed improved epithelialization and vessel density in treated wounds, demonstrating the potential of LNP-based mRNA delivery systems in diabetic wound care.

Accumulating evidence indicates that application of LNPs in diabetic wound healing is multifaceted, involving the modulation of inflammatory responses, promotion of angiogenesis, and enhancement of tissue regeneration, thereby offering a promising avenue for the development of effective therapeutic strategies for diabetic wounds.[113,114] A comprehensive overview on the role of LNPs in diabetic wound healing is described in Table 1.

4.2.2 | Metallic nanoparticles

MNPs show promise for diabetic wound healing due to their unique properties. MNPs made from silver, gold, and zinc promote wound healing and prevent bacterial infections through their large surface area, enhancing tissue interaction and drug delivery.[122,123] However, their biological effectiveness depends on particle size, shape, surface charge, and synthesis method, which impact their antibacterial efficacy, stability, and cytocompatibility.[124,125]

The unique properties of AgNPs, including broad-spectrum antimicrobial activity, low cytotoxicity, and efficacy at lower concentrations, make them suitable for wound healing.[126] Combining AgNPs with quercetin provides synergistic effects, enhancing antimicrobial efficacy and re-epithelization in diabetic wounds.[115] The combined use of nano-silver dressings with EGF accelerated wound healing and reduced bacterial culture rates after treatment, creating a favorable environment for wound repair in diabetic foot patients.[127] Biosynthesized MNPs, particularly Ag and Au nanocomposites, offer potential for enhanced wound healing in diabetic patients by combining noble metals with plant extracts. Biosynthesis using plant extracts like *Solenostemma argel*, *Trigonella foenum-graecum*, and *Cinnamomum cassia* produces MNPs with antibacterial properties due to bioactive molecules capping the NPs surface. This nanocomposite approach presents a novel therapeutic strategy for diabetic wounds.[128]

AuNPs show promise in treating diabetic wounds through antibacterial, anti-inflammatory, and pro-angiogenic properties. Meng et al.[116] developed chitosan-modified Au NPs (CS-AuNPs) in hydrogel dressings (Gel/CS-AuNPs) for diabetic wounds. The dressings were created by cross-linking CS-AuNPs with gelatin and sodium alginate (SA), producing biodegradable hydrogels with water absorption properties (Figure 8a). Gel/CS-AuNPs showed strong antibacterial effects against gram-negative and gram-positive bacteria, including MRSA (Figure 8b). In diabetic rats, Gel/CS-Au25 enhanced wound healing by reducing inflammation, promoting

FIGURE 7 (a) Synthesis and encapsulation of HYP within liposomes, with subsequent in vivo application. Mechanism of action showing HYP-INPS-induced polarization of M1 to M2 macrophages, thereby enhancing wound healing through inflammatory modulation and ASB10 regulation. Reproduced with permission from ref.[107] Copyright 2024, Wiley-VCH. (b) Schematic of the preparation and function of RC-Lips. Preparation of RC-Lips by fusing liposomes with red blood cell membranes through extrusion (upper one). Mechanism of action showing how RC-Lips adsorb Hlα, reducing inflammation by releasing curcumin, modulating macrophage polarization, and promoting healing in diabetic wounds (lower one). Reproduced with permission from ref.[108] Copyright 2023, Elsevier. (c) Schematic diagram of the LNP/VEGF-A mRNA complex prepared using a microfluidic chip (upper one). Mechanism of LNP/VEGF-A mRNA in diabetic wound healing, illustrating cellular uptake and subsequent VEGF-A protein expression to promote angiogenesis and wound repair (lower one). Reproduced with permission from ref.[102] Copyright 2022, Elsevier. HYP, hypahorine; LNP, lipid nanoparticles.

TABLE 1 Comprehensive overview of nanoparticle-based therapeutics for diabetic wound healing.

Category	Intervention/ technology	Mechanism of action	Target pathway/ cells	Wound type	Key results	Advantage	References
Lipid nanoparticles	VEGF-A mRNA-LNP	Facilitates angiogenesis and vascular regeneration	Endothelial cells	Diabetic ulcers	Particle size: 101 nm; complete wound closure by day 14	Direct vascular targeting	[102]
	TS2-IL4 LNP	ROS scavenging; immune modulation through M1 to M2 macrophage polarization	ROS, macrophages	Diabetic wounds	Complete healing; ROS reduction; faster closure in diabetic mice	Targets immune pathways; multifunctional	[103]
	rhTM-NLC; 20 (S)-protopanaxadiol NLC	Sustained drug release; encapsulates therapeutic agents	Epidermal keratinocytes	Chronic wounds	Encapsulation efficiency: 92%; sustained release for 72 h	Prolonged therapeutic effect	[105]
	Curcumin liposomes (RC-lips)	Adsorbs bacterial toxins; modulates inflammatory cytokines	Bacterial toxins, IL-1β, IL-10	Infected diabetic wounds	Reduced IL-1β, elevated IL-10; accelerated epithelialization	Anti-inflammatory; bacterial toxin neutralization	[109]
Metallic nanoparticles	Nano-silver dressings with EGF	Broad-spectrum antimicrobial; re-epithelialization	Bacteria, inflammatory pathways	Diabetic wounds, infections	Lower bacterial culture rates; accelerated granulation	Effective at low concentrations	[115]
	Gel/CS-AuNP hydrogel dressings	Antimicrobial and pro-angiogenic; incorporated into hydrogel dressings	MRSA, epithelial cells	Infected diabetic wounds	95.3% MRSA inhibition; reduced inflammation; increased collagen deposition	Combats antibiotic-resistant infections	[116]
	Zinc sulfide NPs	Promotes cell migration and wound closure	Fibroblasts, keratinocytes	Chronic wounds	Accelerated wound closure and cell migration	Effective cell stimulation; scalable	[117]
	Metal-phenolic nanozymes (TA-Fe/Cu)	Photothermal and peroxidase-like activity; promotes angiogenesis	Biofilms, oxidative stress	Chronic wounds	Biofilm eradication, vascular regeneration; reduced oxidative stress	Multifunctional for infection and healing	[118]
Polymeric nanoparticles	Chitosan-CeO_2 NPs in nanofibers	Antioxidant and antibacterial; encapsulated in nanofibers	Fibroblasts, *S. aureus*	Diabetic wounds	Antibacterial MIC <58.59 μg/mL; 95.47% healing in 15 days	High cell migration rates	[119]
	Gelatin-based AST PNPs	Sustained asiaticoside release; promotes collagen biosynthesis	Collagen synthesis pathways	Diabetic ulcers	Superior healing outcomes; sustained release of asiaticoside	Prolonged therapeutic action	[120]
	DSPVA hydrogel composite	ROS scavenging; supports antioxidative and cellular repair	ROS, L929 cells	Diabetic wounds	30% wound area on day 10 versus 56.5% in controls; enhanced re-epithelialization	Multifunctional: Antioxidative and structural	[95]

TABLE 1 (Continued)

Category	Intervention/ technology	Mechanism of action	Target pathway/ cells	Wound type	Key results	Advantage	References
	HA-curcumin coordination NPs	Combines anti-inflammatory and regenerative properties	Macrophages, angiogenic pathways	Chronic wounds, infections	Enhanced diabetic wound healing and bacterial control	Dual-action: Infection and regeneration	[121]

angiogenesis, and increasing collagen deposition. SEM analysis confirmed bacterial cell damage after treatment (Figure 8c), demonstrating Gel/CS-AuNPs as a viable solution for diabetic wounds with antibiotic-resistant infections.[116]

Advanced applications of AuNPs show promising antibacterial and wound-healing effects through photothermal properties. Zhao et al.[129] developed Au NCs@PCN, combining gold nanoclusters with zirconium-based porphyrin metal-organic frameworks for treating diabetic wound infections (Figure 8d). This nanoplatform acts as an antibacterial agent through photothermal effects and ROS generation under NIR laser irradiation. The 190 nm Au NCs@PCN particles reached 56.2°C within 15 min of NIR exposure (Figure 8e), disrupting the bacterial membranes and achieving high inhibition rates for MRSA (95.3%) and Amp^r *E. coli* (90.6%). In diabetic rats, Au NCs@PCNs with NIR treatment showed nearly complete wound closure after 21 days, with enhanced angiogenic and epithelial proliferation factors (Figure 8f). These results demonstrate Au NCs@PCN's potential as a therapeutic tool combining nanozyme activity with photothermal antibacterial effects for infected diabetic wounds.[129]

Despite therapeutic potential, cytotoxicity remains a challenge for MNPs, particularly at higher concentrations where they may induce oxidative stress. Ag NPs can be cytotoxic at 2–5 μg/mL in human skin fibroblasts, leading to mitochondrial dysfunction and ROS generation.[126] AuNPs show lower toxicity,[130] though this varies with particle properties, as rod-shaped AuNPs exhibit higher cytotoxicity than spherical ones, requiring careful design for clinical use.

In addition to Ag and Au, Zn-based MNPs, particularly ZnO-NPs biosynthesized through eco-friendly methods, show therapeutic potential in diabetic wound healing through their anti-inflammatory, antibacterial, and pro-regenerative properties. ZnO-NPs synthesized with *Althaea officinalis* extract in chitosan gel demonstrated anti-inflammatory effects by regulating cytokines, enhancing wound healing in diabetic models.[131] Soliman et al. developed a biocompatible ZnO-NP formulation using *A. officinalis* extract in 2% chitosan gel. This A. O.-ZnO-NPs-CS gel combines antioxidant, anti-inflammatory, and antibacterial properties for diabetic wounds. Studies in diabetic rats showed that the gel reduced pro-inflammatory cytokines while increasing anti-inflammatory IL-10, creating favorable conditions for accelerated healing.[132] Further extending the applications of Zn-MNPs, Xiang et al. developed a cascade nanoreactor hydrogel (Arg@Zn-MOF-GOx Gel, AZG-Gel) incorporating an arginine-loaded Zinc metal organic framework and GOx. The hydrogel addresses diabetic wound healing by using GOx to reduce glucose levels and pH, while producing hydrogen peroxide to combat infections and inflammation in diabetic wounds.[133] Hu et al. developed a Zn-MOF loaded with berberine (BR@Zn-BTB NPs) in a ROS-scavenging hydrogel. This system reduces oxidative stress, promotes collagen synthesis, and accelerates wound closure in diabetic models, demonstrating Zn-MNPs' efficacy in tissue regeneration.[134]

Copper and iron show promise for diabetic wound management through metal-phenolic nanozymes (TA-Fe/Cu nanocapsules), which combine photothermal antibacterial properties, peroxidase-like activity, and copper's angiogenic effects. These nanozymes fight biofilms, reduce oxidative stress, and promote vascular regeneration, addressing infections and inflammation in diabetic wound healing.[118] Insulin-cobalt core-shell nanoparticles merge insulin's healing properties with cobalt's stability and fluorescent characteristics for therapeutic and bioimaging applications, offering dual benefits for diabetic wounds.[135]

The integration of MNPs with hydrogels and chitosan has created novel dressings that provide stable conditions for wound healing.[125] These composites enhance MNP efficacy through sustained release, biocompatibility, and moisture retention; key factors for diabetic wound healing. Green synthesis using plant extracts produces MNPs with antimicrobial and healing properties, offering a sustainable approach.[136] Additionally, sophisticated metal nanocomposites, including platinum clusters and NIR light-activatable systems, show promise for diabetic wounds.[137] These innovations demonstrate MNPs' potential in diabetic wound management, addressing

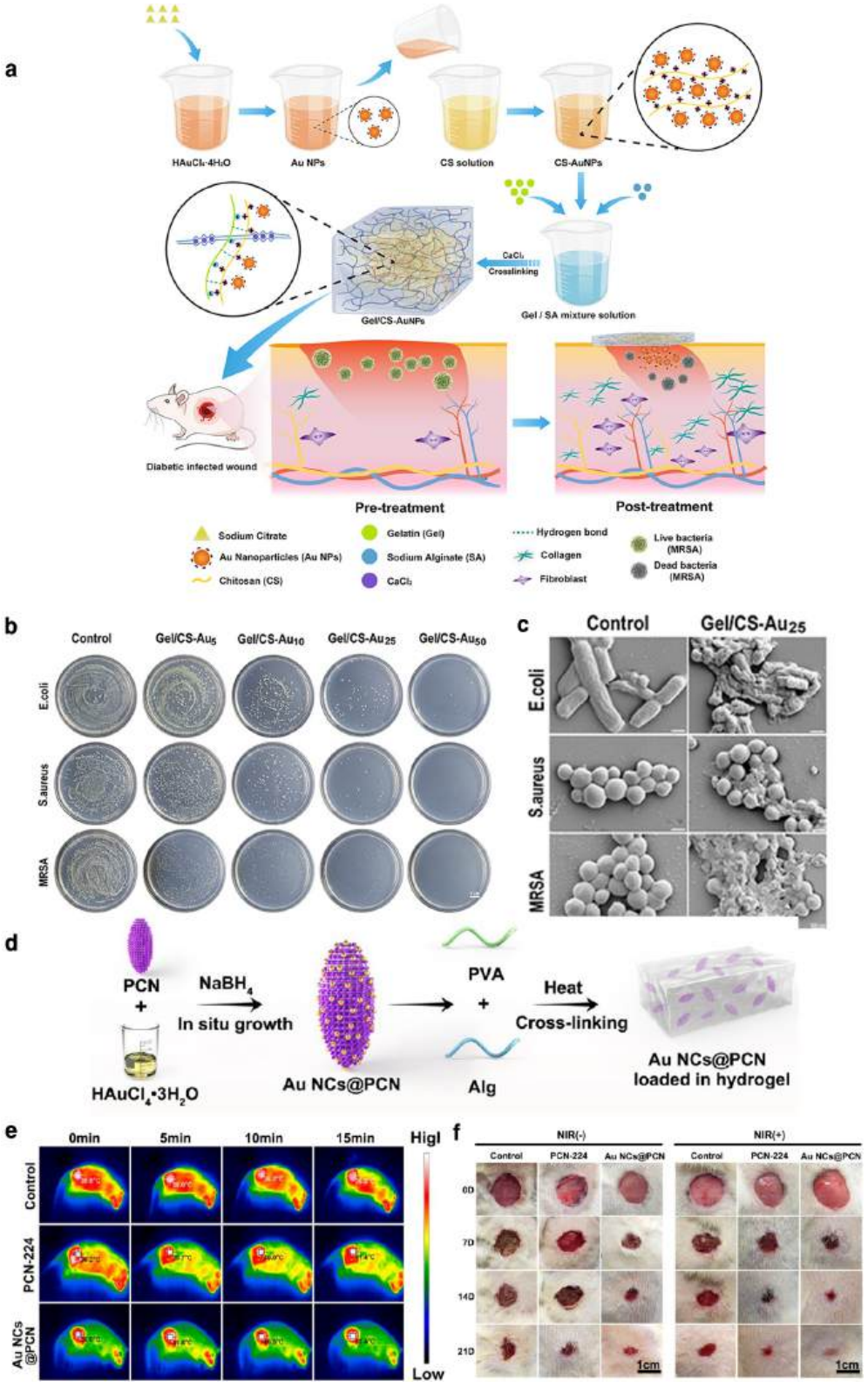

FIGURE 8 (a) Schematic illustration of the synthesis of Gel/CS-AuNPs and their application in MRSA-infected diabetic wounds in rats, showing pre-treatment and post-treatment effects. (b) Antibacterial efficacy of Gel/CS-AuNPs against *E. coli*, *S. aureus*, and MRSA, demonstrated through colony counts on agar plates after different treatments. (c) SEM images of bacterial cells (*E. coli*, *S. aureus*, MRSA) before and after treatment with Gel/CS-Au25, showing significant cell membrane disruption and bacterial death. Reproduced under the term of the CC-BY license with permission from ref.[116] Copyright 2024, The Authors. (d) Preparation of Au NCs@PCN and (e) in vivo thermal imaging of temperature after different treatments at different time points. (f) Images showing wound healing in diabetic rats treated with Au NCs@PCN under NIR, illustrating accelerated healing and effective infection control within 21 days. Reproduced with permission from ref.[129] Copyright 2022, American Chemical Society.

complex pathophysiology and future applications.[123,125] A comprehensive overview on the role of MNPs in diabetic wound healing is described in Table 1.

4.2.3 | Polymeric nanoparticles

PNPs offer a versatile approach to diabetic wound healing through precise therapeutic agent delivery. Made from biocompatible polymers like chitosan, alginate, and PLGA, these NPs enhance drug stability and provide controlled release. Their nanoscale size enables cellular uptake and interaction with biological structures, promoting angiogenesis, cellular proliferation, and immune modulation. PNPs can respond to physiological cues for targeted drug delivery that accelerates wound healing.[138] These organic nanomaterials protect bioactive compounds, maintain moisture, prevent infection, and stimulate vascularization, thereby creating optimal conditions for diabetic wound healing.

Polymeric nanofibers developed by Kamalipooya et al.[119] integrate chitosan NPs with green-synthesized cerium oxide NPs (CeO_2-CSNPs) using Thymus vulgaris extract for diabetic wound healing. The PCL/cellulose acetate (CA)/CeO2-CSNPs nanofibers showed strong antibacterial activity against *S. aureus* with inhibitory concentration below 58.59 μg/mL and antioxidant activity up to 89.59%. The nanofibers enhanced cell viability with 90.3% migration rate after 48 h. In vivo studies showed that these nanofibers improved diabetic wound healing by 95.47% after 15 days, demonstrating their effectiveness in treating diabetes-related wounds.[119]

Building on PNPs' therapeutic potential, a study explored asiaticoside-loaded polymeric nanoparticles (AST PNPs) in gelatin-based hydrogel for diabetic wound healing. The PNPs enhanced collagen biosynthesis and wound closure in both in vitro and in vivo models. The hydrogel provided sustained asiaticoside release, optimizing its therapeutic effect. This polymeric nanoformulation demonstrated superior outcomes in diabetic wound management compared to conventional treatments.[120] Another study utilized polymeric nanofibrous wound dressings enriched with propolis, a natural healing agent. PVA scaffolds combined with propolis NPs showed no cytotoxicity to fibroblasts and achieved 68% wound closure after 7 days, outperforming controls. The combination enhanced wound healing, indicating potential application in tissue regeneration for diabetic wounds.[139]

Biopolymer-based NPs, like chitosan and alginate, demonstrate polymeric nanomaterials' versatility in diabetic wound healing. Advanced silk-fibroin ε-poly-l-Lysine NPs with polydeoxyribonucleotide and exosomes promote granulation tissue formation and collagen deposition.[140] Incorporation of zinc sulfide NPs into PVA and chitosan enhances cell migration and wound closure.[117] HA-decorated curcumin-based coordination polymers promote diabetic wound healing.[121] pH-responsive nanozyme hydrogels with enzyme-like activities manage bacterial infections while promoting angiogenesis in diabetic wounds.[141] Another compelling advancement involves the integration of tadalafil-loaded NPs into a PVA/*Withania somnifera* extract nanofiber matrix, which has shown promise in reducing inflammation and enhancing angiogenesis, further supporting the role of PNPs in diabetic wound management.[142]

These diverse studies collectively underscore the versatility and effectiveness of PNPs in addressing the complex pathophysiology of diabetic wounds, offering targeted and personalized therapeutic solutions that enhance tissue regeneration and accelerate wound healing. A comprehensive overview on the role of PNPs in diabetic wound healing is described in Table 1.

The biocompatibility and safety of NPs in diabetic wound healing are strongly influenced by their physicochemical properties, including particle size, surface charge, dose, and degradation behavior. Smaller NPs generally exhibit enhanced cellular uptake, which can improve therapeutic efficacy but may also raise cytotoxicity risks at higher concentrations. For instance, cobalt carbonate NPs (~16.6 nm) showed no cytotoxicity at therapeutic levels but exhibited hemolytic activity when overdosed, confirming their size- and dose-dependent safety profile.[130,143,144] NPs within the 100–200 nm range, such as lecithin–chitosan formulations (~160 nm), demonstrated excellent in vivo biocompatibility and wound healing efficacy with no significant toxicity. Surface charge also plays a pivotal role, positively charged particles (e.g., zeta potential ~25 mV) enhance cellular adhesion and uptake, yet may increase the risk of inflammation or hemolysis if not appropriately controlled.[130,145] Coating NPs with biopolymers or embedding them in hydrogel matrices has been shown to reduce adverse immune responses and improve compatibility.[145,146]

The safety of these systems also hinges on optimized dosing and controlled degradation. Studies have shown that lower concentrations of therapeutic NPs, such as 0.8% w/w CuO or biodegradable chitosan and cellulose-based systems, yield favorable outcomes with minimal cytotoxicity or chronic inflammation.[144,146–149] Sustained release profiles within biopolymer matrices mitigate risks associated with sudden NP accumulation or reactive byproducts.[146,147] While most well-engineered NPs exhibit low in vivo toxicity and even anti-

inflammatory effects, certain materials, such as silver or copper-based NPs, require careful dose regulation to avoid inflammation or oxidative stress.[130,143,147] Importantly, repeated or long-term application raises legitimate regulatory and translational concerns, particularly regarding cumulative toxicity, immune modulation, and production reproducibility.[130,143] These challenges highlight the need for standardized synthesis protocols, rigorous safety evaluation, and scalable quality control systems to ensure the successful clinical translation of NP-based therapeutics for chronic diabetic wounds.

These findings indicate that nanotechnology-driven strategies and smart biomaterials present a transformative leap in diabetic wound care, yet their utility and readiness vary across platforms. Hydrogels, particularly those integrated with NPs or bioactive agents, offer biocompatible scaffolds with moisture-retentive and drug-delivery capabilities, making them highly effective for chronic wound environments. Among them, next-generation hydrogels such as DSPVA and SMPAAM show strong antioxidative and antimicrobial potential, supporting accelerated healing. LNPs stand out for their ability to deliver mRNA, growth factors, and anti-inflammatory agents with high specificity and minimal systemic toxicity; their success in reprogramming the wound microenvironment and modulating immune responses marks them as leading candidates for clinical translation. MNPs, notably silver-, gold-, and zinc-based, demonstrate broad-spectrum antimicrobial and pro-angiogenic effects, although concerns around cytotoxicity and biocompatibility at higher doses necessitate cautious design. PNPs provide a versatile and tunable platform for sustained stimuli-responsive delivery of phytochemicals, peptides, and regenerative compounds, with added benefits in biocompatibility and scalability. Overall, hybrid systems that synergize the strengths of these technologies, such as polymeric nanofiber scaffolds embedded with MNPs or hydrogel matrices loaded with LNPs, emerge as the most promising approach for next-generation diabetic wound care. Their multifunctionality, capacity for stage-specific intervention, and increasing evidence from in vivo models position them well for clinical advancement, providing challenges in regulatory approval, reproducibility, and cost-efficiency are addressed.

While smart biomaterials and nanotechnology have significantly advanced the precision and functionality of wound care, the integration of emerging technologies is taking this progress even further. The next section explores how cutting-edge innovations such as 3D/4D printing and AI are shaping the future of diabetic wound management through personalized, adaptive, and data-driven therapeutic strategies.

5 | ADVANCED TECHNOLOGIES: THE FUTURE OF DIABETIC WOUND CARE

5.1 | 3D printing for customized wound solutions

3D printing has emerged as a key technology in diabetic wound care, enabling customized scaffolds for chronic diabetic wounds. Using computer-aided design, it allows fabrication of scaffolds with precise structures and controlled properties that promote wound healing. 3D printing can incorporate bioactive agents like drugs and growth factors into the scaffold for localized therapeutic release. Various printing methods, including extrusion, inkjet, laser-assisted, and digital light processing, offer advantages based on bioink viscosity, speed, and cell viability.[150] This versatility enables the creation of advanced wound dressings that enhance tissue regeneration and expedite healing in diabetic patients.

5.1.1 | Innovative hydrogel-based approaches

Harnessing the versatility of bioactive hydrogels, Lin et al.[151] developed 3D-printed porous scaffolds using SA, oxidized sodium alginate (OSA), gelatin (Gel), and $CaCO_3$ microspheres. Pre-crosslinking with Ca^{2+} improved printability via Schiff base reactions between OSA and Gel (Figure 9a). These scaffolds showed excellent biocompatibility and enhanced tissue regeneration, achieving 93% collagen deposition in diabetic rat models (Figure 9b), making them promising for diabetic wound repair. Similarly, Liao et al.[152] developed angiogenic patches using calcium ions and UV photocrosslinking of alginate (ALG) and chondroitin sulfate methacryloyl, functionalized with acrylate-modified VEGF (mVEGF). This approach enabled sustained VEGF release and improved mechanical properties. The patches demonstrated superior wound healing in diabetic mouse models (Figure 9c,d).

5.1.2 | Bioinspired nanocomposite designs

Expanding on bioinspired designs, Kim et al.[153] developed 3D-printed hydrogel dressings using DNA-induced biomineralization (Figure 10a). Incorporating DNA from salmon sperm and biosilica inspired by marine sponges, these hydrogels inks demonstrated excellent porosity, mechanical tunability, and ROS scavenging capacity. Enhanced anti-inflammatory and angiogenic properties accelerated diabetic wound healing, with the use of shellac as an adhesive component enabling high

print fidelity. This study underscores the integration of machine learning (ML)-guided 3D printing in designing advanced wound care materials tailored for chronic wounds.

A similar strategy was also employed in another study by Ding et al.[154] They utilized an in situ microfluidic 3D printing technique to fabricate MoS_2-accelerated gelling hydrogels for diabetic wound healing (Figure 10b). The hydrogel scaffold rapidly forms through mixing benzaldehyde- and cyanoacetate-functionalized dextran solutions with MoS_2 nanosheets, which impart photothermal antibacterial and antioxidant properties. When directly applied to infected diabetic wounds, the scaffold alleviated oxidative stress, eradicated bacterial infections, and accelerated wound closure, demonstrating its robust therapeutic potential.

5.1.3 | Personalization and multi-cell strategies

Personalization in wound care has also been explored through innovative hydrogel designs. Wu et al.[155] developed 3D-printable hydrogels composed of polyurethane and gelatin for irregular chronic wounds. These hydrogels, loaded with fibroblasts, keratinocytes, and endothelial progenitor cells, promoted reepithelization, collagen deposition, and neovascularization in wounds. Teoh et al.[156] used chitosan methacrylate and integrated Lidocaine Hydrochloride and Levofloxacin for controlled drug release. Further advancing the scope of 3D printing, Karavasili et al.[157] developed alginate-methylcellulose hydrogels with Manuka honey, aloe vera gel, and eucalyptus oil, exhibiting antimicrobial efficacy and biocompatibility. Using experimental techniques and finite element analysis, the mechanical behavior was evaluated for diabetic wound care applications. Finally, Tsegay et al.[158] created an auxetic hydrogel wound dressing with pH-sensitive phenol red dye. The design enhanced adhesion to curved surfaces, while enabling wound monitoring via smartphone, making it suitable for managing diabetic wounds.

5.1.4 | Multifunctionality with electrical stimulation and peptide hydrogels

Incorporating novel stimulation methods, Yang et al. showed that 3D-printed scaffolds with electrical stimulation promoted collagen fiber arrangement and accelerated wound healing in diabetic rats by enhancing the endogenous electric field.[159] Further exploring hydrogel versatility, Lihao et al. designed 3D-printed scaffolds with Salvianolic acid B, demonstrating antioxidant and angiogenic properties for diabetic wound repair.[160] Peptide-based and amyloid composite hydrogels improved cell viability and wound healing,[161,162] while Metwally et al. incorporated nanofibrous microspheres into scaffolds to enhance antibacterial activity for tissue regeneration.[163]

3D printing enables the creation of optimized wound dressings that integrate therapeutic agents for diabetic wounds. The technology offers a versatile platform for developing personalized treatment strategies by controlling scaffold composition and architecture. Future integration of ML and bioinks will enhance its precision for wound care solutions.

5.2 | 4D printing for responsive and adaptive healing

4D printing revolutionizes diabetic wound healing through materials that change properties in response to stimuli like heat, light, or moisture.[164] Unlike 3D printing, 4D printing enables dynamic post-production changes for medical applications requiring adaptability. Incorporating methacrylated ECM (MA-ECM) from autologous fat tissue into 4D-printed hydrogel dressings creates a natural scaffold rich in proteins, growth factors, and cytokines, establishing an optimal environment for cell proliferation.[165] In 4D-printed hydrogels, MA-ECM supports tissue repair while ensuring continuous contact with the wound bed. Clinical studies of DFUs showed substantial wound reduction within 1 week, with complete closure achieved in 2–5 weeks post-application.[165] While Kim focused on MA-ECM and 4D printing, Hsieh et al. demonstrated that combining acellular ECM hydrogel from porcine skin with sacchachitin accelerated healing and stimulated hair follicle growth, suggesting that pairing MA-ECM with other bioactive components could enhance therapeutic outcomes.[166]

Researchers developed a multifunctional 4D-printed hydrogel dressing for diabetic wound healing that adapts to wound contours and supports tissue regeneration. Created via digital light process 3D printing, the hydrogel combines N-isopropylacrylamide for temperature-responsive contraction, curcumin-loaded Pluronic F127 micelles as antibacterial agents, and PEG diacrylate-dopamine for tissue adhesion and biodegradability. In MRSA-infected diabetic rat models, the hydrogel showed effective wound closure. The hydrogel's body-temperature-activated contraction and anti-inflammatory effects enable wound contour conformity and accelerated healing in clinical settings.[167] Wang et al. evaluated a 4D printed chitosan-based

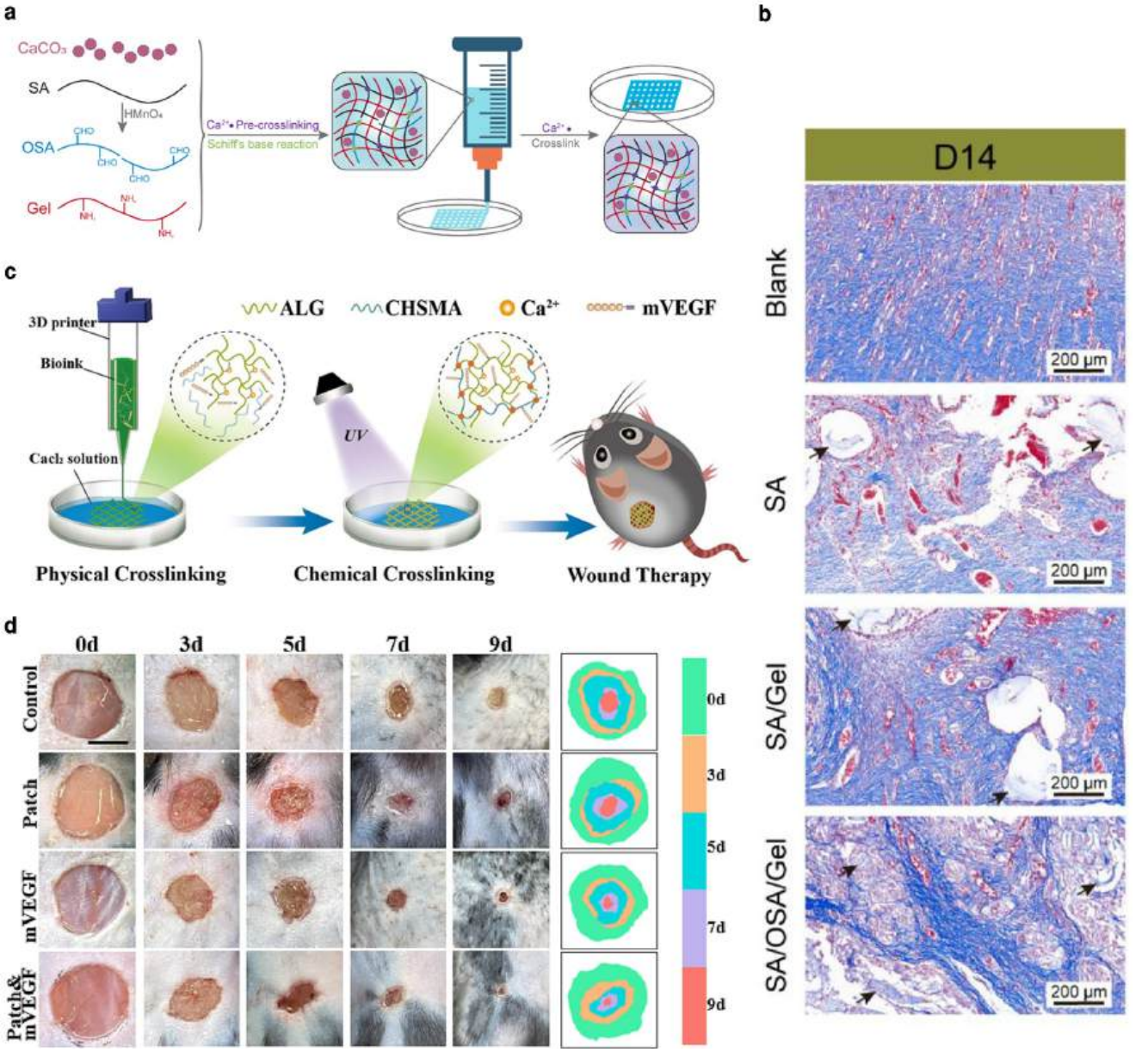

FIGURE 9 (a) Schematic representation of the 3D printing process for SA/OSA/Gel scaffolds and (b) M-stained sections showing enhanced tissue regeneration in diabetic wounds treated with SA/OSA/Gel scaffolds (scale bar: 200 μm). Reproduced under the term of the CC-BY license with permission from ref.[151] Copyright 2023, The Authors. (c) Schematic of 3D-printed double-crosslinked angiogenic patches showing VEGF release, mechanical reinforcement, and enhanced diabetic wound healing and (d) representative healing pattern of diabetic wounds in different groups after treatments with the patches. Reproduced with permission from ref.[152] Copyright 2023, Elsevier. OSA, oxidized sodium alginate; SA, sodium alginate.

thermosensitive hydrogel (4D-CTH) for treating severe corneal alkali burns. The 4D-CTH provides uniform pore size and adjustable shape, improving cell compatibility for limbal epithelial stem cells (LESCs). In rat models, 4D-CTH-loaded LESCs reduced corneal opacity (1.2 ± 0.4472 vs. 0.4 ± 0.5477, $p < 0.05$) and neovascularization scores (5.5 ± 1.118 vs. 2.6 ± 0.9618, $p < 0.01$), while accelerating corneal epithelial healing ($72.09 \pm 3.568\%$ vs. $86.60 \pm 5.004\%$, $p < 0.01$) compared to standard treatment.[168]

5.3 | Artificial intelligence and machine learning to optimize wound healing formulations

AI has revolutionized pharmaceutical formulations by offering solutions for wound healing by enhancing precision in drug design and treatment strategies. AI's capacity to process complex datasets enables accurate wound assessment, prediction of healing outcomes, and optimization of therapeutic interventions.[169] Using

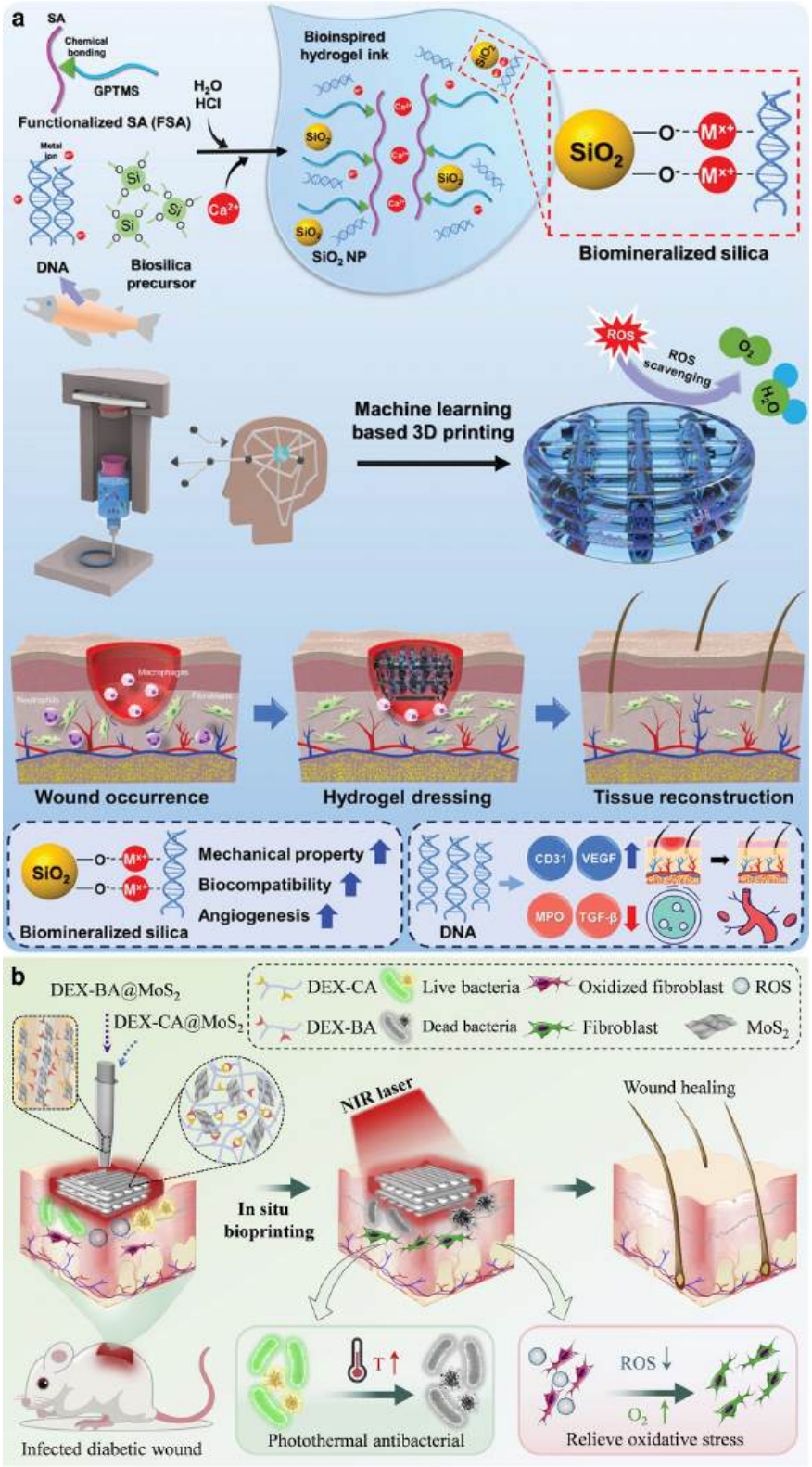

FIGURE 10 (a) Bioinspired 3D-printed hydrogels incorporating DNA-induced biomineralized silica. These hydrogels, developed using machine learning-based 3D printing, exhibit enhanced ROS scavenging, angiogenesis, and anti-inflammatory properties, accelerating diabetic wound healing. Reproduced with permission from ref.[153] Copyright 2023, The Authors. (b) Schematic of in situ 3D-printed MoS_2 hydrogel scaffold showing photothermal antibacterial activity, ROS scavenging, and wound healing efficacy in diabetic wounds. Reproduced with permission from ref.[154] Copyright 2023, Elsevier. ROS, reactive oxygen species.

artificial neural networks (ANNs), ML, and deep learning (DL), AI can manage non-linear relationships between formulation variables and therapeutic effects, accelerating drug development and enabling personalized wound care solutions.[170]

AI enhances advanced DDSs by predicting key physicochemical properties such as solubility, stability, permeability, and bioavailability. ML models such as support vector regression and gated recurrent units extract molecular features to predict these properties, enabling effective wound-healing formulations.[171,172] AI-driven electrospun nanofiber scaffolds and intelligent wound dressings with real-time monitoring capabilities exemplify this integration. These platforms optimize drug delivery and adaptive therapeutic responses for dynamic wound environments.[173] AI models like conditional generative adversarial networks have been used to develop novel drug delivery platforms, including 3D-printed formulations.[174] Similarly, nuclear magnetic resonance spectroscopy combined with AI helps predict critical properties like logD, enhancing the efficacy of wound-healing drugs.[175]

AI-driven bioinformatics tools have identified therapeutic targets and agents, such as Trichostatin A (TSA), which are key for promoting tissue regeneration in chronic wounds. Tools like ANN, fuzzy logic, and neuro-fuzzy logic have enabled superior formulations by predicting the solubility, stability, and bioavailability of active compounds.[111] AI integration with nanotechnology, including nanobots and electrospun nanofiber scaffolds, has advanced drug delivery, enabling precise microscopic interventions.[176] AI-driven models have optimized electrospun nanofibers for wound dressings, improving mechanical properties and drug release profiles for diabetic ulcers.[177] AI also supports the development of microneedle patches, which deliver growth factors and antimicrobial agents directly to the wound site, accelerating tissue repair.[178] By leveraging ANN and response surface methodology, AI has optimized the design of NPs to promote angiogenesis and deliver therapeutic agents effectively in diabetic wounds.[179]

AI-powered liposomes, initially developed for cancer therapy, have been adapted to deliver insulin analogs, anti-inflammatory agents, and growth factors for chronic diabetic wounds, addressing complex wound environments.[180] AI models predict skin permeability to enhance the design of transdermal patches that provide sustained, localized delivery of bioactive agents, ensuring targeted treatment with minimal side effects.[181] Advanced DL frameworks like convolutional neural networks aid in biomarker identification, further enabling the personalization of therapies.[182] These AI-driven solutions optimize treatment efficacy, improve healing outcomes, and reduce recovery time for diabetic wound care.

3D/4D printing and AI-driven technologies offer promising advancements in diabetic wound care by enabling personalized multifunctional wound dressings and dynamic therapeutic platforms. While initial studies report favorable biocompatibility for 3D-printed hydrogels and scaffolds, especially those constructed from chitosan, decellularized extracellular matrix, and DNA-biomineralized hydrogels, comprehensive assessments of long-term safety remain scarce.[167,183–185] Incorporation of antimicrobial agents such as curcumin, silver, gold, and titanium dioxide improves infection control, but their cytotoxic potential over extended use has not been fully characterized.[167,186] Although many of these platforms are biodegradable and demonstrate favorable tissue integration, systematic studies evaluating chronic exposure, immunogenicity, or repeated application in diabetic wound settings are still limited.

Preclinical in vivo studies have shown that several 3D/4D-printed scaffolds can accelerate wound closure, enhance tissue regeneration, and exhibit minimal acute toxicity.[167] However, long-term studies addressing adverse effects such as chronic inflammation or delayed toxicity are lacking. From a translational perspective, regulatory frameworks for 3D/4D-printed and AI-enabled wound therapies remain underdeveloped, with challenges including the need for standardized materials, validated manufacturing processes, and quality assurance measures. The limited scope of large-scale clinical trials highlights the urgent need for rigorous, long-duration safety and efficacy studies to support regulatory approval and real-world implementation.[187,188] While these technologies are at the forefront of innovation, addressing these safety and regulatory gaps is essential for their successful translation into routine diabetic wound care.

Collectively, emerging technologies such as 3D printing, 4D printing, and AI are redefining the future of diabetic wound care by enabling tailored, responsive, and intelligent therapeutic strategies. 3D printing excels in creating patient-specific scaffolds with high spatial precision, allowing integration of bioactive agents, living cells, and antimicrobial components. It offers a versatile platform for producing multifunctional wound dressings, especially when combined with hydrogel matrices or biologically inspired materials. 4D printing builds on this foundation by introducing time-dependent responsiveness, offering dynamic wound dressings that adapt to environmental stimuli (e.g., pH, temperature, light), enhancing tissue conformity and treatment precision. These stimuli-responsive systems represent the next frontier in personalized wound care, though clinical

evidence remains limited. Meanwhile, AI and ML tools are driving innovation upstream, optimizing DDSs, material selection, and treatment algorithms. AI enhances prediction of drug behavior, assists in designing intelligent delivery systems (e.g., nanofibers, microneedles), and enables real-time wound assessment and personalization of therapy. While 3D/4D printing technologies focus on device fabrication, AI offers data-driven decision-making that supports design, monitoring, and therapeutic optimization. When integrated, these technologies promise a closed-loop system for diabetic wound management, ranging from diagnosis to personalized treatment and adaptive healing. However, scalability, regulatory clarity, and long-term validation remain critical barriers to clinical integration. The convergence of biofabrication and intelligent systems holds immense promise for reshaping diabetic wound care into a more personalized, efficient, and outcome-driven domain.

Although emerging technologies like 3D/4D printing and AI are revolutionizing the design and personalization of diabetic wound therapies, their true impact depends on their successful translation into clinical settings. The following section examines the current state of clinical implementation, highlighting real-world applications, regulatory pathways, and the challenges that must be addressed to bring these innovations to patients.

6 | CLINICAL TRANSLATION AND REAL-WORLD IMPLEMENTATION

The therapeutic armamentarium for DFU care has steadily broadened beyond standard debridement, offloading, and infection control. Among the first advanced products to gain regulatory traction were cellular or tissue-based constructs. The bilayer living-skin equivalent *Apligraf*® closed 51%–56% of neuropathic DFUs within 12 weeks, roughly doubling the healing probability and shortening the median time-to-closure by a month in a pivotal randomized trial.[189] *Dermagraft*®, a fibroblast-derived dermal matrix, achieved a 30% closure rate at 12 weeks versus 18% with gauze dressings, while maintaining an excellent safety profile.[190] Topical rhPDGF-BB (*becaplermin*) likewise accelerated healing (43% vs. 28% closure at 20 weeks) but carries a black-box warning when cumulative exposure exceeds three tubes.[191] A 2024 systematic review of 14 HBOT trials reported a relative risk of 0.52 for major amputation and a ≈15% absolute increase in healing for Wagner grade II–IV wounds.[192]

Translational momentum is strongest in regenerative and smart-material approaches. In February 2025, the FDA granted Breakthrough Therapy designation to *SkinTE*®, an autologous heterogeneous skin construct, after a Phase II RCT showed 70% complete closure at 12 weeks versus 34% with standard care; the multicentre Phase III COVER-DFUS II trial is already >75% enrolled.[193,194] Mesenchymal-stem/stromal-cell (MSC) therapy has also moved into late-phase testing: aggregated Phase I/II data reveal 75%–100% closure within 6 months, with consistent gains in angiogenesis and no serious safety signals.[195] At the materials interface, electro-spun nanofibre dressings that co-deliver antimicrobials and antifibrotic agents have progressed from 46% faster closure in murine models to a first-in-human safety/feasibility pilot in 2024, showing an 83% mean area reduction by week 8.[196] The clinical pipeline is therefore expanding rapidly: a recent scoping review identified 59 late-stage interventions spanning growth-factor dressings, energy-based devices, regenerative scaffolds and cell therapies, underscoring the field's diversity.[197]

Regulatory frameworks are adapting in tandem. The FDA's final 2024 guidance on "Diabetic Foot Infections: Developing Drugs for Treatment" explicitly streamlines endpoints for combination drug–device products and clarifies the evidentiary bar for adjunctive wound therapies.[198] These policy shifts coincide with an escalating economic imperative. Direct global spending on DFU care is projected to approach US $ 74 billion per year by 2025, with the United States and Europe already shouldering annual costs of US $ 9–13 billion and ≈US $ 10 billion, respectively, driven largely by extended hospitalization and amputation-related rehabilitation.[199] Implementation challenges remain. Autologous constructs and 3D-printed grafts must overcome batch-to-batch variability and scale-up bottlenecks; closed bioreactor systems and portable printers are being tested to address these issues. Equally critical is workforce training: multidisciplinary "toe-and-flow" teams integrating vascular surgery, endocrinology and podiatry have been shown to halve major amputation risk, yet remain inconsistently available. Finally, mandatory 5-year post-approval registries (e.g., SkinTE PASS) are expected to generate the longitudinal safety and effectiveness data required for value-based reimbursement models. Table 2 summarizes key clinical studies on advanced therapeutics for diabetic wound healing, highlighting innovative approaches and their outcomes.

Although several advanced therapies have shown encouraging clinical progress and regulatory interest, their widespread adoption remains limited by a range of unresolved scientific, logistical, and regulatory issues. The next section explores into these persistent challenges and translational barriers, with a focus on formulation

complexities and clinical validation hurdles that must be overcome to enable broader clinical integration.

7 | CHALLENGES AND TRANSLATIONAL BARRIERS

The design and development of effective materials and formulations for diabetic wound healing presents several unique challenges that must be addressed to enhance efficacy and promote healing. Here we illustrate (Figure 11) and describe some of the major challenges faced by researchers and formulators whilst developing a novel and robust dosage form for diabetic wound healing.

7.1 | Formulation and delivery challenge

7.1.1 | Biocompatibility and material selection

Biocompatibility is a critical concern when developing formulations for diabetic wounds. The materials used must not elicit adverse immune responses or toxicity in the already compromised wound environment. One of the main stability concerns is the ability of formulations to maintain their physicochemical and mechanical properties in the wound environment. Polysaccharide-based formulations are widely favored for their biodegradability and biocompatibility, but they often require modifications to enhance stability. Techniques such as crosslinking, grafting, quaternation, and nanoformulation are commonly applied to improve the physicochemical and mechanical properties of these formulations, enabling them to withstand the challenging conditions of diabetic wounds while maintaining therapeutic efficacy.[200] Similarly, natural polymers like silk, collagen, gelatin, chitosan, and HA are chosen for their inherent biocompatibility and biodegradability.[201] Additionally, the formulation of polyphenols faces challenges due to their inherent instability, such as light sensitivity and rapid systemic elimination, which complicates their clinical application.[202] However, achieving consistent biocompatibility across diverse patient populations and wound types remains a significant challenge.

Material selection is complex due to the unique pathophysiology of diabetic wounds. The chosen materials must address multiple aspects of impaired healing, including chronic inflammation, oxidative stress, impaired angiogenesis, and bacterial colonization.[203,204] For instance, hydrogels composed of natural polysaccharides show promise due to their biocompatibility, biodegradability, hydrophilicity, and stimuli-responsiveness.[203] However, optimizing these properties while maintaining mechanical strength and drug delivery capabilities is challenging. An interesting contradiction arises in designing asymmetric wettable dressings. While a hydrophobic outer layer is desirable to prevent bacterial colonization and tissue dehydration, it must also maintain biocompatibility and permeability.[205] This highlights the complexity of balancing multiple, sometimes conflicting, material properties in a single formulation.

A key technical challenge in 3D-printed pharmaceuticals is the limited formulation space, largely because of the unsuitable mechanical and rheological properties of materials used, especially in filament-based extrusion methods. This limitation often requires additional steps, such as filament production, which are both resource-intensive and time-consuming.[206] Moreover, there is a shortage of pharmaceutical-grade polymers suitable for tablet printing, and issues like low drug-polymer miscibility and the need for high processing temperatures further complicate the scale-up.[207]

7.1.2 | Specificity of response to stimuli

Traditional hypoxia-responsive DDSs often lack the ability to specifically target the infection site and penetrate bacterial biofilms, limiting their effectiveness.[208] Additionally, the emergence of bacterial resistance after long-term medication use further complicates treatment strategies, necessitating the development of innovative approaches to combat this issue.[209] Another significant challenge lies in creating multifunctional systems that can respond to multiple stimuli present in diabetic wounds. While various endogenous (e.g., glucose, enzyme, hypoxia, and acidity) and exogenous (light, magnetism, and temperature) stimuli-responsive systems have been developed, integrating these into a single, effective therapeutic system remains a complex task.[209,210] Furthermore, ensuring spatiotemporal release of drugs and maintaining sufficient drug concentrations at the wound site are critical factors that need to be addressed in the design of these systems.[210]

7.1.3 | Optimization of drug delivery systems

One of the primary challenges is to achieve controlled and sustained release of therapeutic agents at the wound site. While advanced DDSs such as NPs, hydrogels, and scaffolds offer promising solutions, optimizing their release kinetics and ensuring long-term stability remains challenging.[204,211] Additionally, ensuring proper

TABLE 2 Clinical studies evaluating advanced therapeutics for diabetic wound healing.

Clinical trial identifier	Phase	Treatment	Number of participants	Mechanism of action
NCT06616844	-	InnovaMatrix® AC	194	Enhances wound healing via porcine placental extracellular matrix, supporting tissue repair and regeneration
NCT06492811	II	GAT@F nanoenzyme hydrogel complex	49	Dual enzyme cascade catalysis: Glucose consumption, ROS reduction, and oxygen generation for improved wound healing
NCT03700580	II	P1G10	50	Proteolytic fraction from *Vasconcellea cundinamarcensis* promotes tissue repair by enhancing protease activity and reducing necrosis
NCT04450693	III	TTAX01 (biotherapy using cryopreserved human umbilical cord)	220	Cryopreserved umbilical cord tissue supports wound healing via structural scaffolding, anti-inflammatory effects, and enhanced epithelialization
NCT04176120	III	TTAX01	220	Cryopreserved human umbilical cord tissue (TTAX01) enhances wound healing by providing a biological scaffold, modulating inflammation, and promoting tissue regeneration
NCT02120755	IV	AmnioClear™ human allograft amniotic membrane	-	Promotes healing via anti-inflammatory effects, growth factors, and tissue regeneration support

penetration and targeting of the delivered drugs to the affected tissues is crucial for efficacy.[212] Interestingly, the development of nanofiber-based formulations, particularly those containing HA, has shown promise in addressing some of these challenges. However, issues related to reproducibility, proper characterization, and biological evaluation of nanofibers persist.[213] Similarly, while microspheres and nanospheres offer advantages in terms of biocompatibility and drug delivery capacity, optimizing their long-term sustained release profile remains a challenge.[214]

7.2 | Regulatory and clinical translation hurdles

7.2.1 | Standardization issues

Biodegradable materials are crucial in creating effective wound healing systems due to their biocompatibility and ability to integrate with active substances like drugs and stem cells, promoting angiogenesis and tissue regeneration.[215] However, the absence of standardized degradation assessment protocols complicates the evaluation of these materials' performance and safety. Current techniques, such as gravimetric analysis and surface erosion, have limitations, including technical errors and misinterpretation of material solubility as degradation, which can lead to inconclusive results.[216] This uncertainty hinders the optimization of biopolymeric formulations, which are essential for controlled drug release and enhanced wound closure in diabetic wounds.[204] Moreover, the development of smart biomaterials that respond to wound microenvironment stimuli, such as pH and ROS, is promising but requires reliable degradation assessments to ensure their efficacy and safety.[161] The need for updated ASTM guidelines that incorporate real-time, non-invasive, and automated degradation assessment techniques is critical to advance the clinical translation of these biomaterials.[216] Without standardized protocols, the therapeutic efficacy and stability of these innovative materials remain difficult to ascertain, posing a significant barrier to their widespread clinical application.[204,215]

Regulatory compliance and quality control pose significant hurdles for 3D printed pharmaceuticals. The lack of standardized regulatory frameworks for clinical approval complicates progress.[217] Current Good Manufacturing Practice, in-process tests, process control, and cleaning validation are some of the pertinent regulatory issues that need to be addressed.[218] Maintaining consistent quality and precision at larger scales is also

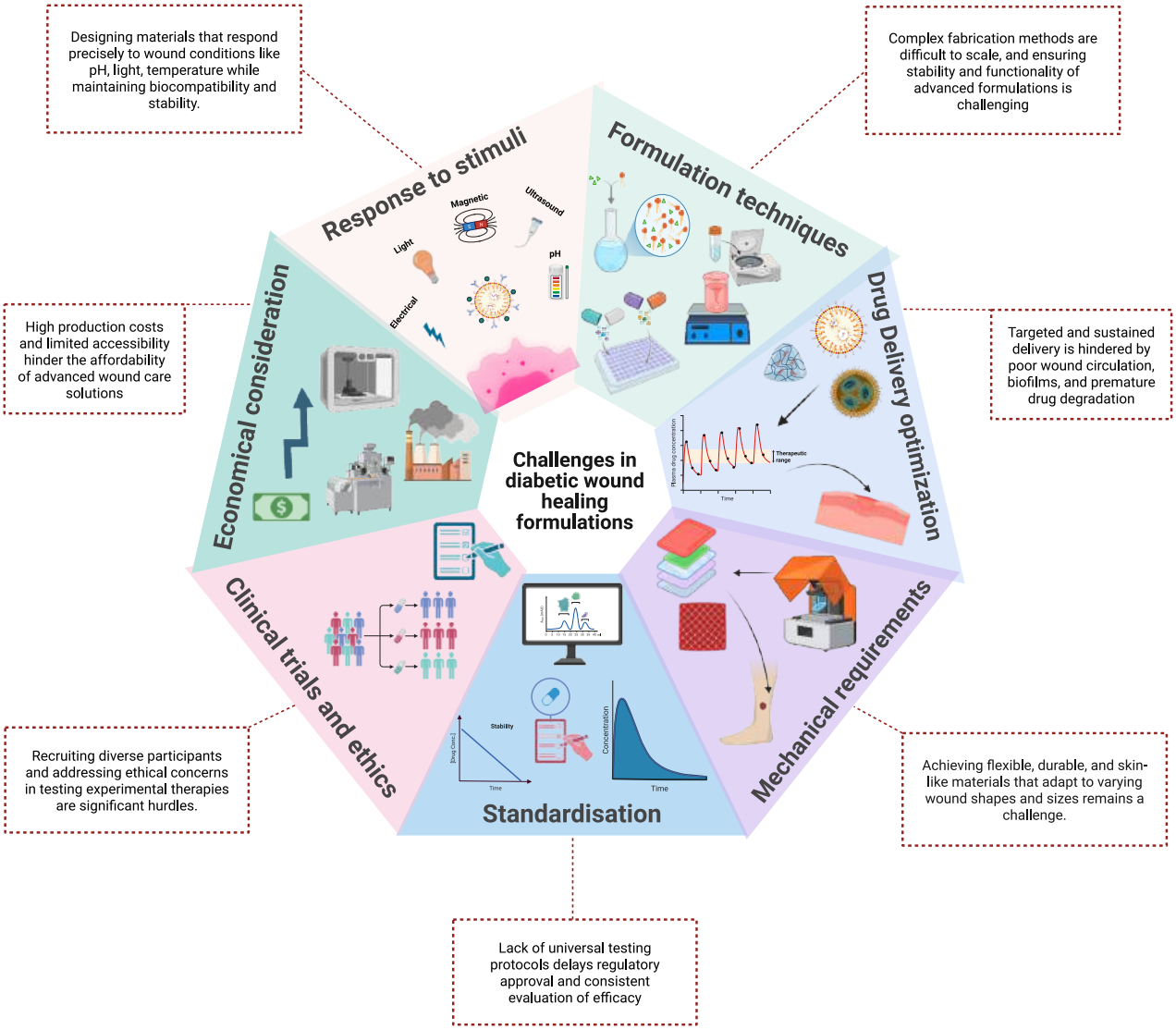

FIGURE 11 Illustration of the primary factors complicating the development of effective wound healing formulations for diabetic patients, including wound complexity, material selection, mechanical requirements, formulation techniques, response to stimuli, drug delivery optimization, clinical trial considerations, economic and ethical challenges, and standardization needs (created with Biorender).

challenging. Technical limitations include the shortage of suitable and safe pharmaceutical feedstock for 3D printing.[219] There are also difficulties in scaling production while maintaining quality control.[217] The 3D printing process currently cannot compete with well-established conventional processes for mass production of solid dosage forms.[218] Limited compatibility with thermosensitive materials is another technical challenge.[217]

7.2.2 | Clinical trial limitations

Despite substantial progress in preclinical research, particularly with nanotechnology-based therapies and intelligent hydrogels, their successful clinical translation remains a formidable challenge due to scalability, safety, and regulatory complexities.[220,221] The lack of high-quality clinical trials limits the establishment of clinical efficacy for novel treatments, such as resveratrol-based therapies.[222] This gap between preclinical research and clinical validation slows down the development of new formulations. The variability in wound healing processes among diabetic patients poses another challenge in clinical trials. Factors such as glucose control, wound care practices, and individual patient characteristics can significantly influence healing outcomes, making it difficult to standardize and compare results across different studies.[223] This variability necessitates larger sample sizes and longer follow-up periods, which can be logistically challenging and costly. Additionally, the translation of innovative materials such as glucose-responsive smart gels into clinical practice is fraught

with challenges, including ensuring biocompatibility, stability, and effective drug release in the high-glucose environment typical of diabetic wounds.[224] The need for sustained and localized drug delivery, as seen in the development of insulin-loaded organogels, requires rigorous testing to validate efficacy and safety, which can be resource-intensive and time-consuming.[225]

7.2.3 | Economic and ethical considerations

Economically, the high costs associated with the research, development, and production of advanced biomaterials, such as intelligent hydrogels and nanomaterials, pose significant barriers. These materials often require sophisticated technology and resources, which can lead to expensive treatments that are not accessible to all patients, particularly in low-income settings.[221,226] Additionally, the complexity of maintaining a sustainable supply chain for these materials further exacerbates the cost issues, making it difficult to ensure consistent availability and affordability.[226] From an ethical standpoint, the use of stem cells and other bioactive agents in biomaterials raises concerns about the sourcing and handling of biological materials, as well as the potential for unforeseen long-term effects on patients.[227] Moreover, the clinical application of these biomaterials necessitates rigorous testing to ensure safety and efficacy, which can be ethically challenging given the vulnerable nature of diabetic patients who may be at risk of complications.[215,228] The integration of new technologies, such as extracellular vesicle biopotentiated hydrogels, also presents ethical dilemmas related to patient consent and the transparency of treatment outcomes.[229]

Addressing formulation complexities, delivery limitations, and regulatory hurdles is essential for bridging the gap between promising research and real-world impact. With these challenges in mind, the final section outlines future directions that can guide the next wave of innovation in diabetic wound healing research, emphasizing on interdisciplinary collaboration, clinical validation, and personalized therapeutic strategies.

8 | FUTURE DIRECTIONS IN DIABETIC WOUND HEALING RESEARCH

Diabetic wounds continue to pose a significant clinical challenge. Despite recent advancements, a comprehensive solution remains elusive. Future research must adopt a multidisciplinary approach, leveraging innovative technologies and therapies to address the multifaceted nature of diabetic wounds and improve patient outcomes.

Stem cell therapies, particularly MSC therapy, represent another transformative avenue for future research. MSCs hold great promise for promoting tissue regeneration and angiogenesis, yet challenges persist in their retention and delivery within wound sites. Encapsulating MSCs within SA-based hydrogels or other biomaterials can enhance their stability, functionality, and therapeutic efficacy.[230] Incorporating ECM mimetics alongside MSCs may further bolster their regenerative potential, making them indispensable tools for future diabetic wound therapies. Epigenetic markers, such as microRNAs and histone modifications, also emerge as promising therapeutic targets.[231] These regulators influence key processes such as angiogenesis, inflammation, and cellular differentiation. However, optimizing delivery systems for epigenetic therapies remains a significant challenge. Future research must prioritize the development of precise delivery systems to minimize off-target effects and maximize therapeutic benefits.

Emerging technologies and novel therapeutic strategies offer immense promise for advancing diabetic wound care by addressing current challenges and driving innovation. Hydrogels infused with bioactive agents such as growth factors, cytokines, and antimicrobial peptides represent a versatile platform for optimizing the wound microenvironment. These materials enable controlled and sustained therapeutic delivery, reducing inflammation, enhancing angiogenesis, and combating infection. Hybrid systems, such as NP-loaded hydrogels, offer multifunctional benefits, including photothermal, antimicrobial, and anti-inflammatory properties, while promoting tissue regeneration and vascularization.[232] Figure 12a,b illustrate the integration of advanced biomaterials and NP-loaded hydrogels in diabetic wound care, highlighting their potential to address key barriers in chronic wound management. Future research should focus on refining these systems, incorporating innovative crosslinking techniques, and developing stimuli-responsive hydrogels for adaptable applications in diabetic wound therapy.

Another groundbreaking area is 3D and 4D printing, which offers immense potential for personalized wound care by creating skin-like dressings. These technologies may enable localized drug delivery, enhanced tissue regeneration, and adaptation to environmental cues, making them ideal for chronic wounds. Incorporating microfluidic-assisted fabrication of NPs, as illustrated in Figure 12a,b, could further enhance the therapeutic potential of printed constructs.

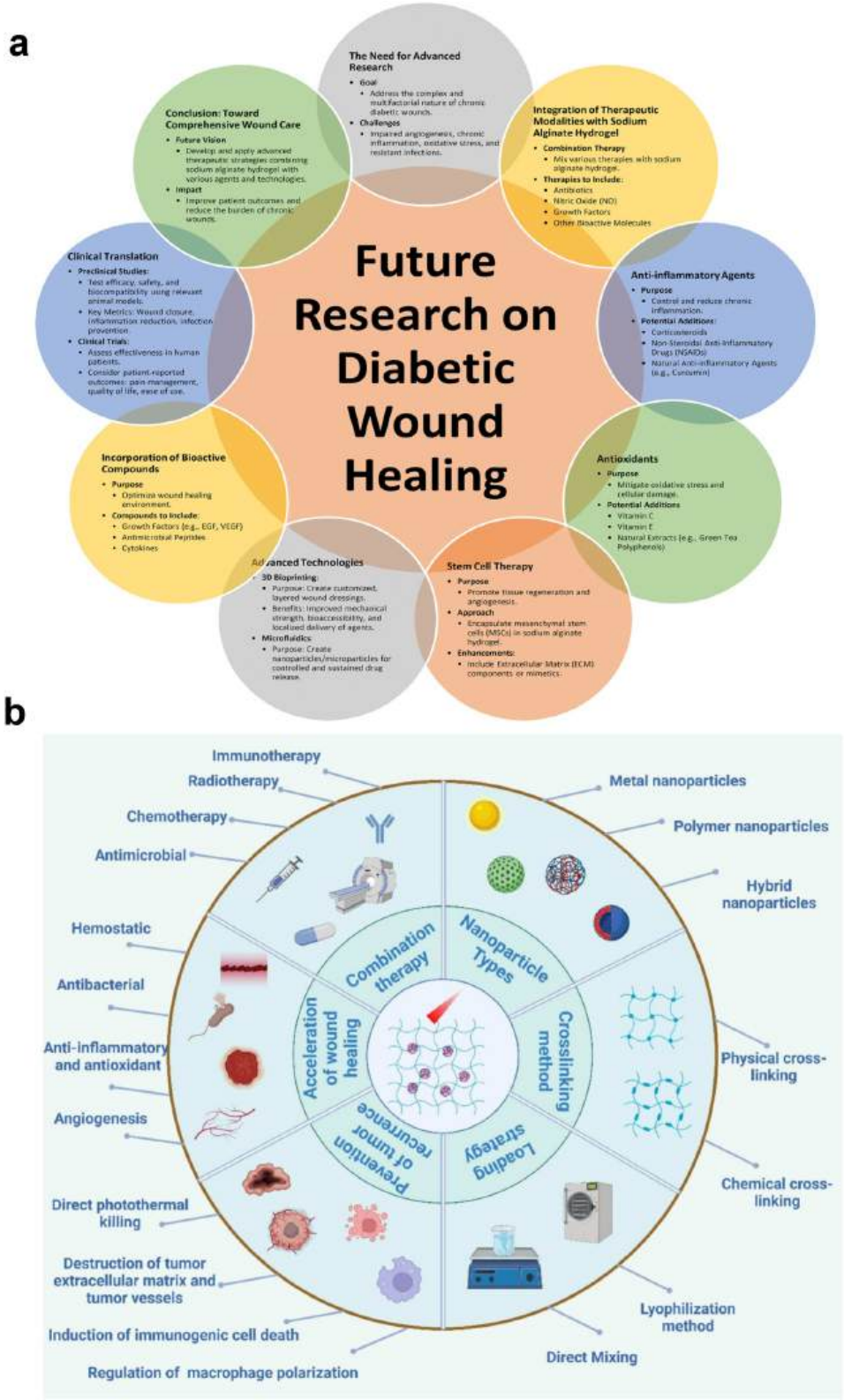

FIGURE 12 (a) Framework for future research in diabetic wound healing, highlighting the integration of advanced technologies, bioactive compounds, and translational approaches to enhance therapeutic outcomes. Reproduced with permission from ref.[230] Copyright 2024, The Royal Society of Chemistry. (b) Schematic of nanoparticle-loaded hydrogels for diabetic wound care, illustrating multifunctional properties such as antimicrobial, anti-inflammatory, and angiogenic capabilities through advanced crosslinking and combination therapies. Reproduced with permission from ref.[232] Copyright 2024, Elsevier.

Advanced "OMICS" technologies, including single-cell transcriptomics, proteomics, and metabolomics, offer a systems-level understanding of diabetic wound pathophysiology. These tools can unravel complex molecular and cellular networks, enabling the identification of novel therapeutic targets and biomarkers.[233,234] Integrating "OMICS" data with AI and ML platforms will enhance predictive modeling and accelerate the translation of preclinical findings into clinical applications. AI-powered algorithms, fueled by real-world clinical data, can guide patient-specific treatment planning, optimize therapeutic regimens, and uncover new drug combinations. These technologies collectively hold immense potential for driving the development of precision therapies tailored to individual patient needs, revolutionizing diabetic wound care.

Lastly, clinical translation must remain a central focus of future efforts. Developing preclinical models that accurately replicate human diabetic wound pathology is essential for bridging the gap between laboratory findings and clinical implementation. Expanding clinical trials to include diverse patient populations will ensure that therapeutic innovations are broadly applicable and effective across different demographic and socioeconomic groups. Moreover, endpoints in clinical trials should extend beyond wound closure to include metrics such as pain relief, mobility improvement, and enhanced quality of life.

By seamlessly integrating regenerative medicine, advanced biomaterials, cutting-edge technologies, and data-driven insights, the future of diabetic wound care holds transformative potential.

9 | CONCLUSION

Diabetic wound healing constitutes a multifaceted clinical conundrum which is driven by the interplay of impaired angiogenesis, chronic inflammation, and oxidative stress. All of them collectively thwart effective tissue regeneration. While therapies such as growth factors, antioxidants, and HBOT have shown efficacy in modulating specific pathways, the heterogeneity of diabetic wounds necessitates a paradigm shift toward integrative, precision medicine. Emerging strategies including lipid, metallic, and PNPs offer unparalleled specificity in drug delivery and facilitate controlled pharmacokinetics. They can also offer synergistic therapeutic effects. Concurrently, advancements in 3D/4D printing and AI herald a new epoch in personalized wound care, enabling the fabrication of biomimetic scaffolds and predictive algorithms to optimize treatment strategies. As illustrated in this review, these innovations hold promise for reconfiguring diabetic wound management through multifactorial intervention frameworks. Overcoming barriers of scalability, biocompatibility, and regulatory stringency will necessitate transdisciplinary collaboration and rigorous translational research. By integrating next-generation biomaterials, bioinformatics, and regenerative technologies, the field can transition from incremental improvements to transformative paradigms, fostering a robust and scalable approach to chronic wound care that redefines therapeutic benchmarks and patient outcomes.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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