

Recent Advancement in Hybrid and Stimuli-Responsive Hydrogels for Chronic Wound Healing

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Abstract

Chronic wounds — including diabetic ulcers, pressure sores, venous leg ulcers and non-healing surgical or trauma wounds — pose a persistent global health challenge due to their complex pathophysiology characterized by persistent inflammation, oxidative stress, elevated protease activity, microbial biofilms, impaired angiogenesis and extracellular matrix (ECM) degradation. Conventional dressings often fail to address the dynamic and multifactorial microenvironment of such wounds. Hybrid and stimuli-responsive hydrogels have recently emerged as promising multifunctional platforms: by combining natural and synthetic polymers, nanomaterials and bioactive agents, these “smart” dressings offer mechanical robustness, controlled therapeutic release, redox regulation, antimicrobial activity and environment-responsiveness. This review examines the design principles, biological functions and recent advances in such hydrogels, summarizes *in vitro* and *in vivo* evidence, discusses translational challenges and outlines future directions toward clinical application.

Keywords: Chronic wounds, hybrid hydrogel, stimuli-responsive, thermoresponsive, nanozyme, antimicrobial, ROS scavenging, angiogenesis, wound healing.

1. Introduction

Chronic wounds—commonly defined as wounds that fail to progress through the orderly phases of physiological healing in a timely manner—represent a significant and growing challenge globally. These wounds include diabetic foot ulcers, pressure injuries, venous leg ulcers and non-healing surgical or trauma wounds, all of which are characterized by dysregulated cellular and molecular processes. Instead of transitioning through hemostasis, inflammation, proliferation and remodeling, chronic wounds remain trapped in a prolonged inflammatory state, driven by elevated reactive oxygen species (ROS), sustained inflammatory cell infiltration, increased cytokine expression and impaired cell signaling required for tissue repair (J. Chen et al., 2025; X. Zhang et al., 2025).

A hallmark of chronic wounds is a protease-rich environment, particularly with elevated matrix metalloproteinases (MMPs), which degrade newly formed ECM components and hinder granulation tissue formation (J. Liu et al., 2024). Additionally, chronic wounds often harbor bacterial biofilms, which protect pathogens from antibiotics and immune responses, exacerbate inflammation and impair re-epithelialization (H. Wang et al., 2024). The microenvironment is further compromised by poor angiogenesis, reduced oxygenation, fibroblast dysfunction and impaired keratinocyte migration — collectively contributing to delayed or incomplete wound closure.

Traditional wound dressings — such as gauze, hydrocolloids, foams, films and simple hydrogels — primarily provide moisture retention and basic protection but are severely limited in addressing the multifactorial pathology of chronic wounds. They lack capabilities to regulate oxidative stress, modulate inflammation, deliver therapeutics in a controlled fashion, respond dynamically to biochemical cues, or disrupt biofilms effectively (W. Zhang et al., 2024).

Hydrogels — hydrophilic polymer networks capable of retaining substantial water — are especially attractive for wound management due to their softness, elasticity, tunable porosity and ECM-like physicochemical properties. They also serve as excellent carriers for drugs, growth factors, nanoparticles, peptides, or even cells. However, conventional hydrogels composed of single polymers often suffer from insufficient mechanical stability, limited responsiveness, poorly controlled degradation, or lack of multifunctionality needed for chronic wounds.

To overcome these limitations, there has been increasing interest in hybrid and stimuli-responsive hydrogels — systems integrating multiple polymer types (natural and synthetic), nanomaterials or bioactive molecules and stimuli-sensitive linkers. Among these, thermoresponsive hydrogels, which undergo sol–gel transitions near physiological temperature, are particularly promising owing to their injectability or sprayability and ability to conform to irregular wound geometries (J. Wang et al., 2025b). This review highlights recent advances (primarily 2023–2025) in the development of hybrid and stimuli-responsive hydrogels for chronic wound healing. It discusses design strategies, physicochemical characteristics and biological mechanisms; reviews *in vitro* and *in vivo* performance; and outlines translational challenges and future opportunities for clinical application.

2. Design Principles of Hybrid and Stimuli-Responsive Hydrogels

2.1 Polymers: Natural, Synthetic and Hybrid Networks

Hybrid hydrogels combine natural polymers — such as chitosan, gelatin, hyaluronic acid — with synthetic polymers (e.g., poly(ethylene glycol) (PEG) derivatives, poly(N-isopropylacrylamide) (PNIPAAm), Pluronic) to achieve an optimized balance of biocompatibility, biodegradability, mechanical integrity and functional versatility (J. Mo, Sun, et al., 2025; L. Wang et al., 2025). Natural polymers provide favorable cell–matrix interactions, biodegradability and bioactive signals, while synthetic polymers impart mechanical strength, tunable degradation and controlled drug-loading/release capabilities.

Recent work on chitosan-based thermosensitive hydrogels demonstrates how sol–gel transition mechanisms and hybrid formulations can be leveraged for effective skin wound repair (J. Wang et al., 2025a). The modularity of hybrid networks allows fine-tuning of physical, chemical and biological properties according to wound type and healing stage.

2.2 Stimuli-Responsiveness: Temperature, Enzyme, ROS, pH, etc.

Modern hybrid hydrogels are increasingly engineered to respond to wound-associated stimuli, enabling on-demand, localized therapeutic actions. Common responsiveness modalities include:

- **Temperature:** Thermoresponsive hydrogels (e.g., PNIPAAm- or Pluronic-based) undergo sol–gel transitions near physiological temperature, allowing minimally invasive administration (spray, injection) and *in situ* gelation (R. Wei & Zhang, 2025; L. Wang et al., 2025).
- **Enzyme activity (e.g., MMPs):** Chronic wounds often exhibit elevated levels of proteases like MMP-2 and MMP-9. Hydrogels incorporating MMP-cleavable linkers or enzyme-sensitive polymer networks can degrade selectively under high protease conditions, enabling controlled release of therapeutics such as anti-inflammatory or ECM-supportive agents (P. Zhou et al., 2025).

- **Redox / ROS:** Excessive ROS in chronic wounds contributes to cellular and ECM damage, inflammation and delayed healing. By integrating antioxidant molecules or catalytic nanozymes, hydrogels can scavenge ROS, restore redox balance and protect resident cells, promoting survival and regeneration (J. Mo, Sun, et al., 2025; J. Pu et al., 2022).
- **Other stimuli:** pH fluctuations (due to infection or inflammation), light, magnetic field, or mechanical stress have also been leveraged in advanced hydrogel designs to control drug release or activity, enabling precise spatiotemporal therapeutic control (L. Zhang & Hu, 2024).

By integrating multiple stimuli-responsive mechanisms, “smart” hydrogels can more closely mimic the dynamic and changing wound microenvironment, delivering therapeutic effects (antimicrobial, antioxidant, regenerative) in response to local cues.

2.3 Incorporation of Functional Nanomaterials and Bioactive Agents

To maximize therapeutic potential, hybrid hydrogels often incorporate nanomaterials and bioactive compounds:

- **Nanoparticles or nanozymes:** Metal nanoparticles (e.g., Ag, Zn, Cu), metal-oxide nanozymes (e.g., ceria, manganese–cobalt oxides), or other catalytic nanostructures provide antimicrobial activity, ROS scavenging, oxygen generation, or catalytic regulation of the wound microenvironment (Y. Mo, Zhou, et al., 2025a; Y. Wang et al., 2024).
- **Antibiotics or antimicrobial agents:** Localized, sustained release of antibiotics or antiseptics helps control infection without systemic toxicity, particularly important in poorly perfused or biofilm-laden chronic wounds (Z. Zhou et al., 2025; Y. Wang et al., 2024).
- **Growth factors, pro-angiogenic moieties, ECM-mimetic components:** Delivery of angiogenic or ECM-supportive factors (e.g., VEGF, TGF- β), or designing hydrogels with ECM-mimicking architecture, supports angiogenesis, granulation tissue formation, re-epithelialization and balanced ECM remodeling (Y. Zhang et al., 2024).
- **Antioxidants or ROS scavengers:** To mitigate oxidative stress, antioxidants and catalytic nanozymes reduce ROS, protect cells and support tissue regeneration in hostile wound microenvironments (J. Mo, Sun, et al., 2025; J. Pu et al., 2022).

This **multifunctional design strategy** enables a comprehensive approach to chronic wound healing — addressing infection, oxidative stress, inflammation, impaired angiogenesis and ECM disruption simultaneously — which is beyond the capacity of traditional dressings.

3. Biological Functions and Therapeutic Mechanisms of Hybrid and Stimuli-Responsive Hydrogels

Hybrid and stimuli-responsive hydrogels contribute to chronic wound management through several complementary biological functions, addressing distinct barriers in non-healing wounds.

3.1 Moisture Retention, ECM-Mimic Environment and Cell Support

A hydrated wound environment is pivotal for cell migration, granulation tissue formation and ECM deposition (Braid et al., 2023). Hydrogels maintain moisture, prevent desiccation and allow gas exchange, creating favorable conditions for healing.

The ECM-mimicking architecture of hybrid hydrogels provides biochemical and mechanical cues for fibroblast adhesion, keratinocyte proliferation and endothelial cell migration — vital for re-epithelialization and dermal regeneration. The hybrid combination of natural polymers (gelatin, hyaluronic acid, chitosan) with synthetic backbones affords tunable mechanical strength, controllable

degradation and optimal porosity, closely resembling native tissue microenvironment (J. Mo, Peng, et al., 2025; L. Wang et al., 2025).

Moreover, such hydrogels can serve as scaffolds for cell delivery, enabling incorporation of stem cells or progenitor cells to augment regeneration — particularly relevant in chronic wounds where endogenous cell recruitment and function are impaired.

3.2 Antimicrobial Activity and Infection Control

Persistent infection and biofilm formation are among the biggest obstacles to chronic wound healing. Hybrid hydrogels provide a platform for local, sustained antimicrobial delivery, embedding metal nanoparticles (Ag, Zn, Cu) or antibiotics for prolonged therapeutic efficacy at the wound site, minimizing systemic side effects (Y. Wang et al., 2024; Z. Zhou et al., 2025a).

Some hydrogels even exhibit intrinsic antimicrobial properties via cationic polymers (e.g., chitosan-based networks), which disrupt bacterial membranes. By reducing microbial burden, these hydrogels help shift the wound environment away from chronic inflammation toward conditions suitable for regeneration. Advanced systems can incorporate stimuli-responsive triggers for antimicrobial release — e.g., increased release when pH changes due to infection — decreasing the risk of drug overuse and resistance (Q. Zhou et al., 2025).

3.3 Redox Regulation and ROS Scavenging

- Chronic wounds are often under oxidative stress, with elevated ROS causing damage to cells and ECM, inhibiting proliferation and delaying healing. Hydrogels embedded with antioxidants or catalytic nanozymes can scavenge ROS, restore redox balance and protect resident cells, thereby promoting survival and regeneration (J. Mo, Sun, et al., 2025; J. Pu et al., 2022).

Notably, a nanozyme-reinforced hydrogel using a metal–organic-framework derived catalase-mimic nanozyme demonstrated both ROS scavenging and in situ oxygen generation — alleviating oxidative stress and hypoxia, protecting keratinocytes, fibroblasts and endothelial cells and accelerating wound closure, re-epithelialization, collagen deposition, neovascularization and macrophage polarization toward anti-inflammatory M2 phenotype in diabetic wound models (X. Zhai et al., 2025). This exemplifies how redox-active hydrogels can re-establish a regenerative wound environment.

3.4 Enzyme-Responsive, Controlled Therapeutic Release

Elevated protease activity (e.g., MMP-2, MMP-9) is a hallmark of chronic wounds. Hydrogels incorporating MMP-cleavable linkers or enzyme-sensitive polymer networks can degrade selectively under high protease conditions, enabling controlled, localized release of therapeutics — anti-inflammatory agents, antioxidants, or ECM-supportive molecules (Q. Zhou et al., 2025; Z. Wei & Zhang, 2025)

Such on-demand delivery avoids premature loss of drugs, reduces systemic exposure and ensures that therapeutics are released precisely when and where needed. By suppressing excessive protease activity, these hydrogels help stabilize the ECM, promote cell proliferation, granulation tissue formation and accelerate healing.

3.5 Angiogenesis and Tissue Regeneration

Effective wound healing requires neovascularization to restore blood flow, deliver oxygen and support tissue regeneration. Composite hydrogels can be engineered to deliver pro-angiogenic factors (e.g., VEGF, TGF- β) or to present ECM-mimetic cues that stimulate endothelial cell proliferation and migration (J. Hou et al., 2024; Y. Zhang et al., 2025).

For example, a 2025 GelMA-based hydrogel targeting senescent cells enhanced angiogenesis and granulation tissue formation in diabetic wounds, significantly accelerating closure and improving tissue

organization (X. Yang et al., 2025). By providing a supportive scaffold, biochemical cues and regenerative signals, such hydrogels facilitate functional tissue regeneration, minimizing scarring.

3.6 Hemostasis and Early Wound Stabilization

Early-stage wound management often requires hemostasis and wound stabilization, especially in fresh or exudative wounds. Some hybrid hydrogels — particularly those containing chitosan or gelatin derivatives — exhibit hemostatic properties, promoting platelet aggregation and blood coagulation (M. Sun et al., 2024).

By combining hemostatic, antimicrobial, antioxidant and regenerative functions, these hydrogels serve as “all-in-one” dressings — capable of controlling bleeding or exudate while simultaneously preventing infection and supporting later-phase tissue regeneration.

4. Recent Advances and Representative Systems (2023–2025)

Recent studies illustrate the rapid evolution of hybrid and stimuli-responsive hydrogels toward multifunctional, intelligent wound dressings. Table 1 summarizes notable examples.

Sl. No.	Hydrogel Type / Design	Key Components	Stimuli Responsiveness	Primary Functions	Key Findings	Citation
1	Thermoresponsive chitosan–Pluronic hybrid	Chitosan, Pluronic F127	Temperature	Moisture balance, antimicrobial	Improved collagen deposition and reduced inflammation in diabetic wounds	(L. Wang et al., 2025)
2	PNIPAAm–MOF nanozyme hydrogel	PNIPAAm, catalase-mimic MOF	Temperature + ROS	ROS scavenging, oxygen release	Enhanced angiogenesis and fibroblast survival	(F. Zhai et al., 2025)
3	MMP-responsive PEG–gelatin hydrogel	PEG, gelatin, MMP-cleavable peptide	Enzyme (MMP-2/9)	Controlled drug release	Reduced protease activity, improved granulation tissue	(P. Zhou et al., 2025)
4	pH-responsive Ag–chitosan hydrogel	AgNPs, carboxymethyl chitosan	Low pH	Anti-biofilm	Effective biofilm clearance in infected wounds	(T. Liu et al., 2024)
5	Dual ROS/pH-responsive antioxidant gel	HA, tannic acid, Mn-oxide nanozyme	ROS + pH	Antioxidant	Significant ROS reduction	(J. Mo, Sun, et

				antimicrobial	and faster closure	al., 2025)
6	Anti-senescence GelMA hydrogel	GelMA, senolytic peptides	Enzyme-sensitive	Anti-aging, pro-angiogenic	Improved neovascularization and collagen maturity	(X. Yang et al., 2025)
7	Sprayable antibiotic thermogel	Pluronic, PEG, vancomycin	Temperature	Sustained antibiotic release	Reduced MRSA burden, rapid wound coverage	(Q. Zhou & Han, 2024)
8	Nanozyme + VEGF-mimetic hybrid gel	Ceria nanozyme, VEGF-peptides	ROS-responsive	Angiogenesis, antioxidant	Thick granulation tissue and improved vascularization	(Y. Zhang et al., 2025)
9	Self-healing chitosan-PDA hydrogel	Chitosan, polydopamine	Dynamic covalent bonding	Adhesive, antibacterial	Enhanced wound sealing and bacterial inhibition	(M. Sun et al., 2024)
10	Photoresponsive antibacterial hydrogel	GelMA, Au nanorods	NIR-light	Photothermal killing	Efficient MRSA eradication and re-epithelialization	(J. Wang & Hu, 2023)
11	Magneto-responsive composite gel	Alginate, Fe ₃ O ₄	Magnetic field	Enhanced drug penetration	Better antibiotic infusion into biofilms	(Zhao et al., 2024)
12	Exosome-loaded injectable hydrogel	HA, PEG, MSC-exosomes	Enzyme-sensitive	Anti-inflammatory, regenerative	High collagen maturity, increased vascular density	(Q. Hou et al., 2024)
13	Oxygen-releasing thermogel	Calcium peroxide, PNIPAAm	Temperature + oxygen release	Hypoxia relief	Strong granulation formation in ischemic wounds	(Fang et al., 2024)
14	Fibrin-PEG hybrid scaffold	Fibrin, MMP-sensitive PEG	Protease-responsive	ECM stabilization	Balanced remodeling, fibroblast activation	(Kim et al., 2023)

15	Conductive polypyrrole–gelatin hydrogel	Gelatin, polypyrrole	Electrical stimulation sensitive	Cell migration support	Faster re-epithelialization, improved fibroblast alignment	(Li et al., 2024)
16	Thermoresponsive HA–PNIPAAm hybrid	HA, PNIPAAm	Temperature	Moisture balance, flexibility	Excellent conformability on irregular wounds	(R. Wei & Zhang, 2025)
17	ROS-scavenging lignin hydrogel	Lignin nanoparticles, PEG	ROS	Antioxidant	Reduced oxidative stress and accelerated closure	(Park et al., 2023)
18	Cu ²⁺ -releasing hybrid hydrogel	PEG, copper nanoparticles	Ion-responsive	Angiogenesis, antibacterial	Strong antimicrobial effect + microvessel formation	(Huang et al., 2024)
19	Enzyme-triggered antibiotic-eluting gel	Gelatin, lipase-cleavable linkers	Bacterial enzymes	On-demand drug release	Targeted delivery reduced antibiotic usage	(Ramos et al., 2025)
20	Light-triggered growth factor hydrogel	HA, photo-cleavable VEGF conjugate	UV/light	On-demand angiogenesis	Controlled VEGF activation, improved tissue regeneration	(R. Chen et al., 2023)
21	Thermo-adhesive gelatin–PCL hybrid	Gelatin, PCL fibers	Temperature	Mechanical reinforcement	High tensile strength and faster wound closure	(Braid et al., 2023)
22	Antioxidant polyphenol–gelatin hydrogel	Gelatin, catechin/polyphe nols	ROS	Anti-inflammatory	Reduced cytokine levels and improved ECM quality	(J. Pu et al., 2022)
23	Moisture-regulating nanoclay hydrogel	Nanoclay, HA	Swelling-responsive	Moisture balance	Stable hydration and reduced scarring	(Salazar et al., 2024)
24	Chitosan–ZnO hybrid nanogel	Chitosan, ZnO nanoparticles	pH + ROS	Antibacterial, wound debridement	Strong bacterial killing and enhanced	(K. Wang et al., 2024)

					keratinocyte migration	
25	Glycosaminoglycan-mimetic hybrid hydrogel	Sulfated HA, PEG	Enzyme-responsive	ECM mimicry	Improved fibroblast–ECM interactions	(Dere et al., 2025)
26	Thermogelling peptide–polysaccharide hybrid	Self-assembling peptides, alginate	Temperature	ECM-mimetic support	Dense granulation tissue and rapid closure	(Qin et al., 2023)
27	ROS-triggered NO-releasing hydrogel	NO donor nanoparticles, HA	ROS	Vasodilation, angiogenesis	Significant enhancement in microcirculation	(Abbas et al., 2024)
28	Smart hemostatic chitosan-based hydrogel	Chitosan, Ca ²⁺	Ionic crosslinking	Hemostasis + antimicrobial	Rapid clotting and reduced infection	(R. Sun et al., 2024)
29	Collagen–PVA hybrid hydrogel	Collagen, PVA	Mechanical stress responsive	ECM mimicry	High mechanical stability and improved re-epithelialization	(Meng et al., 2023)
30	Thermoresponsive exosome–nanozyme hybrid	PNIPAAm, ceria nanozyme, MSC exosomes	Temperature + ROS	Regeneration + redox balance	Synergistic healing, strong angiogenesis and ECM restoration	(J. Mo, Peng, et al., 2025)

5. In Vitro and In Vivo Evidence for Efficacy

5.1 In Vitro Evidence

- **Cell viability, proliferation and migration:** Hybrid hydrogels support fibroblast and keratinocyte adhesion, proliferation and migration in scratch assays, demonstrating cytocompatibility and a favorable microenvironment for re-epithelialization (Y. Mo, Zhou, et al., 2025b; Y. Zhang et al., 2024).
- **ROS scavenging & oxidative stress mitigation:** Nanozyme-embedded hydrogels or antioxidant-loaded composites effectively neutralize ROS in vitro, protecting skin cells (fibroblasts, keratinocytes, endothelial cells) from oxidative damage and enhancing survival under oxidative stress (J. Pu et al., 2022; F. Zhai et al., 2025).
- **Antimicrobial activity:** Hydrogels incorporating metal nanoparticles or antibiotics inhibit growth of common wound pathogens (e.g., *Staphylococcus aureus*, *Escherichia coli*) while maintaining mammalian cell viability — demonstrating selective antimicrobial action (Y. Wang et al., 2024; Z. Zhou et al., 2025b).

5.2 In Vivo Evidence

Animal studies — mostly murine diabetic or infected wound models — provide robust evidence for the therapeutic potential of hybrid hydrogels:

- **Accelerated wound closure:** Thermoresponsive, injectable hydrogels or multifunctional nanohybrid systems maintain conformal wound coverage and moisture, promoting faster closure compared to control dressings (J. Wang et al., 2025b; Z. Zhou et al., 2025a).
- **Angiogenesis and ECM remodeling:** Hydrogels delivering pro-angiogenic cues or supporting endogenous angiogenesis lead to increased capillary density, enhanced granulation tissue formation and improved collagen deposition, resulting in more mature and organized healed tissue (Y. Pu et al., 2022; H. Yang et al., 2025)
- **Inflammation and oxidative stress modulation:** ROS-scavenging hydrogels reduce inflammatory cytokine expression, decrease oxidative stress markers and facilitate macrophage polarization toward anti-inflammatory (M2) phenotypes — essential for transitioning from inflammation to the proliferative phase (J. Pu et al., 2022; F. Zhai et al., 2025).
- **Infection control:** In infected wound models, antibacterial hydrogels prevent biofilm formation, reduce bacterial load and promote healing; when combined with antioxidant and regenerative functions, they address both microbial burden and impaired healing simultaneously (Z. Zhou et al., 2025b).

Collectively, these in vitro and in vivo studies confirm that hybrid, multifunctional hydrogels can effectively overcome multiple pathological barriers in chronic wounds, demonstrating therapeutic efficacy that surpasses conventional dressings.

6. Challenges, Limitations and Translational Considerations

Despite encouraging preclinical results, several challenges remain before widespread clinical translation:

1. **Biocompatibility and Long-term Safety:** The long-term effects of synthetic polymers, metal nanoparticles, or nanozymes (e.g., potential cytotoxicity, local or systemic accumulation) require thorough investigation through chronic toxicity studies and large-animal models (H. Wang et al., 2024).
2. **Complex Fabrication and Reproducibility:** Multifunctional hydrogels often involve multiple components — polymers, crosslinkers, nanomaterials, bioactive agents — complicating scalable manufacturing, standardization and quality control.
3. **Regulatory Hurdles:** Given the combination of biomaterials, drugs and possibly nanomaterials, regulatory pathways for such “combination products” may be complex, requiring extensive safety and efficacy data.
4. **Storage, Stability and Shelf-life:** Stimuli-responsive hydrogels may lose responsiveness, bioactivity, or stability over time; ensuring shelf-stability, sterility and reproducibility under clinical storage conditions is non-trivial.
5. **Cost and Accessibility:** Advanced hybrid systems may be more expensive than conventional dressings, posing barriers for large-scale or resource-limited healthcare settings — especially in low- and middle-income regions where chronic wounds are common.
6. **Patient-Specific Variation and Wound Heterogeneity:** Chronic wounds vary widely in etiology (diabetic, venous, pressure), microbial colonization, exudate level and comorbidities. A “one-size-fits-

all” hydrogel may not be ideal; personalized or tunable systems may be necessary, increasing complexity.

7. Future Directions

Based on recent literature and current challenges, we identify the following promising directions for future research and development:

- **Multi-stimuli responsive hydrogels:** Combining temperature, pH, enzyme, ROS and external triggers (e.g., light, electrical) to allow adaptive, phase-specific therapeutic delivery tailored to wound status (Y. Mo, Zhou, et al., 2025a; L. Zhang & Hu, 2025).
- **Smart dressings with real-time monitoring:** Incorporating conductive or biosensing components (e.g., conductive hydrogels) to enable real-time monitoring of wound parameters (pH, temperature, exudate, infection) and trigger therapeutic release or alert clinicians — bridging therapy with diagnostics (X. Zhang et al., 2025).
- **Cell / exosome / growth factor-loaded hydrogels:** Embedding stem cells, exosomes, or growth factors in supportive hybrid matrices to promote true regenerative healing, especially for large or chronically non-healing wounds.
- **Personalized medicine approaches:** Designing hydrogels tailored to patient-specific wound characteristics (microbial profile, protease levels, exudate, comorbidities) for precision wound care.
- **Scale-up, GMP production and regulatory preparation:** Developing robust manufacturing protocols, ensuring stability, sterilization, reproducibility and safety — prerequisites for clinical trials and eventual commercialization.
- **Large-animal and clinical studies:** Transitioning from rodent models to large-animal wound models, followed by well-designed human clinical trials to assess safety, efficacy, usability and cost-benefit in real-world chronic wound care.

8. Conclusions

Hybrid and stimuli-responsive hydrogels represent a paradigm shift in chronic wound management. By integrating multifunctionality — via polymeric design, nanomaterials and bioactive agents — these hydrogels can dynamically respond to the complex and changing microenvironment of chronic wounds, addressing infection, oxidative stress, inflammation, impaired angiogenesis and ECM disruption in a coordinated fashion. Recent advances (2023–2025) demonstrate significant progress: injectable thermogels, nanozyme-laden ROS-scavenging hydrogels, multifunctional antimicrobial/ antioxidant/ hemostatic dressings and senescence-targeting regenerative scaffolds.

However, substantial challenges remain: long-term biocompatibility and safety, manufacturing scalability and reproducibility, regulatory classification of multifunctional dressings, stability and shelf life and cost-effectiveness. Moving forward, research should focus on multi-stimuli responsive, adaptive hydrogels, smart dressings with diagnostic capability, cell or exosome-based regenerative strategies and clinical translation via large-animal studies and human trials.

With interdisciplinary collaboration among biomaterials science, nanotechnology, pharmacology and clinical wound care, hybrid hydrogels hold the promise of becoming next-generation standard-of-care dressings for chronic, non-healing wounds — offering improved healing rates, reduced complications and better quality-of-life for patients.

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