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REVIEW

Innovative Nanocomposite Scaffolds Containing ZIF-8 Nanoparticles for Improving Wound Healing: A Review

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Abstract

Multifunctional nanocomposite scaffolds, particularly those incorporating zeolitic imidazolate framework-8 nanoparticles (ZIF-8 NPs), are emerging as effective solutions for skin and tissue injuries due to their biocompatibility, structural stability, and antibacterial properties. Integrating ZIF-8 NPs into polymeric scaffolds has significant potential for improved tissue regeneration. This review examines recent advancements in ZIF-8 NP-integrated scaffolds, including their applications in nanofibers, hydrogels, microneedles, and 3D-printable scaffolds. It details the synthesis methods, structural characteristics, and physicochemical properties of ZIF-8 NPs, highlighting their role in enhancing wound healing. The methodological basis of ZIF-8 in wound healing applications involves its synthesis and functionalization to enhance biocompatibility, enabling the creation of drug delivery systems that release bioactive agents in a controlled manner to promote tissue regeneration and accelerate wound healing. This review highlights the biocompatibility and biosafety of ZIF-8 NPs, noting their non-toxic nature within specific concentration ranges and their multifunctional capabilities, such as antibacterial and anti-inflammatory effects that facilitate angiogenesis and infection management. The review also addresses current challenges and future perspectives in developing and clinically translating ZIF-8-based nanocomposite scaffolds as next-generation materials for improving wound healing.

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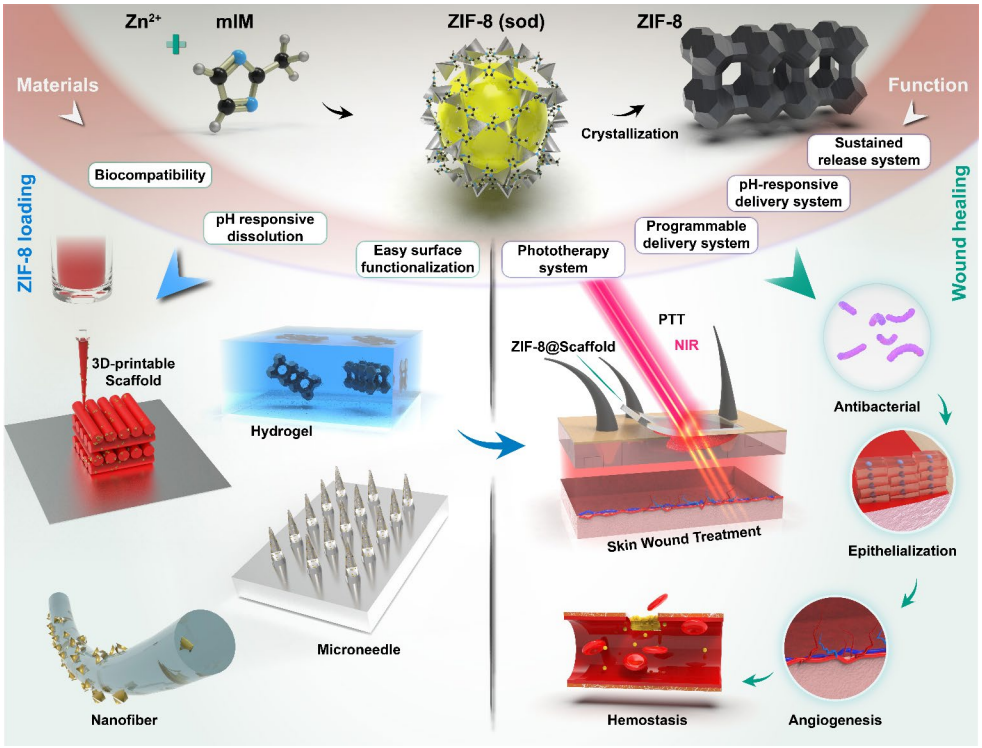
Graphical abstract



Keywords ZIF-8 Metal-organic Frameworks · Nanocomposite Scaffolds · Skin Tissue Engineering · Wound Healing

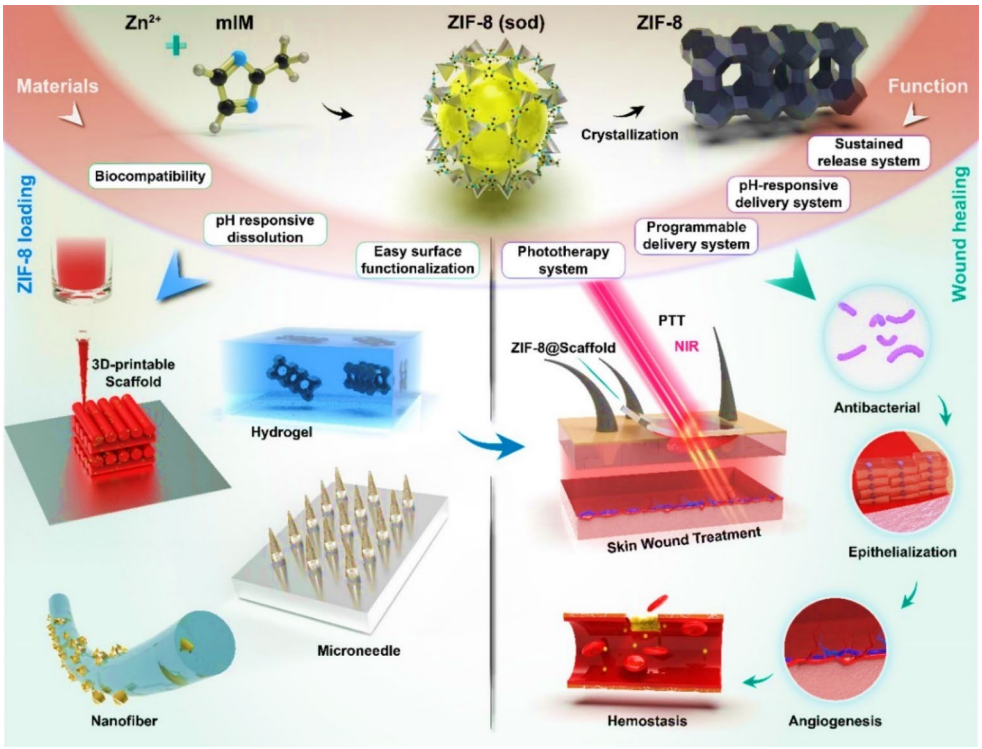
Abbreviations

BG	Bioactive glass
CFU	Colony-forming unit
CCM	Curcumin
DMOG	Dimethyloxalylglycine
ECM	Extracellular matrix
GOx	Glucose oxidase
GSH	Glutathione
GR	Glutathione reductase
AuNCs	Gold nanoclusters
GF	Growth factor
HRP	Horseradish peroxidase
MOFs	Metal-organic frameworks
MeHA	Methacrylated hyaluronic acid
GelMA-CDH	Methacrylated gelatin
MNs	Microneedles
NIR	Near-infrared
PTT	Photothermal therapy
PDA	Polydopamine
PCL	Polycaprolactone
PLLA	Poly(L-lactic acid)
PVA	Polyvinyl alcohol
PHDs	Prolyl hydroxylases
ROS	Reactive oxygen species
AgNCs	Silver nanoclusters
MPSS	Sodium succinate
SCI	Spinal cord injury
SPR	Surface plasmon resonance
TRG	Trigonelline
ZIF-8 NPs	Zeolitic imidazolate framework-8 nanoparticles

Introduction

Recent advances in skin tissue repair and wound care are becoming more important globally. This is due to the increasing number of chronic wounds, infections that resist antibiotics, and traumatic injuries [1–3]. These issues pose considerable economic burdens and negatively impact the quality of life for individuals worldwide, particularly affecting the aging population [4]. The skin, an essential organ responsible for protection against external threats and the regulation of bodily functions, frequently suffers compromised integrity and considerable morbidity from injuries such as burns, trauma, and chronic wounds [5]. Following a skin injury, if wounds are not effectively managed, they may progress to chronic non-healing wounds. This underscores

the critical importance of addressing the limitations of traditional wound dressings through innovative materials and methodologies to ensure efficient wound repair and regeneration [6, 7]. Traditional dressings, such as bandages and gauze, have significant limitations in wound healing including inadequate moisture management, weak antibacterial properties, poor adhesion, limited ability to promote tissue regeneration, and weak mechanical durability [8]. Therefore, advancements in skin tissue engineering technologies are crucial for effectively addressing these challenges and improving patient outcomes globally [9]. An ideal wound dressing should protect the wound from environmental factors and microorganisms while also being comfortable. It should facilitate rapid healing, manage exudate, ensure moisture and gas exchange, and be durable and biocompatible. To address these challenges, the development of advanced wound dressings using various materials has been explored, with advanced technologies playing a crucial role [8]. Among them, multifunctional nanocomposite scaffolds have emerged as ideal wound dressing materials due to have above-mentioned diverse beneficial properties [10–12]. In terms of biomaterials and nanotechnology, metal-organic frameworks (MOFs) have gained considerable attention within the field of regenerative medicine [13]. These MOFs, composed of metal ions and organic ligands, exhibit unique properties and diverse functionalities, making them a promising class of crystalline porous nanomaterials [14, 15]. Zeolitic Imidazolate Framework-8 nanoparticles (ZIF-8 NPs), a notable subclass within MOFs, have attracted considerable interest due to their unique composition of zinc ions and imidazolate ligands [16–18]. They share structural similarities with conventional aluminosilicate zeolites, embodying a fusion of characteristics from both traditional zeolites and MOFs [19]. Significant research efforts are directed towards exploring various synthesis methods of ZIF-8 and its potential applications in tissue engineering [20, 21]. ZIF-8 boasts facile synthesis under mild conditions, tunable porosity, high drug loading capacity, inherent biodegradability, biocompatibility, and sensitivity to pH changes, along with outstanding thermal and chemical stability [22]. These features enable their use in various biomedical fields such as bioimaging, biosensing, gas storage, drug delivery, photodynamic therapy, and gene delivery [23]. Zn-ZIF-8 stands out for its exceptional ability to combat bacteria, thanks to the presence of zinc ions and its photodynamic properties, which effectively disrupt bacterial cell membranes [24]. Moreover, beyond their role in antibacterial action, the rigid structure and porous nature of ZIF-8 NPs have propelled their use in biomimetic mineralization applications [25]. Researchers have leveraged ZIF-8 as a platform for creating biomineralized materials that encapsulate and safeguard the functionality of various biological molecules, such as enzymes, nucleic acids, proteins, and more [26]. As a result, combining MOFs with various scaffolds leads to modifications that enhance scaffold properties. These modifications foster improved cell adhesion and responses, while simultaneously enhancing the capacity for drug loading. Therefore, the integration of ZIF-8 NPs into various scaffolds, including nanofibers, hydrogels, microneedles (MNs), and 3D-printable scaffolds, not only enhances mechanical characteristics, biological activity, and responsiveness to external stimuli but also offers the potential for multifunctional wound dressings (Scheme 1). Developing these scaffolds based on various natural and synthetic polymers, along with proteins, has enabled the creation of versatile biomaterials that can be tailored for specific applications in tissue engineering and regenerative medicine. Notably, the growing interest in biopolymer- and protein-based wound dressings stems from their unique physical, chemical, and biological properties, including exceptional biocompatibility, biodegradability, and responsiveness, all of which significantly enhance wound healing [27, 28]. Additionally, nanofiber and hydrogel-based scaffolds offer numerous advantages in wound healing by closely mimicking human tissues in their ability to absorb water, making them breathable, soft, and flexible [3, 29, 30]. This helps maintain moisture, promote cell proliferation, and facilitate the delivery of essential nutrients to the wound site. Hydrogels generate an ideal environment for repair, regeneration, and overall wound healing. Their biocompatibility, biodegradability, and resemblance to the extracellular matrix (ECM) make them particularly effective. In general, natural-based scaffolds, in particular, are promising biomaterials for wound treatment due to their numerous beneficial properties [31]. MNs offer unique advantages in wound healing and tissue regeneration by easily penetrating physical barriers such as scars, clots, and exudates to sustainably release drugs, while also being easy to self-administer, cost-effective, and highly efficient for transdermal drug delivery [32]. Similarly, 3D-printable scaffolds for wound healing offer customizable structures that enhance tissue regeneration, promote cell growth, and can be tailored to fit specific wound sites, thereby improving healing outcomes [33]. These attributes make these scaffolds highly promising candidates for developing future advanced wound dressings [34]. In this review, we aim to provide a comprehensive overview of recent advancements in ZIF-8-based nanocomposite scaffolds for wound healing and skin tissue engineering. We will discuss synthesis strategies, structural characteristics, and physicochemical properties of ZIF-8-based scaffolds, highlighting their potential advantages over conventional wound dressings. Furthermore, we will investigate the mechanisms underlying the bioactivity of ZIF-8 NPs, including their interactions with cells and ECM components, and their ability to



Scheme 1 Schematic illustration of the formation of ZIF-8 nanoparticles (NPs) and their incorporation into various scaffolds (ZIF-8@Scaffolds). These advanced scaffolds represent next-generation approaches for skin tissue engineering and wound healing

promote tissue regeneration. Additionally, we will explore the challenges and opportunities associated with the translation of ZIF-8-based scaffolds. By offering insights into their potential for advancing wound healing, this review aims to inspire further research and development in this dynamic field.

Production and Physicochemical Properties of ZIF-8 NPs

Various approaches and conditions have been investigated to develop ZIF-based NPs and nanocomposites for biomedical uses, each offering unique advantages [35]. These processes mainly involve the coordination of zinc ion (Zn^{2+}) with imidazole derivatives, serving as metal cations and bidentate organic ligands. These ligands act as linkers, connecting the metal centers of $Zn(Im)_4$ units [36]. The fabrication of ZIF-8 nanostructures is achieved through hydrothermal or solvothermal methods, using solvents such as methanol, ethanol, and water, with widely varying reaction parameters. Scaling up production while maintaining high yields can indeed be challenging with solvothermal techniques. Optimizing synthetic conditions to favor nucleation overgrowth is crucial for achieving the desired NP size. In 2011, for the first time, a cost-effective method was described for preparing ZIF-8 crystals in water at room temperature, yielding crystals within approximately 5 min with a size of around 85 nm and demonstrating excellent solvothermal and thermal durability [37]. The room temperature solution reaction and solvothermal methods produce hollow ZIF-8 structures with high crystal quality and significant capacity for anticancer drug loading, facilitating targeted drug delivery. The electrodeposition-solvothermal method creates a uniform ZIF-8 membrane from a ZnO/2-methylimidazole composite, enhancing the adsorption capacity for acidic drugs like ibuprofen. These methods collectively highlight the versatility and efficacy of ZIF-8 synthesis for various biomedical applications. Adjustments in synthesis conditions, such as the molar ratio of reactants, duration, reaction temperature, solvent type, and solution pH, significantly impact the physicochemical properties of ZIF-8 NPs [35]. These variations can lead to the formation of ZIF-8 colloids with specific morphologies, pore characteristics, and chemical compositions. Their ability to modify surface chemistry to incorporate targeting ligands enhances drug delivery specificity, positioning ZIF-8 NPs as promising materials for biomedical applications in drug delivery systems and tissue engineering [38]. The functionality of ZIF-8 NPs is a crucial aspect that can be controlled through various methods. While ZIF-8 NPs alone may not exhibit significant effectiveness in medicine, their therapeutic potential and biocompatibility can be greatly enhanced when combined with other substances. One approach involves encapsulating different guest species inside ZIF-8 NPs, such as medications, contrast agents, or biomolecules. This showcases the effectiveness of ZIF-8-integrated nanocomposites in antibacterial treatments, drug delivery, and tissue engineering

applications. Regarding the methods for loading drugs into ZIF-8, there are two primary strategies [38]. The first is the impregnation method, where drugs are introduced into the pores of MOFs through electrostatic interactions, coordination reactions, or capillary forces. The second strategy involves in situ encapsulation during the MOF growth process, using a one-pot method to integrate functional molecules and create drug/MOF composites. Another approach involves using various polymers to coat the surface of ZIF-8 NPs [39]. ZIF-8 NPs can be incorporated into polymeric matrices through physical or chemical crosslinking methods to form ZIF-8-based nanocomposite scaffolds. These networks exhibit unique physicochemical properties, including high porosity, large surface area, and tunable mechanical strength, which can be tailored by adjusting the size and concentration of ZIF-8 NPs. The most commonly utilized technique for creating ZIF-8-integrated nanocomposites is the in-situ process, which involves incorporating the chosen material into ZIF-8 precursors during synthesis, followed by an encapsulation process under mild conditions [21]. Moreover, green nanotechnology is a rapidly growing field that offers innovative NPs drug formulations, significantly enhancing bioactivity and therapeutic performance [40]. The biosynthesis of ZIF-8 NPs in the presence of herbal extracts also emerges as an eco-friendly and sustainable approach that leverages the natural stabilizing agents found in plants [41]. For instance, herbal extracts like those from Allium sativum (garlic) have been successfully used to synthesize ZIF-8 NPs, which exhibit significant antimicrobial properties [42]. These green-synthesized ZIF-8 NPs have shown promising applications in the biomedical field, particularly in drug delivery and wound healing. The biocompatibility and low toxicity of these NPs further enhance their potential for clinical applications. Overall, these approaches enhance the potential of ZIF-8 NPs in developing safer and more effective therapeutic strategies.

Biocompatibility and Biosafety of ZIF-8 NPs

The biomedical community's emphasis on addressing safety concerns underscores the importance of ensuring the biocompatibility and biosafety of MOFs for various applications, particularly in biomedical settings where these considerations may take precedence over efficacy. Due to the significant potential of ZIF-8 NPs in biomedical applications, there has been growing interest in investigating their associated toxicity. ZIF-8 NPs offer a notable advantage in biomedical applications due to their suitable biosafety and biocompatibility characteristics [43]. These NPs undergo biodegradation under physiological conditions, releasing harmless degradation products that are easily metabolized and excreted from the body. The toxicity of ZIF-8 is intricately linked to its surface properties, including size and hydrophilicity balance. The critical factors determining cell viability of ZIF-8 include the cell's tolerance to the material, the level of free Zn^{2+}, and the rate of ZIF-8 release, where faster release leads to increased accumulation of zinc ions within cells [44]. Numerous in vitro and in vivo studies have demonstrated that ZIF-8 NPs and their composites are non-toxic when used within appropriate concentration ranges, confirming their suitability for biological applications. Zinc ion concentrations below 12.5 μg/mL exhibited no cytotoxicity towards RTG-2 and RTH-149 cell lines [45]. A recent study using single-cell analysis revealed that the cytotoxicity of ZIF-8 is influenced by both dose and particle size [46]. This study found that cells incubated with ZIF-8 NPs accumulated more zinc than those exposed to ZnO NPs, likely due to the higher bioavailability of ZIF-8 NPs. This increased zinc uptake led to elevated reactive oxygen species (ROS) levels and inflammation, ultimately inducing necrosis. Although cells can metabolize or excrete some ZIF-8, the remaining intracellular particles pose potential risks. They also showed that ZIF-8 NPs were more toxic than ZnO NPs of similar sizes, with lower IC50 values observed for ZIF-8, indicating higher toxicity. The IC50 values for 200, 90, and 50 nm ZIF-8 were 19.7 17.5, and 15.6 mg/L, respectively, indicating that the smaller size of ZIF-8 was more toxic. As they reported, the multiple toxic effects of ZIF-8 NPs on cells are primarily due to their high bioavailability, leading to increased zinc absorption compared to traditional ZnO NPs [47]. Another study examined the effect of varying ZIF-8 concentrations on six cell lines and revealed that toxicity escalated when ZIF-8 concentrations surpassed 30 μg/mL, primarily due to the generation of mitochondrial ROS triggered by the release of zinc ions [48]. The accumulated zinc can inhibit the glutathione reductase (GR) enzyme, reducing glutathione (GSH) production and elevating cellular ROS levels, which triggers inflammation and upregulates genes like CCL4 and IL6, potentially causing cell necrosis. Therefore, to further enhance ZIF-8 biomedical suitability, strategies such as modifying surface interactions to reduce toxicity and leveraging their inherent degradability to prevent accumulation in biological systems, while maintaining appropriate concentration ranges to ensure safety, are employed.

Application of ZIF-8 NPs for Improving Wound Healing

As aforementioned, due to their structural diversity, high porosity, and capability to deliver vital zinc ions, ZIF NPs have been widely applied in wound healing [43]. ZIF-8

NPs, characterized by ion connectors within a monocrystalline structure, hold considerable promise in biomedicine, notably for its sustained release of Zn^{2+}, fostering angiogenesis and antibacterial effects. This positions ZIF-8 as a promising material for enhancing skin wound healing.

Physiology of Wound Healing

Before exploring the potential applications of ZIF-8 NPs in wound healing, it is essential to understand the physiological processes involved in this intricate phenomenon. Wound healing occurs through a dynamic sequence of stages: hemostasis, inflammation, proliferation, and remodeling [49]. These phases involve intricate interactions among various cell types and growth factors (GFs). The initial hemostasis phase involves the formation of a blood clot to stop bleeding. Platelets and clotting factors work together to temporarily seal the wound. In the inflammation phase, the body's immune system responds to the wound by removing debris, pathogens, and damaged cells [50]. Inflammatory cells, such as neutrophils and macrophages, clean the wound site and release signaling molecules to initiate the healing process. In the proliferation stage, new tissue forms to replace lost or damaged areas [51]. Fibroblasts produce collagen, the primary structural protein in connective tissue, creating a framework for repair. Endothelial cells generate new blood vessels to deliver nutrients and oxygen to the healing tissue. The final remodeling phase strengthens and refines the newly formed tissue. Collagen fibers undergo rearrangement and maturation, resulting in improved tissue strength and flexibility [52]. This phase can last for months or even years, gradually reducing the size and visibility of scar tissue. Each stage of wound healing is characterized by specific cellular and molecular activities regulated by numerous GFs, cytokines, and ECM components. Successful wound healing depends on the coordinated cooperation of these cells to repair tissue and restore normal function. Disruption of this process can lead to chronic wounds, where inflammation persists for months or even years, significantly slowing healing and increasing the risk of complications such as infections and excessive protease activity [53]. In contrast to acute wounds, which typically resolve within a few weeks, chronic wounds persist for more than three months [54].

ZIF-8 NPs Potential in Wound Healing

Considering the aforementioned challenges in skin wound healing, ZIF-8 NPs have shown great potential in expediting the process of wound healing by stimulating cell proliferation, migration, and angiogenesis while simultaneously reducing inflammation and microbial colonization [55]. By interacting with various cell types involved in wound healing, ZIF-8 NPs promote cellular responses that aid in tissue repair [56]. The porous structure of ZIF-8 NPs enables the controlled release of bioactive substances like zinc and oxygen, which are vital for wound healing [57, 58]. Additionally, the antibacterial properties of ZIF-8 NPs arise from the release of Zn^{2+} and the creation of ROS under physiological conditions, proving effective against various types of bacteria [59]. Their superior antibacterial properties and biocompatibility make them valuable additions to wound dressings and hemostatic agents, providing effective solutions for combating infections and promoting hemostasis. Overall, these NPs offer exciting prospects for advanced therapies that accelerate wound closure, improve tissue regeneration, and enhance patient outcomes.

ZIF-8 NPs Potential in Angiogenesis

Enhancing angiogenesis, the formation of new blood vessels, is a key strategy for skin tissue regeneration, especially in conditions like diabetes and peripheral vascular disease where microvascular repair is compromised [60]. As mentioned in Sect. 4.1, following injury, inflammatory cells release angiogenic factors that promote new blood vessel growth. Successful healing is marked by the formation of granulation tissue, characterized by intense angiogenesis, essential for restoring nutrient and oxygen supply while removing waste. However, in chronic wounds, damaged microvessels cause fluid retention, inflammation, and hypoxia, which provoke a robust inflammatory response that hinders wound healing [61]. These conditions trigger endothelial cells and immune responses, with macrophages pivotal in healing and angiogenesis. The polarization of macrophages significantly impacts wound repair and the angiogenic process. Angiogenesis in the provisional matrix is driven by GFs. However, insufficient levels of key GFs, such as VEGF and TGF-β, along with their receptors, can hinder vascular and epithelial recovery, causing wounds to remain in the inflammatory phase [62]. If angiogenesis is impaired during this phase, chronic wounds may develop due to delayed healing, underscoring the importance of targeting angiogenesis in therapeutic strategies. Consequently, recent advancements in tissue engineering have increasingly focused on nanomaterials to enhance wound healing through angiogenesis [61]. In this context, ZIF-8 NPs emerged as a promising ally in promoting angiogenesis [63, 64]. They enhance angiogenesis by upregulating the expression of VEGF and promoting endothelial cell proliferation and migration. The porous structure of ZIF-8 facilitates the controlled release of vital molecules and ions, including zinc and oxygen, which are essential for stimulating angiogenesis. In this regard, Wang et al. [65] devised a zinc-based MOF incorporating curcumin (CCM) as the ligand, loaded

into poly(L-lactic acid) (PLLA) scaffolds to create a dual-release system for wound repair in diabetic conditions. In vivo studies on diabetic mice revealed that these scaffolds expedited wound healing by fostering angiogenesis, reducing inflammation, boosting collagen deposition, and promoting lesion re-epithelialization. Notably, they effectively reduced ROS production and inflammatory responses during the acute inflammation phase, highlighting the efficacy of their mechanism. By enhancing blood vessel formation, ZIF-8 NPs accelerate tissue oxygenation and perfusion, thereby expediting healing and minimizing complications.

Antibacterial and Anti-inflammatory Effects of ZIF-8 NPs

As mentioned in the earlier sections, ZIF-8 NPs and their derivatives show great antibacterial potential in wound infection management owing to their distinctive characteristics. Since bacterial infections commonly obstruct wound healing, these materials represent a significant advancement. The inherent antibacterial properties of ZIF-8, stemming from the imidazole ring, make it particularly promising for combating wound infections. As reported, imidazole derivatives demonstrate potent biological activity, disrupting liposomes sensitive to gram-positive bacteria and fungi while preserving mammalian cells and gram-negative bacilli [69–71]. Moreover, the zinc ions released from ZIF-8 structures further augment their antimicrobial properties, effectively preventing microbial growth [70]. Although the exact antimicrobial mechanism of ZIF-8 requires further research, its potential in combating wound infections is evident [24]. Zinc ions exhibit antimicrobial properties by deforming cells and rupturing walls, ultimately impeding bacterial growth or causing their death [66]. Additionally, through Fenton-like reactions, they generate ROS, which destroys bacterial components and leads to cell death [67, 68]. ZIF-8 NPs combat bacteria and regulate inflammation by suppressing pro-inflammatory cytokines and recruiting macrophages toward an anti-inflammatory state. Consequently, this multifaceted approach positions ZIF-8 NPs as promising antibacterial candidates for wound dressings and scaffolds, providing optimism for acute and chronic wound treatments.

ZIF-8 NPs in Photothermal Therapy

PTT has developed as a promising method for treating bacterial infections, offering advantages over traditional antibiotic therapy [69]. It utilizes light-absorbing substances to create localized heat, inducing hyperthermia and thermal ablation in diseased tissues. PTT's benefits include shorter treatment duration, reduced likelihood of bacterial resistance, and broad-spectrum antibacterial effectiveness against various pathogens. These qualities highlight PTT's potential as a valuable tool in combating bacterial infections, particularly in scenarios where drug resistance poses a significant challenge. ZIF-8 NPs stand out among near-infrared (NIR)-responsive materials due to their strong light absorption in the NIR spectrum, making them ideal for PTT [70, 71]. Upon NIR irradiation, these NPs efficiently convert light energy into heat, leading to localized hyperthermia and elimination of bacterial cells. Additionally, the photothermal properties of ZIF-8 NPs stimulate collagen synthesis and angiogenesis, facilitating tissue regeneration, and promoting wound closure. For example, a recent study unveiled a groundbreaking method for photo-enhanced antibacterial research employing gold nanocluster-decorated ZIF (AuNCs@ZIF-8) [72]. This pioneering system shows potential to boost antibacterial effectiveness via photo-activation, marking a substantial advancement in the quest for efficient and precisely targeted antibacterial therapies.

ZIF-8 NPs Carrying Biomolecules and Ions

In addition to their outstanding attributes, as noted earlier, ZIF-8 NPs provide a versatile foundation for delivering essential biomolecules and ions vital for wound recovery [73]. These MOFs feature exceptional porosity, facilitating the encapsulation of various therapeutic substances, ranging from medications to proteins and imaging agents. Their pH-responsive degradability further amplifies their efficacy in crafting intelligent drug delivery systems, ensuring precise and regulated release of healing agents at the target site. GFs like platelet-derived GF (PDGF) and TGF-β can be accurately released from ZIF-8 carriers, fostering cell proliferation and ECM deposition-critical steps in tissue repair [72]. Furthermore, the incorporation of ions like zinc and copper into ZIF-8 matrices can modulate cellular signaling pathways, promoting tissue regeneration [72]. So, combining ZIF-8 NPs with other structures has led to the development of multifunctional systems, laying the foundation for advanced theranostic approaches [68]. These multifunctional systems hold promise for advancing wound healing therapies, offering improved efficacy and safety profiles, and potentially transforming the landscape of regenerative medicine.

Nanocomposite Scaffolds Containing ZIF-8 NPs

Nanofiber-Based Scaffolds

Nanofibers incorporating NPs represent a cutting-edge category of biomaterials poised to revolutionize wound healing therapies [74, 75]. Electrospinning is a versatile method in biomedical engineering that produces micro/nanofibers from

various polymers or polymer-embedded therapeutic NPs [76–78]. These fibers closely mimic the ECM, fostering an ideal environment for cellular activities crucial in tissue regeneration [79]. Electrospun constructs facilitate cellular migration, proliferation, and differentiation, accelerating the formation of new tissue [80]. These nanocomposites combine the structural characteristics of nanofibers with the functional properties of NPs, presenting distinct advantages such as a high surface area-to-volume ratio, bolstered mechanical strength, and regulated release kinetics. Additionally, the incorporation of therapeutic NPs enables the targeted delivery of bioactive molecules, GFs, or antimicrobial agents, enhancing wound healing while reducing infection risks [81]. This fosters cellular proliferation and angiogenesis while curbing infection and inflammation [82, 83].

In this context, Hang et al. [84] fabricated a pioneering composite consisting of polycaprolactone (PCL) and CUR-incorporated ZIF-8 (abbreviated as PCL/ZIF-8/CUR) via a seed-free soaking technique. PCL, a biodegradable synthetic polymer, forms the foundation for incorporating powdered crystalline ZIF-8, transforming it into a versatile wound-healing dressing. The nanostructures of ZIF-8 and the presence of hydroxyl groups on the polymer surface enhance the polarity of electrospun PCL films, significantly boosting breathability and hydrophilicity. This innovative approach not only overcomes the inherent limitations of each material but also amplifies their functionalities synergistically. CUR, sourced from the rhizomes of Zingiberaceae and Araceae, holds substantial medical value due to its various pharmacological benefits, particularly in wound healing, where it acts as an antioxidant, stimulates collagen synthesis, and displays anti-inflammatory and antibacterial properties. Despite its therapeutic potential, CUR faces challenges such as insolubility in water and susceptibility to degradation under neutral and alkaline conditions. Ingeniously addressing this issue, this study developed an acid-responsive composite transmembrane dressing by loading CUR-incorporated ZIF-8, safeguarding CUR from degradation in alkaline and neutral environments, thereby boosting its durability and biomedical applicability. As they reported, ZIF-8/CUR showed pH-responsive Zn^{2+} controlled release in acidic environments, with approximately a 3-fold increase in Zn^{2+} concentration at pH 5.5 compared to pH 7.5. Moreover, the developed PCL/ZIF-8/CUR composite demonstrated outstanding permeability, biocompatibility, hydrophilicity, thermal durability, and antibacterial activity, with a notable H_2O_2-scavenging efficiency of $95.01 \pm 0.15\%$. They conducted both in vitro and in vivo investigations, including immunohistochemical staining, to examine the effects of PCL/ZIF-8/CUR on wound healing. Results revealed that this composite material promotes wound healing by enhancing angiogenesis factors, particularly VEGF while reducing inflammatory factors like TNF-α, thereby facilitating vascular regeneration and mitigating inflammation at the wound site. Consequently, it was concluded that the designed membrane was a resourceful approach as advanced wound coverings with potential applications in clinical settings. Similarly, Yin et al. [85] introduced an innovative wound dressing with both proangiogenic and antibacterial properties by encapsulating dimethyloxalylglycine (DMOG) within ZIF-8 NPs and electrospinning it with gelatin-PCL (DMOG@ZIF-8/Gel-PCL, abbreviated as DZGP). This study designed a network with a dual loading structure and sequential release properties. As the Gel-PCL nanofibers degrade in the moist wound environment, the ZIF-8 NPs are exposed, leading to their breakdown and subsequent release of angiogenic DMOG molecules and bactericidal Zn^{2+} ions. This orchestrated cascade aligns with the phases of inflammation response and tissue regeneration in ulcer healing, ensuring optimal bioavailability and sustained activity of therapeutic components while minimizing potential adverse effects. In vitro experiments demonstrated that the developed dressing, particularly at a DMOG@ZIF-8 content of 2.5%, effectively eliminated over 90% of *S. aureus* and *E. coli* bacteria without compromising fibroblast cell adhesion and proliferation. Their findings indicated that while ZIF-8 exhibited some hydrophobic properties, encapsulating it within the fibers had a negligible impact on the fiber membrane's hydrophilicity. Moreover, in vivo studies on diabetic rats infected with *S. aureus* showed significant wound healing within 14 days facilitated by DMOG molecules released from ZIF-8 NPs. Moreover, immunohistochemical examination confirmed the regulated expression of factors crucial for wound healing. Overall, this study demonstrates that leveraging ZIF-8 as both an antibacterial agent and drug carrier not only enhances chronic wound healing but also addresses concerns related to antibiotic misuse and burst release commonly encountered in conventional approaches, offering valuable insights into combating bacterial resistance and controlling drug release in wound dressings.

Similarly, in one of our studies, we utilized chamomile essential oil (MCEO) incorporated in ZIF-8 NPs to increase the antibacterial effectiveness of electrospun nanofibers for wound treatment applications [86]. By incorporating ZIF-8 NPs and MCEO into biodegradable and environmentally friendly nanofibers based on N-(3-sulfopropyl) chitosan/poly(ε-caprolactone), we achieved minimal alteration in the morphology of the nanofibers. The optimized nanofibers (PCL/SPCS (90:10)) exhibited a uniform structure with an average diameter of 90 ± 32 nm, alongside improved mechanical and thermal stability compared to pristine nanofibers. Notably, the developed nanofibers demonstrated remarkable antibacterial properties against *E. coli* and *S. aureus*, evidenced by inhibition zones of 31.2 mm and 32.3 mm, respectively. The findings from cytocompatibility assessments, DAPI staining, and SEM imaging revealed

that the formulated nanofibers exhibited favorable adhesion and proliferation characteristics when exposed to normal human foreskin fibroblasts-2 (HFF-2 cell line). In summary, our development of ZIF-8 NPs incorporated into electrospun nanofibers underscores their potential as impactful biomaterials for wound healing applications, akin to findings from other studies. The improved mechanical properties, cytocompatibility, and antibacterial efficacy of these nanofibers suggest their suitability as dynamic platforms for wound healing therapy.

Recently, bioactive glass (BG) has garnered significant attention among the various biomolecules loaded into ZIF-8 NPs, emerging as a promising candidate for wound healing applications, attributed to its capacity to stimulate GF secretion, enhance vascularization, and alleviate chronic inflammation [87]. However, the absence of a covalent bond between BG and the polymer network presents challenges regarding the durability and dispersion of inorganic NPs within the polymer matrix, thereby restricting their practical applications. As an example of this type of hydrogel, Hou et al. [88] engineered a novel composite network incorporating ZIF-8 NPs and BG into PCL/PVA matrices via microfluidic electrospinning (see Fig. 1). According to their findings, integrating ZIF-8 enhances the stability of bioactive BG, while also facilitating the controlled release of essential ions to stimulate GF expression and promote skin regeneration. In vitro and in vivo assessments confirmed that scaffolds loaded with BG/ZIF-8 exhibited outstanding biocompatibility and mechanical strength, with a notable tensile strength of 26 MPa. Furthermore, the resulting network displayed excellent antibacterial properties, achieving inhibition rates of 78.8% and 89.64% against *S. aureus* and *E. coli*, respectively. The BG/ZIF-8-loaded scaffold significantly improved wound shrinkage compared to the unloaded version, with the PCL/PVA@BG/ZIF-8 (1 wt %) group achieving a 95% shrinkage rate and 2.2 mm granulation growth thickness within 12 days. This innovative skin scaffold shows great promise for wound healing and potential commercialization in skin regeneration therapies.

In another interesting example, Yuan et al. [89] developed an innovative multifunctional hydrophilic wound dressing comprising PAN/PVP nanofibers embedded with ZIF-8-derived carbon NPs (ZnO@CNPs). This dressing provides adjustable moisture levels for quick wound disinfection and effective exudate management (see Fig. 2). Utilizing electrospinning, these NPs were seamlessly integrated into PAN/PVP nanofibers, culminating in the creation of a layered nanofiber sponge (ZnO@CNP-NFS) using gas foaming technology. The incorporation of ZnO@CNPs into the hydrophilic nanofiber sponge yielded significant results both in vivo and in vitro. The resulting ZnO@CNP-NFS exhibited notable photothermal conversion capability and sustained zinc ion release, facilitating synergistic antibacterial activity for rapid wound disinfection. Its hydrophilic

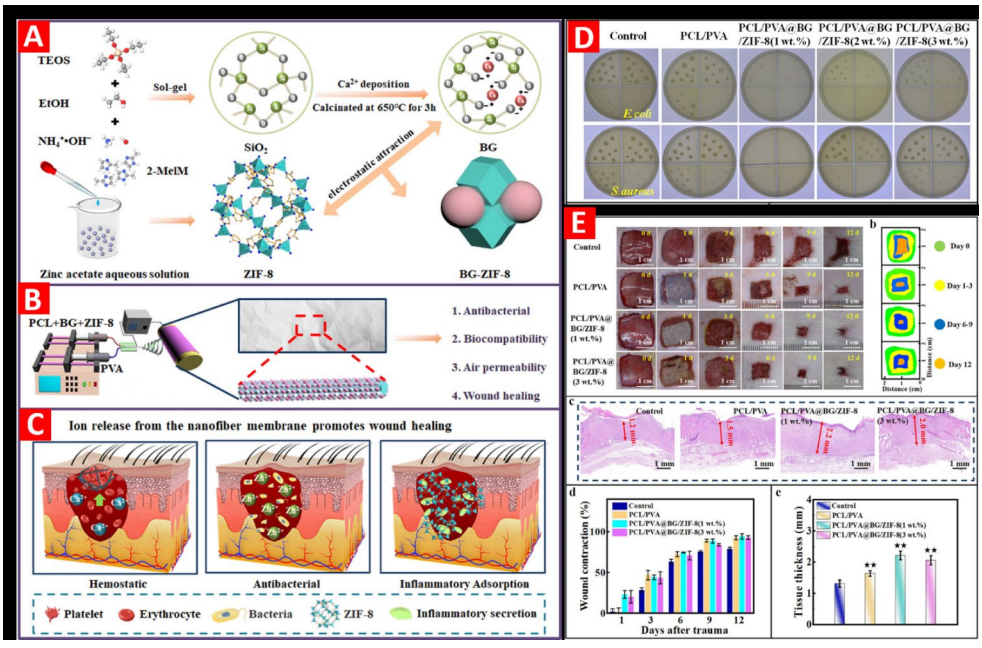


Fig. 1 **(A)** Diagram showing the synthesis of ZIF-8 and BG. **(B)** Schematic of gourd string nanofiber synthesis. **(C)** Illustration of how the skin scaffold promotes wound healing. **(D)** Growth inhibition plots of different skin scaffolds against *S. aureus* and *E. coli*. **(E)** (a) Photos of wound size changes in diabetic mice across four groups during 12 days of post-surgery. (b) Traces of wound bed closure for each treatment group in vivo. (c) Histological analysis of longitudinal sections using H&E staining. (d) Statistical analysis of wound shrinkage rate for each group post-surgery. (e) Statistical analysis of relative connective tissue thickness. Data are shown as mean values ± SD. $^{**}P < 0.01$ compared to the control group. [Reproduced (adapted) from Ref. [88] with permission from the ACS Applied Materials & Interfaces]

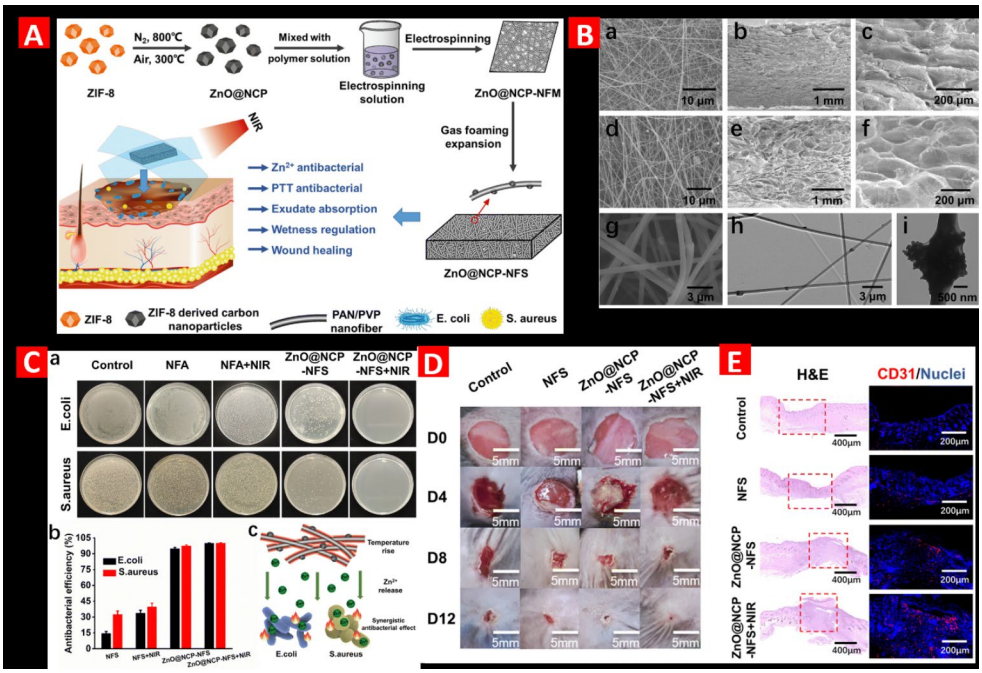


Fig. 2 **(A)** Preparation process of the nanofiber sponge dressing and its use in treating infected wounds. **(B)** SEM images showing (a) surface and cross-section views at (b) low and (c) high magnification of the NFs. SEM images of (d) surface and cross-section views at (e) low and (f) high magnification of ZnO@CNP-NFs. SEM image (g) and TEM image (h) of NFs doped with ZnO@CNPs. TEM image (i) showing ZnO@CNPs embedded in NFs. **C)** Broad-spectrum antibacterial activity of ZnO@CNP-NFS against *S. aureus* and *E. coli*. Photographs of agar plates (a) and antibacterial efficiency (b) of different treatment groups. (c) Schematic diagram of the chemical photothermal synergistic antibacterial mechanism of the NFs sponge. **D)** Photographs of the in vivo skin wound curing process on days 0, 4, 8, and 12. **E)** H&E staining images of healing skin on day 12 and immunofluorescence staining. [Reproduced (adapted) from Ref. [89] with permission from the journal of Materials Chemistry B]

properties enabled swift exudate absorption and enhanced liquid evaporation, aided by both the photothermal effect and its unique nanofiber structure, which could be modulated using irradiation light to optimize dressing wetness. This moist environment promoted skin regeneration without the risk of wound overhydration commonly associated with hydrophilic dressings. Furthermore, the biomimetic nanofiber structure resembling the ECM and its multi-level pore architecture facilitated oxygen permeation and expedited skin wound healing. Overall, this innovative wound dressing offers significant clinical value, presenting a promising solution for multifunctional antibacterial wound dressings and introducing fresh perspectives for rapid wound disinfection and exudate management.

In conclusion, the integration of ZIF-8 NPs into nanofiber-based wound dressings presents a promising and versatile approach for enhancing wound healing outcomes. The utilization of nanofibers in wound care has consistently shown compelling results across various research endeavors. These dressings have proven highly effective in fostering wound closure, expediting tissue regeneration, and minimizing scar formation. Furthermore, nanofibers excel in managing moisture, ensuring an optimal environment for wound healing.

Hydrogel-Based Scaffolds

Hydrogels, 3-dimensional networks of hydrophilic polymers capable of absorbing and retaining large amounts of water, have emerged as versatile platforms for biomedical applications [27, 90]. Hydrogel-based scaffolds can be created from a variety of natural and synthetic polymers using different techniques, such as radiation, freeze-thawing, or chemical methods [29, 91]. The synthesis often involves cross-linking processes, including physical, chemical, or radiation cross-linking, as well as grafting polymerization. These methods allow for the customization of hydrogels' mechanical properties, swelling behavior, and loading capabilities [92, 93]. Key factors influencing hydrogel functionality include the size of their pores and the molecular weight of the cross-linked polymer chains. Functionalization strategies for hydrogels commonly involve chemical modifications, covalent cross-linking, biomimetic enhancements, and the incorporation of bioactive molecules. These strategies enable the design of hydrogels with specific properties for diverse biomedical applications. In particular, hydrogel nanocomposites, a cutting-edge class of biomaterials that combine hydrogels with NPs, stand out as highly valuable scaffolds in biomaterials engineering [94–96].

As previously mentioned regarding nanofibers incorporating NPs, the synergistic integration of hydrogels and NPs in these nanocomposites offers several key benefits. These include enhanced mechanical strength, adjustable porosity, controlled release mechanisms, and improved bioactivity [97]. These nanocomposites serve as useful platforms for the targeted delivery of therapeutics, including GFs, antimicrobial agents, and anti-inflammatory drugs, directly to the wound site. This targeted delivery supports angiogenesis, cellular proliferation, and the reduction of infection and inflammation [98, 99]. Additionally, the biocompatibility, biodegradability, and ability of hydrogel nanocomposites to mimic the native ECM make them ideal for creating a favorable microenvironment that promotes efficient wound healing [100].

For example, Cai et al. [101] developed a multifunctional hydrogel scaffold, named HPZ8, designed to treat chronic infected wounds. As shown in Fig. 3, this hydrogel integrates polydopamine NPs (PDA NPs) within a dynamic cross-linked network of hydrazide-modified hyaluronic acid (HA-CDH) and oxidized HA (HA-CHO). PDA NPs are celebrated for their potent antioxidant properties, impressive photothermal capabilities, and excellent biocompatibility, making them effective as photothermal agents and ROS scavengers in skin rejuvenation [21]. These properties help mitigate oxidative stress and combat bacterial infections [102, 103]. However, the surface of PDA NPs is rich in primary and secondary amine, as well as catechol groups, which makes them prone to aggregation, thus reducing their effectiveness and hindering clinical applicability. In this

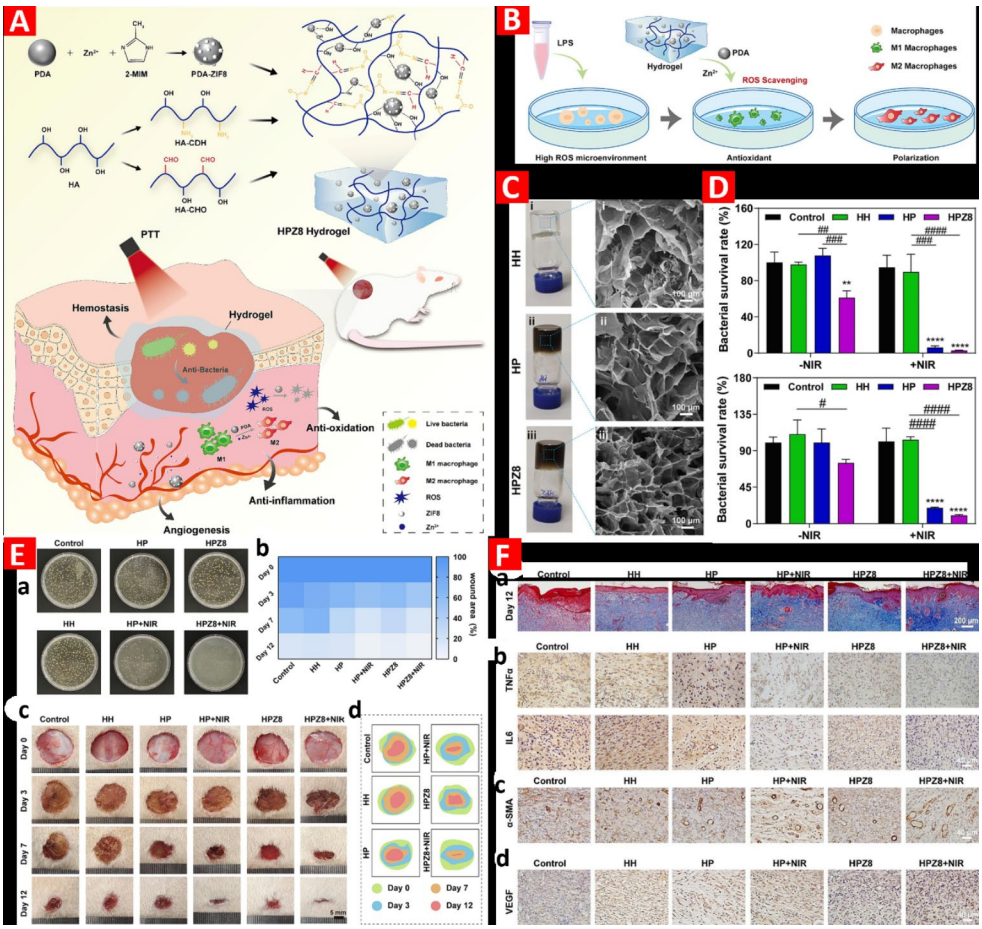


Fig. 3 **(A)** Schematic showing the formation and application of photothermal HPZ8 hydrogel for healing infected chronic wounds, emphasizing its anti-inflammatory, antioxidant, and M2 macrophage polarization properties. **(B)** Diagram illustrating HPZ8 hydrogel's role in scavenging ROS, reducing inflammation, and promoting M2 macrophage polarization. **(C)** Microscopic and SEM images of HH (i), HP (ii), and HPZ8 (iii) hydrogels in an inverted state. **(D)** Images of *S. aureus* suspensions treated with various hydrogels, with or without NIR laser irradiation (808 nm, 1.0 W/cm²), and the corresponding statistical analysis. **(E)** (a) Images of *S. aureus* colonies on LB plates from different wound areas on day 1. (b) Wound areas treated with different hydrogels during 12 days (**$P < 0.01$). (c) Macroscopic images of wound areas with different treatments. (d) Schematic images of wound areas with various treatments during 12 days. **F)** Histological staining evaluation: (a) Masson staining results of tissue after diverse treatments collected on day 12. (b) Immunohistochemical staining images of TNFα and IL6 for tissue collected on day 7. (c) Immunohistochemical staining images of α-SMA and (d) VEGF for tissue collected on day 7. [Reproduced (adapted) from Ref. [101] with permission from the Chemical Engineering Journal]

study, they synthesized PDA-ZIF8 NPs and incorporated them into the hydrogel, aiming to create a dressing that can sustain the release of active ingredients. This design reduces NP aggregation, drug resistance, and toxic side effects while preserving the biological functions of HA hydrogels. The resulting HPZ8 hydrogel represents a significant advancement in chronic wound treatment, combining the strengths of both PDA and ZIF-8 NPs within a biocompatible and functional hydrogel matrix. HPZ8 exhibited injectability, self-healing abilities, a porous structure, and numerous functional adsorption sites, facilitating application to irregular wounds and rapid hemostasis. The inclusion of PDA-ZIF8 NPs provided potent anti-inflammatory, antioxidant, and photothermal antibacterial properties, crucial for chronic wound healing. When co-cultured with bacteria and exposed to NIR laser irradiation, HPZ8 showed remarkable antibacterial effects, significantly reducing the survival rates of *S. aureus* and *E. coli* to 10.3% and 2.9%, respectively. Additionally, the hydrogel released Zn^{2+}, promoting angiogenesis, cell migration, and M_2 macrophage polarization, which accelerates the transition from inflammation to the proliferation stage, ultimately enhancing the infected wounds healing. The HPZ8 hydrogel's excellent adhesive and hemostatic properties were demonstrated by its relative hemostasis rate of 69.8%. Overall, the HPZ8 multifunctional nanocomposite hydrogel, combining HA derivatives with PDA-ZIF8 NPs, showed promising potential in addressing the complex therapeutic needs of chronically infected wounds, offering a comprehensive solution for accelerated wound healing.

In another recent landmark study, Han et al. [104] fabricated an adhesive bacterial cellulose (BC)-based hydrogel containing ZIF-8 NPs to accelerate wound healing. This multifunctional hydrogel was designed to provide long-term stable release of Zn^{2+}, offering exceptional angiogenic and antibacterial activities. BC is an excellent biomaterial for hydrogel scaffolds due to its outstanding mechanical strength, water retention, substantial porosity, and biocompatibility [105]. Its 3D network structure, formed by loosely arranged nanofibrils, enhances cell adhesion and facilitates NP integration. A significant challenge in hydrogel design is effectively loading antibacterial agents while maintaining their activity. This innovative approach overcame that challenge by facilitating NP deposition and preventing agglomeration. Using PDA, ZIF-8 was grown in situ within the BC porous structure, resulting in the BC/PDA/ZIF8-3 hydrogel [104]. This hydrogel exhibited notable antimicrobial activity, achieving killing rates of 69.3% and 61.6% against *E. coli* and *S. aureus*, respectively, related to the presence of Zn^{2+}. In vivo experiments demonstrated the hydrogel's effectiveness in expediting wound curiong in a full-thickness defect ulcer model via stimulating angiogenesis. Zn^{2+}-induced angiogenesis and fibrogenesis enhanced re-epithelialization, as evidenced by immunofluorescence and immunohistochemistry staining, which showed that the BC/PDA/ZIF-8 hydrogel promoted a higher density of blood vessel formation and more mature blood vessels compared to other groups. The findings indicate that BC/PDA/ZIF-8 hydrogels have significant potential for promoting effective wound healing, demonstrating robust antibacterial properties while enhancing cell proliferation, tissue formation, re-epithelialization, and tissue remodeling.

Similarly, Deng et al. [106] developed a multifunctional BC hydrogel infused with silver-loaded ZIF-8 NPs, termed BPZA, using an environmentally friendly method. This hydrogel exhibited outstanding antibacterial properties and promoted vascularization, making it ideal for wound healing applications. The BPZA hydrogel showcased impressive mechanical strength (> 1 MPa), exceptional swelling capacity (> 3000%), rapid temperature elevation to 50 °C under NIR irradiation, and stable release profiles of Ag^{+} and Zn^{2+} ions. In vitro assessments demonstrated enhanced antibacterial activity, with survival rates of 0.85% and 0.39% for *E. coli* and *S. aureus*, respectivily. Furthermore, in vitro cell experiments confirmed its satisfactory biocompatibility and promising angiogenic potential. In vivo studies on rats with full-thickness skin defects further revealed remarkable wound healing and accelerated skin re-epithelialization. Overall, this multifunctional BPZA hydrogel presents a highly effective solution for wound repair, combining potent photothermal antibacterial properties, pH-responsive ion release, and enhanced angiogenesis.

The increase in antibiotic-resistant bacteria makes it tough to heal wounds, pushing scientists to find new ways to fight bacterial infections [107]. In a groundbreaking advance, researchers have introduced a biomimetic injectable double-network hydrogel with remarkable antibacterial efficacy, harnessing the photocatalytic properties of semiconductor nanomaterials to generate ROS upon light exposure [108]. Their study focuses on the integration of Au NPs into ZIF-8 NPs, resulting in Au@ZIF-8 nanocomposites with augmented photocatalysis-driven ROS generation, capable of locally inhibiting bacterial growth. These nanocomposites are then incorporated into an injectable double-network hydrogel comprising oxidized sodium alginate (OSA) and methacrylated gelatin modified with carbohydrazide (GelMA-CDH) (Au@ZIF@GCOA) via radical polymerization and Schiff base reaction, ensuring optimal biodegradability and biocompatibility. Thanks to the combined effect of gold-mediated surface plasmon resonance (SPR) and Schottky junction, the Au@ZIF@GCOA hydrogels produce more ROS when exposed to visible light (> 400 nm) compared to hydrogels containing only ZIF-8. This leads to significantly improved abilities to kill bacteria

and reduce inflammation (99.1% for *E. coli* and 99.6% for *S. aureus*), as well as faster wound healing. In conclusion, this injectable hydrogel system, incorporating the Au@ZIF-8 composite, holds significant promise as a wound covering material for combating antibiotic resistance and wound curing effects in clinical settings.

Despite their advantages, hydrogels face limitations in clinical application due to shortcomings in mechanical stability, cell affinity, and tissue adhesiveness, particularly in moist environments [109]. Additionally, treating ulcers in specific areas presents further challenges, including movement constraints, fixation difficulties, poor adhesion performance, and inadequate wound site coverage with conventional treatment methods [110, 111]. To tackle these issues, our recent study has concentrated on developing durable self-healing hydrogels with exceptional bio-adhesion, mechanical stability, elasticity, and antimicrobial properties [41]. These hydrogels use dynamic covalent bonds and non-covalent interactions to self-repair in response to daily injuries, making them highly promising for wound healing. In this study, we developed a novel bioadhesive self-healing hydrogel by incorporating Myrtus communis L. extract@ZIF-8 NPs (MC@ZIF-8) into a hydrogel matrix made of dopamine-grafted oxidized sodium alginate/gelatin (DA-OSA/Gel) through dual cross-linking. The optimized hydrogel demonstrated excellent physicochemical properties, good self-healing, and strong tissue adhesion. In vitro tests showed remarkable cell adhesion and cytocompatibility in cultured fibroblasts. Furthermore, the MC@ZIF-8/ hydrogel showed nearly 100% antibacterial activity against both *S. aureus* and *E. coli*, along with significant antioxidant properties of approximately 87.23%. When applied to the injury site, the engineered hydrogel notably accelerated wound healing in a mouse model of cutaneous injury. This was evidenced by the increased thickness of cutaneous tissue, improved arrangement of collagen, enhanced vascularization, and augmented proliferation of fibroblasts compared to alternative treatments. In summary, the developed hydrogel demonstrated promising attributes as a wound dressing for healing joint skin wounds, thanks to its strong self-healing capacity, ability to adhere to the skin, bactericidal effects, antioxidative properties, and promotion of collagen deposition.

Furthermore, drawing inspiration from the concepts mentioned, hydrogel/nanofiber composites have recently also emerged as promising candidates for efficient wound management [112]. These composites address the limitations of traditional pure hydrogels, such as inadequate mechanical strength and rapid substance release. In a notable study, Cheng et al. [113] developed a composite patch by combining calcium alginate hydrogel with polylactic acid nanofibers (CAH/PLANF) into an interpenetrating network structure (see Fig. 4). The electrospun PLA nanofibers provided mechanical support and created an optimal environment for tissue regeneration, while the calcium alginate hydrogel facilitated moisture absorption and managed tissue fluid, thus shielding the wound from external bacterial threats. By incorporating photocatalytic ZIF-8 NPs into the composite, they improved the scaffolds' mechanical properties and endowed them with potent photodynamic antibacterial capabilities. With ZIF-8 concentration reaching 1000 mg/mL, ZIF-8@CAH/PLANF obtained remarkable log colony-forming unit (CFU) reductions exceeding 4 for both *S. aureus* and *E. coli*, conforming to a photocatalytic efficacy surpassing 99.99%. The resulting ZIF-8@ CAH/PLANF patch exhibited exceptional swelling behavior, robust mechanical strength, low cytotoxicity, and sustained photodynamic antibacterial effects. Moreover, in vivo studies confirmed its ability to combat bacterial infection and accelerate wound healing. Therefore, their developed hydrogel/nanofiber composite patch with an interpenetrating network structure demonstrates excellent water absorption, wound fluid management, mechanical strength, and biocompatibility.

In conclusion, the incorporation of ZIF-8 NPs into hydrogel nanocomposites offers a promising approach to enhance wound healing outcomes and address various challenges in wound care. The utilization of hydrogels in wound healing has demonstrated considerable potential in various research studies. These hydrogels exhibit versatility in delivering therapeutic agents, ensuring sustained release of bioactive molecules at the wound site.

Microneedle-Based Scaffolds

MNs, serving as another valuable approach, represent innovative platforms for delivering various medications to accelerate wound healing [114]. They provide a convenient and minimally invasive approach with reduced tissue damage [115]. MNs can administer a diverse array of substances including traditional Chinese medicines, antibiotics, microorganisms, GFs, metal ions, stem cells, and exosomes [116]. Through this delivery, they facilitate diabetic ulcer healing by leveraging multiple mechanisms, including anti-inflammatory, antibacterial, hypoglycemic, antioxidant, and angiogenic effects [117]. Additionally, the controlled release kinetics afforded by MNs further optimize therapeutic efficacy while curtailing potential adverse effects, rendering them suitable for addressing an array of wound etiologies spanning acute traumas to chronic ulcers and burns [118]. However, certain MNs, particularly those made from non-biodegradable materials like stainless steel, may create micro-holes at the wound sites. This poses risks of secondary physical injury and potential microbial

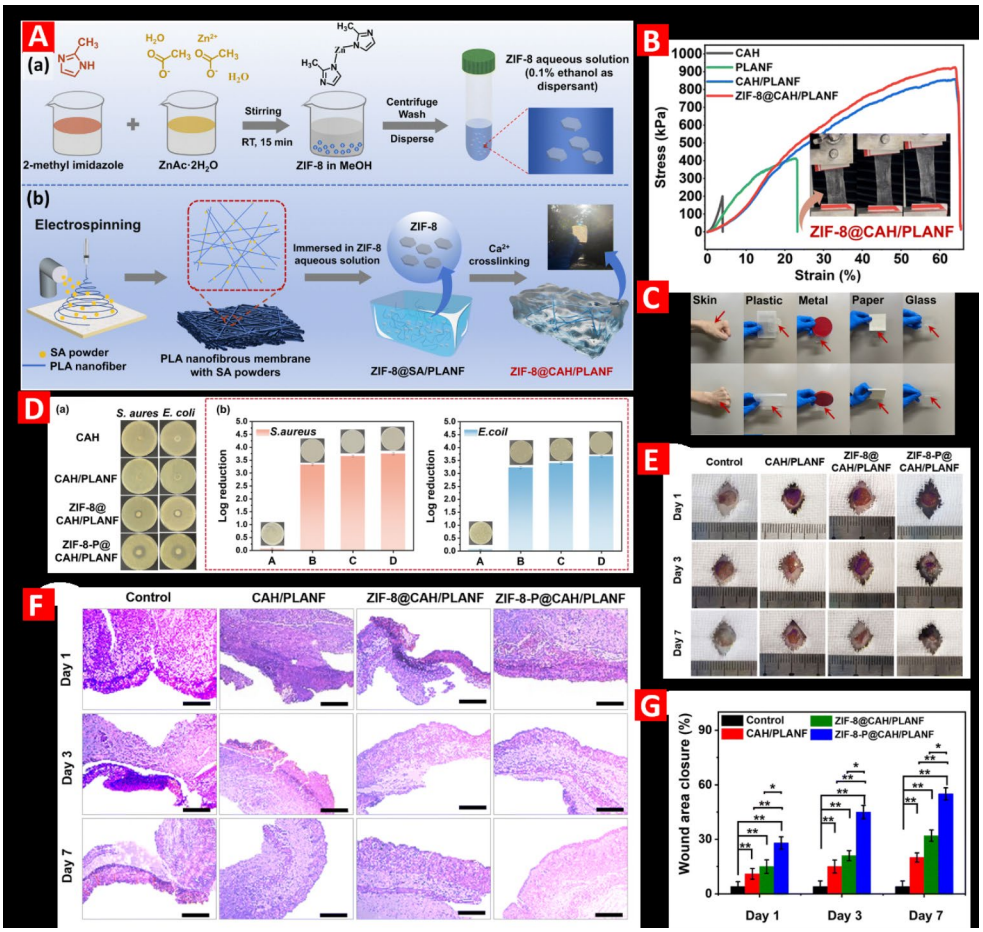


Fig. 4 **(A)** (a) Illustration showing the step-by-step formation of ZIF-8 powders. (b) Diagram depicting the sequential preparation stages of the ZIF-8@CAH/PLANF composite patch. **(B)** Stress-strain curves for CAH, PLANF, CAH/PLANF, and ZIF-8@CAH/PLANF, highlighting their tensile properties, as shown in the insets. **(C)** Adhesion test results for ZIF-8@CAH/PLANF. **(D)** Antibacterial activity evaluation of CAH, CAH/PLANF, and ZIF-8@CAH/PLANF: (a) Inhibition zones. (b) Bacterial growth inhibition assessed via colony counting. **E)** Optical images of wounds. **F)** H&E staining of wound sections, with scale bars of 200 mm. **G)** Evaluation of wound area closure. [Reproduced (adapted) from Ref. [113] with permission from the Journal of Materials Chemistry B]

infections. Despite these challenges, the benefits of MNs for wound healing are driving the development of novel MN arrays with various compositions and expected functionalities, enhancing their clinical utility [119].

As an example, in a groundbreaking development, Xiang et al. [120] designed a minimally invasive MN array composed of Cu@ZIF-8 NPs encapsulated in poly(ethylene glycol) diacrylate/carboxymethyl chitosan (PEGDA/CMCS), exhibiting excellent biocompatibility for promoting wound healing. PEGDA hydrogels, known for their hydrophilic polymeric networks and excellent biocompatibility, find extensive application in tissue engineering. Moreover, PEGDA can undergo photo-crosslinking with a photo-initiator when exposed to UV light. This characteristic renders the solution highly malleable, facilitating the convenient preparation of MNs. The incorporation of Cu@ZIF-8 NPs facilitated the generation of ROS upon exposure to H_2O_2, enhancing their antibacterial properties. The release of cupric ions from Cu@ZIF-8, combined with the antibacterial activity of the PEGDA/CMCS hydrogel scaffold, resulted in exceptional antibacterial efficacy. Additionally, the sustained release of Cu ions promoted angiogenesis. The degradable MN array ensured a continuous and controlled release of active ingredients, preventing secondary wound damage and enhancing epithelial regeneration and neovascularization. PEGDA/CMCS MNs loaded with Cu@ZIF-8 NPs effectively treated full-thickness cutaneous defects, showcasing both high biocompatibility and mechanical integrity. They facilitated re-epithelialization, angiogenesis, collagen deposition, and inflammation reduction in wounds. Overall, this study demonstrated the potential of Cu@ZIF-8 NPs-encapsulated PEGDA/CMCS MNs for wound healing, underscoring their effectiveness in promoting tissue repair and addressing skin defects.

Furthermore, MN technology has garnered significant interest in addressing diabetic wounds, which pose a substantial challenge due to their complex pathology and slow healing process [121]. In this regard, the self-powered enzyme-linked MN patch offers a multifaceted approach: it reduces local blood glucose levels, generates electrophysiological signals, and exhibits excellent antibacterial properties and biocompatibility. These features facilitate the rapid healing of diabetic ulcer and efficiently prevent scar tissue formation, making it a highly promising solution for diabetic wound management. In one of these investigations, Zhang et al. [121] developed a self-powered enzyme-linked MN patch

by integrating MN technology with enzymatic biofuel cells (BFCs) for scar-preventive healing of diabetic wounds. This innovative patch comprises MN arrays encapsulating glucose oxidase (GOx) and horseradish peroxidase (HRP) within ZIF-8 NPs, serving as the anode and cathode, respectively. The system leverages natural GOx bio-enzymes to ensure non-toxicity and reduces glucose concentration around the wound via the GOx-containing anode. Simultaneously, the HRP at the cathode releases oxygen to promote wound healing. This integration ensures a stable bioelectricity output from the abundant glucose supply, providing a straightforward and efficient strategy for wound management. The enzymatic cascade reaction within the MN patch effectively reduces local hyperglycemia in diabetic wounds while generating stable microcurrents, thereby promoting rapid wound healing and preventing scar formation. Notably, all MN patches exhibited a 100% bacterial killing rate, underscoring their exceptional antibacterial effectiveness. In summary, the ZGH-MN patch developed in this study effectively lowered local blood glucose levels in diabetic ulcers, prevented bacterial proliferation, and suppressed pro-inflammatory factors such as IL-1β, IL-6, and TNF-α. It also promoted the secretion of anti-inflammatory factors like IL-4 and IL-13, thereby producing significant anti-inflammatory effects. Additionally, the modulation of ROS and advanced glycation end products (AGEs) facilitated new blood vessel formation, cell proliferation, and migration, hastening wound healing.

Recent studies have demonstrated that creating MN arrays using photo-crosslinked methacrylated HA (MeHA) can be highly effective in wound care research [122]. These MN arrays exhibit excellent biocompatibility and the ability to consistently release active ingredients, thereby minimizing additional harm to the wound site. Furthermore, the hydrolysis of MeHA generates low molecular weight HA, which aids in promoting tissue regeneration. In one instance, Yao et al. [123] developed a flexible, degradable, and skin-friendly MN array by embedding ZIF-8 NPs within a photo-crosslinked MeHA hydrogel using a molding technique. ZIF-8 NPs were encapsulated to leverage their ability to release zinc ions, disrupting bacterial membranes and catalyzing oxygen radicals' generation, thereby eliminating bacteria. Additionally, the rough surface of ZIF-8 NPs enhanced their interaction with bacteria, enhancing antimicrobial activity. Moreover, MeHA within the MNs underwent slow hydrolysis into low molecular weight HA, promoting angiogenesis, collagen deposition, and reducing inflammation in wounds. The MNs were also painless upon contact with wounds due to their ductile nature and small needle size, further enhancing patient comfort during treatment. In conclusion, this study successfully developed ZIF-8-loaded MeHA MNs as a promising drug delivery system for wound healing. By integrating antibacterial activity with tissue regeneration properties, these MNs provide a multifunctional approach to wound treatment.

Similarly, in another of these investigations, Qin et al. [124] developed a novel therapeutic approach using MN arrays loaded with pH-responsive functionalized ZIF-8 NPs and DMOG for treating bacteria-infected cutaneous wounds (see Fig. 5). This MN array, composed of MeHA, enable the controlled release of DMOG@ZIF-8 NPs, which demonstrate potent antibacterial activity and promote angiogenesis by stabilizing HIF-1α expression. DMOG is a small molecule with cell-penetrating capabilities that acts as a pharmacological inhibitor of prolyl hydroxylases (PHDs) [85]. By inhibiting PHDs, DMOG effectively mimics hypoxic conditions by enhancing the stability of HIF-1α expression even in the presence of normal oxygen levels. This combination accelerated the healing of infected wounds by simultaneously addressing bacterial infection and promoting tissue regeneration. Compared to conventional antibiotic therapy, this platform offers enhanced antibacterial, anti-inflammatory, and angiogenic functions. The results suggest that MN arrays containing ZIF-8 NPs have significant potential as versatile delivery systems for different biomolecules to deeper skin layers, paving the way for non-invasive and multifaceted therapeutic approaches in wound management and other applications.

In another study, scientists incorporated clobetasol-17-propionate (CCM) into porous ZIF-8 NPs to create a drug delivery system (CCMZIF) that releases CCM when exposed to acidic dermal fluid at inflammation sites [125]. As illustrated in see Fig. 6, these CCMZIF NPs then integrated into water-soluble poly(vinyl pyrrolidone) MN. The CCM loading capacity in ZIF-8 is approximately 40.5%, facilitated by both chemical bonding and physical adsorption. Inflammatory acidic conditions trigger the degradation of ZIF-8, enabling the controlled release of CCM from the CCMZIF MN array. In vitro experiments conducted with buffered solutions and porcine skin demonstrated that CCM is released more significantly at pH 5.0 compared to pH 7.4, highlighting the pH-responsive drug release capability of the system. This study found that encapsulating CCM in ZIF-8 and embedding it in a dissolvable MN was an effective strategy for drug delivery to dermal lesions. Additionally, the study offers both practical and analytical perspectives on the development of an innovative proof-of-concept device for on-demand treatments.

Moreover, hypertrophic scarring is one of the most challenging fibroproliferative conditions in wound healing, posing significant burdens on global healthcare systems due to the lack of effective treatments [49]. Ferroptosis, a cell death mechanism dependent on iron, has emerged as a promising therapeutic approach for diseases characterized by iron dependence [126]. Interestingly, myofibroblasts in hypertrophic scars exhibit elevated iron levels, making

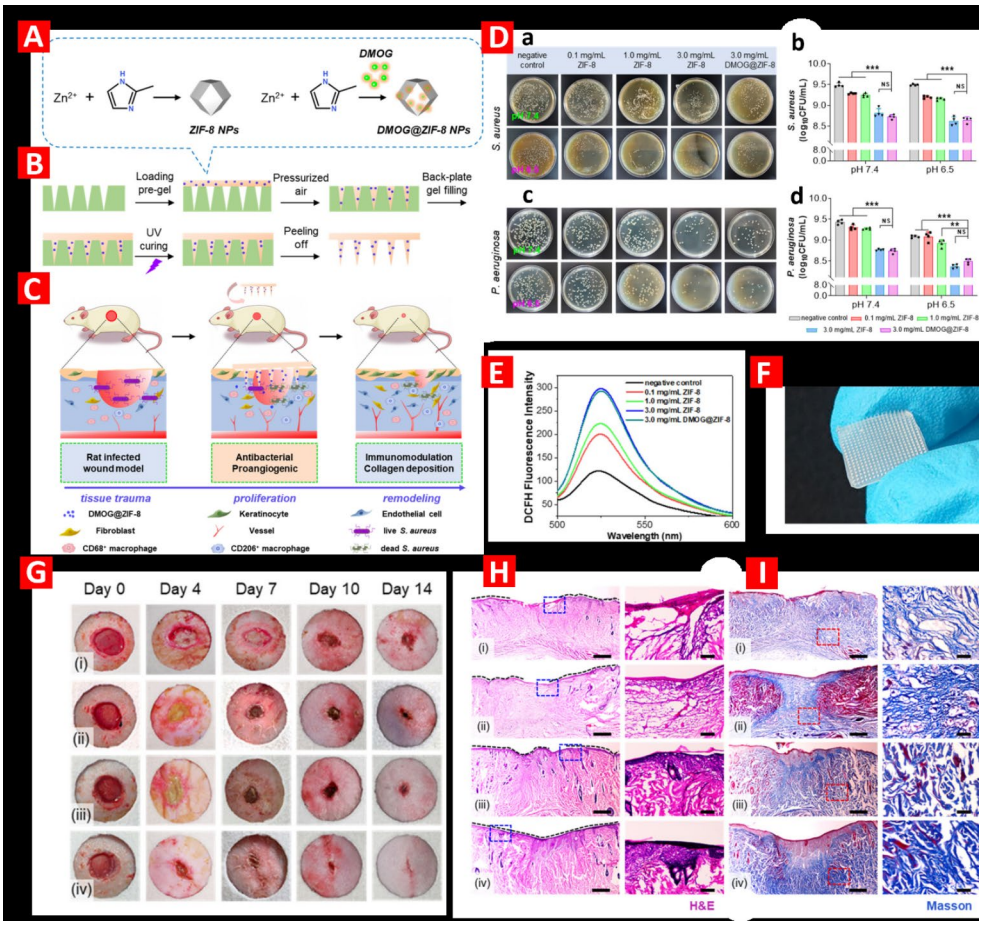


Fig. 5 **(A)** Schematic of the one-pot synthesis process for DMOG@ZIF-8 nanoparticles. **(B)** Fabrication of MN arrays using micro-molding and UV crosslinking. **(C)** Effect of MN arrays on infected wound healing: MN arrays penetrate wounds, releasing DMOG@ZIF-8 NPs to accelerate healing. **(D)** Antibacterial properties: (a) Photos of surviving *S. aureus* colonies on agar plates after treatment with controls and samples at two pH levels for 24 h. (b) Number of S. aureus colonies ($n=4$). (c) Photos of surviving *P. aeruginosa* colonies on agar plates after treatment with PBS controls and samples at two pH levels for 24 h. (d) Number of P. aeruginosa colonies ($n=4$). **E)** Fluorescence emission spectra of DCFH after coincubation with ZIF-8 NPs in PBS. **F)** Photograph of the MNs. **G)** Images of wound closure in control (i), blank MN (ii), ZIF-8 MN (iii), and DMOG@ZIF-8 MN (iv) groups over 14 days in vivo. **H)** H&E staining images and corresponding amplified areas of control (i), blank MN (ii), ZIF-8 MN (iii), and DMOG@ZIF-8 MN (iv) groups on day 14, with lines indicating the length of regenerated epidermis. **I)** Masson's trichrome staining images and corresponding amplified images of wound sites. Scale bars: 500 μm (left) and 200 μm (right). [Reproduced (adapted) from Ref. [124] with permission from the ACS Applied Materials & Interfaces]

them particularly susceptible to ferroptotic induction as a potential scar treatment strategy. For example, in a pioneering investigation, researchers have developed an innovative pH-responsive self-assembling nanoplatform that integrates silver nanoclusters (AgNCs) and trigonelline (TRG), a traditional Chinese herbal medicine, within ZIF-8 NPs [127]. This novel approach aims to harness the properties of ferroptosis to address the challenges of hypertrophic scarring. This platform aims to synergistically combat hypertrophic scarring through ferroptosis therapy. Then, to advance in vivo utilization, GelMA-based MNs were integrated with AgNC/TRG/ZIF-8 nanocomposites, leading to reduced abnormal scarring and improved collagen fiber alignment. GelMA, a methacrylic group-modified derivative of the naturally derived polymer gelatin, offers customizable mechanical properties and efficient drug release characteristics, rendering it an attractive option for fabricating biodegradable MNs. The resulting AgNC/TRG/ZIF-8 composites demonstrated excellent biocompatibility and pH-responsive degradation within myofibroblasts. As they reported these formulated AgNC/TRG/ZIF-8 composites facilitated the generation of lipid ROS and depletion of intracellular GSH, crucial factors in triggering ferroptosis. AgNCs contribute to GSH consumption, while TRG inhibits the activity of GSH peroxidase, collectively enabling effective ferroptotic anti-scarring therapy. Furthermore, MN patches loaded with AgNC/TRG/ZIF-8, and composed of gelatin methacrylate, demonstrate significant therapeutic effectiveness against

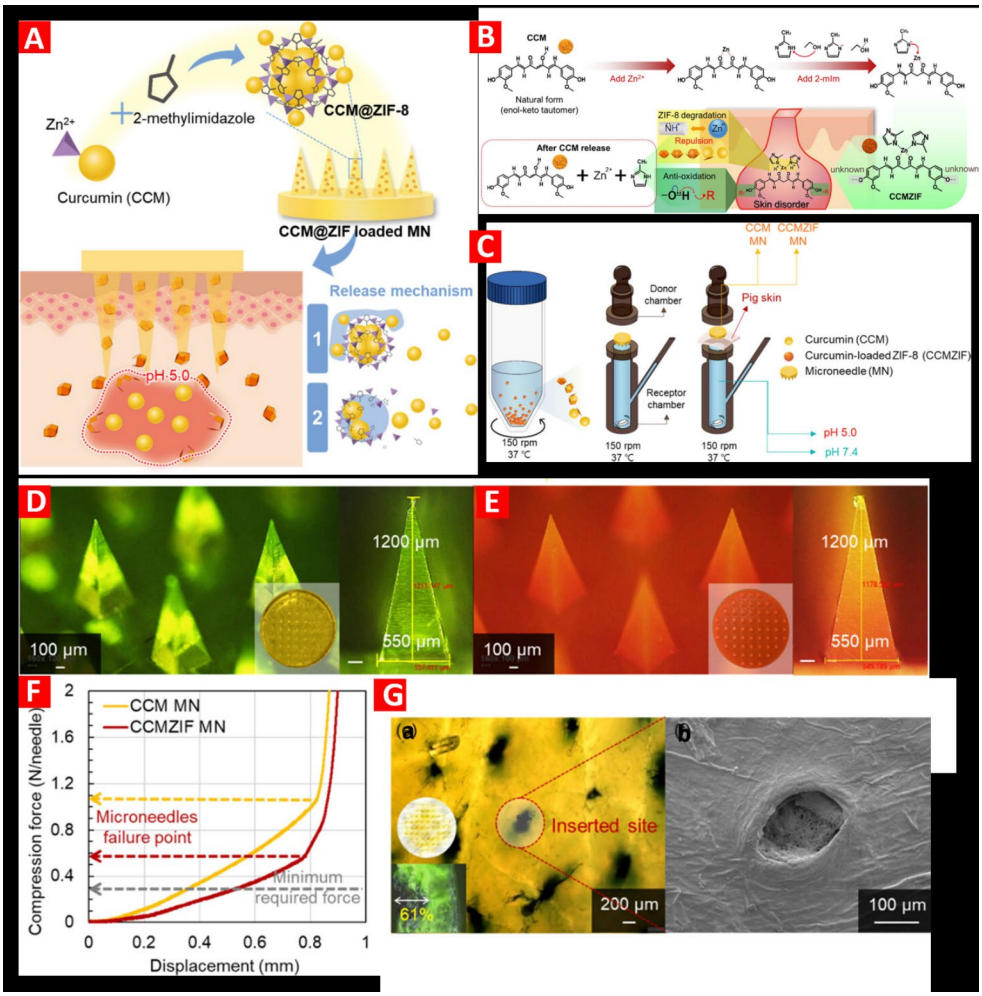


Fig. 6 **(A)** Schematic of pH-responsive ZIF-8-encapsulated MNs for controlled release of the corticosteroid clobetasol propionate (CCM) to treat inflammatory skin conditions. **(B)** Proposed chemical interactions between ZIF-8 and CCM during the fabrication of CCMZIF and the subsequent release of CCM. **(C)** Schematic of the in vitro CCM release test. **D and E)** Microscopic images of CCM MN and CCMZIF MN, respectively. **F)** Compression force testing of CCM MN and CCMZIF MN using 3 × 3 MN arrays. **G)** (a) Microscopic image and (b) FE-SEM images of porcine skin post-MN insertion, with MN-inserted areas stained with trypan blue for visualization. [Reproduced (adapted) from Ref. [125] (open access) from the ACS Applied Nano Materials]

hypertrophic scarring in a rabbit ear model. Consequently, these MN patches, designed with GelMA/AgNC/TRG/ZIF-8, introduce an innovative approach termed "Ferroptosis-mediated scarring therapy," presenting promising prospects for clinical advancements in managing fibrotic skin conditions. Following a similar approach, a versatile drug delivery system was devised, combining ZIF-8 NPs with GelMA MNs, to achieve consistent and regulated release of sodium succinate (MPSS) in spinal cord injury (SCI) cases. This strategy aims to overcome the challenges linked with side effects and the restricted focal concentration observed with conventional treatment modalities [128].

Altogether, using MNs incorporating ZIF-8 NPs in wound healing applications has shown promising results across various studies. MNs have demonstrated the ability to enhance wound healing through controlled release of therapeutic agents, promotion of tissue regeneration, reduction of inflammation, and prevention of scar formation. Therefore, MN-based approaches offer a versatile and efficient strategy for improving wound healing outcomes and hold significant potential for future clinical applications.

3D-Printable Scaffolds

Another advancement in this regard is the 3D bioprinting of tissues, an advanced engineering method utilized to fabricate biocompatible 3D structures closely resembling natural tissues, based on computer-generated designs [129, 130]. Over the past decade, 3D printing has garnered considerable attention in biomedical fields, particularly in the creation of wound dressings [131, 132]. In contrast to traditional methods for skin regeneration, 3D bioprinted dermal replacements offer superior automation, standardization for clinical applications, and precise integration of GFs, living cells, and other biomolecules [133].To fabricate intricate 3-dimensional matrices for wound healing and skin engineering, 3D bioprinting relies on specialized materials known as bioinks [134, 135]. These bioinks, such as alginate, collagen, chitosan, cellulose, and hyaluronic acid, are natural polymer hydrogels that are compatible with the bioprinting process and support cell growth and tissue formation. This state-of-the-art technology offers unmatched precision in regulating mechanical attributes and structural

complexities, enabling the production of custom-made wound dressings tailored to individual patient needs. Its versatility extends beyond traditional wound management, encompassing a wide range of biomedical applications and ushering in a new era of personalized healthcare. One of the key advantages of 3D-printable scaffolds is the ease and efficiency afforded by additive manufacturing technologies, which allow for the rapid production of intricate structures [136]. This scalability and versatility in design empower clinicians and researchers to explore novel therapeutic modalities and quickly adapt to evolving clinical needs. This strategy not only enhances therapeutic efficacy but also underscores the importance of biocompatible materials, which minimize adverse reactions and foster a conducive environment for wound healing. Furthermore, the mechanical properties inherent in these scaffolds play a critical role in providing structural support throughout the healing process, ensuring stability and integrity. For example, in a groundbreaking study, researchers introduced an innovative scaffold made of alginate-gelatin (Alg-Gel) infused with tannic acid-modified ZIF-8 (TA@ZIF-8) and 3D-printed it to enhance wound healing (see Fig. 7) [137]. By integrating ZIF-8 NPs into hydrogel scaffolds, they enhanced the loading of TA, thereby improving the mechanical properties of the 3D-printed hydrogels. The fabrication process involved designing the scaffold dimensions and programming using CAD/CAM software, followed by 3D printing using a specialized bioprinter (3DPL N2 Plus Bioprinter, Iran). The synthesis process involved creating TA@ZIF-8 NPs followed by incorporating them into a Alg-Gel hydrogel solution, which was subsequently used to fabricate the scaffolds using 3D printing technology. The TA@ZIF-8 particles acted as a crosslinking agent and stress transfer capability enhancer. The hydrogel bio-inks, comprising different concentrations of TA@ZIF-8, were dispensed using a syringe and crosslinked using physical and ionic methods to enhance mechanical strength and stability. This study revealed that Alg-Gel scaffolds containing 10% TA@ZIF-8 exhibited superior properties in terms of swelling, degradation, and mechanical strength with a 2.19 increase in elastic modulus, and biological activity compared to other concentrations. These scaffolds exhibited improved adherence of fibroblast cells, greater suppression of bacterial proliferation, quicker wound closure, and enhanced production of anti-inflammatory cytokines. Altogether, these newly developed 3D-printed scaffolds have emerged as promising options for facilitating complete wound healing, holding promise for future utilization in wound therapy.

Furthermore, within the biomedical domain, the popularity of 3D bioprinting has surged due to its ability to print live cells using bioink [138]. This computer-guided technology enables the precise placement of cells and bioinks into

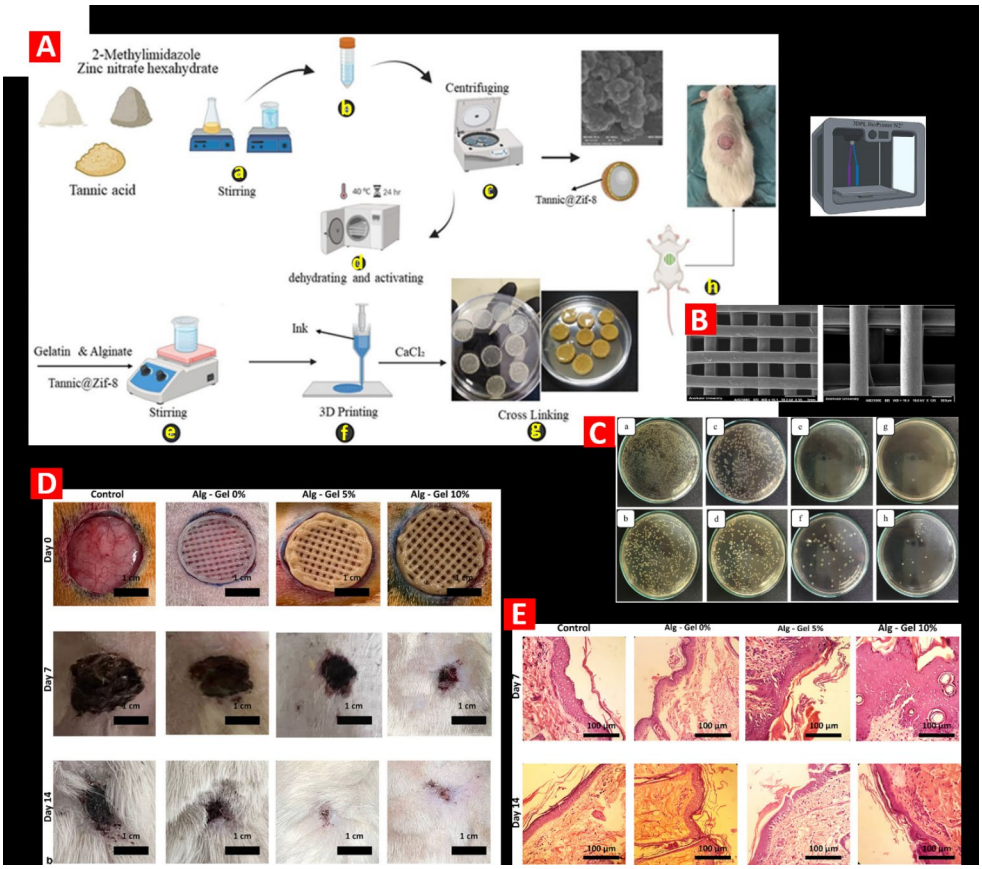


Fig. 7 **(A)** Schematic diagram illustrating the preparation of 3D printed Gel-Alg scaffolds containing TA@ZIF-8 hydrogel. This includes the nanoparticle synthesis process (a-d), 3D printing and crosslinking process (e-g), and animal study (h). The 3D printing is performed using a 3DPL N2 plus bioprinter. **(B)** SEM image showing the morphology of the scaffolds. **(C)** Antibacterial activity evaluation against *S. aureus* and *E. coli* for internal control (a, b), Alg-Gel 0% (c, d), 5% (e, f), and 10% (g, h) scaffolds. **(D)** Wound closure rate assessment for samples on days 0, 7, and 21 post-operation. **(E)** H&E-stained microscopic sections of healed incisions (magnification ×40) at days 7 and 14 post-operation, showing epithelial tissue formation on day 14. Scale bar: 100 µm. [Reproduced (adapted) from Ref. [137] with permission from the International Journal of Biological Macromolecules]

targeted areas, making it highly compatible with tissue and organ models. The precision and versatility of 3D bioprinting offer significant potential for advancing personalized medicine and developing innovative therapeutic solutions. Consequently, it holds great promise for applications in skin regeneration, as well as bone and cartilage tissue engineering. In this line, Zhu et al. [33] investigated the potential of a photocurable solution, by combining methacrylic anhydride-modified sericin with procyanidins loaded PDA modified ZIF-8 NPs (PC@ZIF-8@PDA/SerMA), to function as a bioink for 3D bioprinting, particularly in tissue repair applications. Hydrophilic sericin derived from silkworm cocoons has garnered significant interest among researchers due to its numerous benefits, including biocompatibility, biodegradability, and therapeutic properties such as anti-tyrosinase, anti-inflammatory, anticoagulant, and anti-aging effects. In this study, the SerMA solution, which provided a photo-cross-linkable and injectable formula, transformed into a hydrogel scaffold upon photo-curing, thus aiding in the repair of cartilage and skin. This innovative approach highlights the potential of sericin-based hydrogels in regenerative medicine. Despite its efficacy in tissue repair, it's important to note that the SerMA hydrogel lacks inherent antibacterial properties. However, when exposed to blue light, this engineered hydrogel exhibited photothermal properties capable of eliminating bacteria such as *S. aureus* and *E. coli*. Moreover, it demonstrated antioxidative activity and could be tracked through its fluorescent and photoacoustic properties. Chondrocytes encapsulated within this printed hydrogel maintained healthy morphology and viability, indicating the potential of PC@ZIF-8@PDA/SerMA as a bioink for tissue repair via 3D bioprinting. Moreover, in vivo experiments demonstrated its effectiveness in healing burn wounds in rabbit mice. Accordingly, the multifunctional attributes of PC@ZIF-8@PDA/SerMA hydrogel hold promise for future applications in tissue engineering and therapeutic interventions.

Overall, 3D printing scaffolds represent a versatile and effective approach for addressing various challenges in wound care, offering significant advancements in wound healing treatments. The utilization of 3D-printed scaffolds in wound healing has yielded promising results across multiple studies. As evidenced by mentioned recent studies, these scaffolds incorporating ZIF-8 NPs have demonstrated the ability to provide a customizable and precise platform for delivering therapeutic agents, promoting cell adhesion, inhibiting bacterial growth, and accelerating wound closure. Furthermore, they have shown potential in enhancing tissue regeneration and minimizing scar formation.

Conclusion and Future Perspective

In conclusion, the development of ZIF-8 NP-based nanocomposite scaffolds represent a significant advancement in skin wound healing applications. These scaffolds offer a unique combination of biocompatibility, customizable properties, and multifunctionality, making them promising candidates for addressing the complex challenges associated with wound repair and skin regeneration. ZIF-8 NP-infused wound dressings can significantly speed up wound healing by promoting cell growth, angiogenesis, antibacterial activity, and anti-inflammatory responses. However, challenges remain in bringing these scaffolds from the lab to clinical use. Further research is needed to improve synthesis and manufacturing processes to ensure consistent and scalable production of ZIF-8-based materials. Moreover, innovative approaches such as combining ZIF-8 with other materials, like copper, have been shown to promote epithelial regeneration and neovascularization, further aiding wound repair [120]. The use of intelligent bacteria-targeting ZIF-8 composites for fluorescence imaging and photodynamic therapy is another cutting-edge development. These composites can effectively target bacteria, inhibit inflammation, and promote wound healing under specific conditions [139]. Despite the promising potential of MOFs in clinical diagnosis and treatment, several challenges must be addressed for their clinical translation. These include high synthesis costs that hinder large-scale production and application in tissue regeneration, as well as issues related to scalability and long-term storage. So, comprehensive investigations into the long-term biodegradation kinetics and safety profiles of these materials in living organisms are crucial to confirm their biocompatibility and ensure they are safe for potential clinical applications. Future research is focused on overcoming these limitations and exploring new synthesis methods to enhance the efficacy of ZIF-8 NPs in wound healing applications. Moreover, future research should focus on understanding how ZIF-8-based scaffolds interact with cells, GFs, and the ECM. This knowledge will help in designing ZIF-8-based materials with specific properties and improved therapeutic effectiveness for wound healing applications. Furthermore, the fusion of ZIF-8-based scaffolds with cutting-edge technologies such as 3D bioprinting and microfluidics holds substantial promise for crafting personalized wound healing therapies tailored to the unique needs of individual patients. Through synergistic combinations with bioactive molecules like GFs, cytokines, and stem cells, ZIF-8 NPs can orchestrate amplified effects to augment tissue regeneration and expedite wound closure. In sum, ongoing research and innovation in ZIF-8-based nanocomposite scaffolds offer promising prospects for advancing regenerative medicine and improving the quality

of life for individuals with acute and chronic wounds. With collaborative interdisciplinary endeavors and inventive methodologies, ZIF-8 NP-based materials stand poised to revolutionize wound care practices and lay the groundwork for the emergence of next-generation therapies in skin tissue engineering and wound healing.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no conflict of interest.

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