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Unveiling the potential of inorganic nanoparticle-based scaffolds in wound healing: advances in antimicrobial and regenerative strategies

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Complex wound healing continues to be a significant clinical concern, demanding innovative interventions that actively promote tissue regeneration and infection control beyond the capabilities of standard dressings. Inorganic nanoparticle-based scaffolds have emerged as promising platforms, providing both localized antimicrobial action and regenerative support. The unique physicochemical properties of nanoparticles, including high surface area, controlled ion release, and redox activity, enable multiple mechanisms for the inhibition of biofilm formation and modulation of the wound microenvironment to stimulate immunomodulation, fibroblast migration, angiogenesis, and extracellular matrix deposition. This review critically evaluates scaffold fabrication strategies, including electrospun nanofibers, gas foaming, and 3D-printed constructs, and their influence on structural integrity, ion release kinetics, and biocompatibility. We further analyse the mechanisms underlying inorganic nanoparticle-mediated antimicrobial activity, emphasizing the interplay between direct surface interactions and sustained ionic release, and also provide a detailed assessment of various inorganic nanoparticle-based scaffolds as antimicrobial platforms. Despite considerable clinical progress, challenges remain in optimizing ion release, maintaining scaffold stability, and establishing standardized safety and efficacy evaluations. This review highlights the translational potential of inorganic nanoparticle-integrated scaffolds as multifunctional platforms for advanced wound care and underscores future directions for design optimization and clinical application.

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1. Introduction

As the largest organ of the human body, the skin serves a crucial role in protecting against environmental pathogens, harmful chemicals, dehydration, and thermal shock.[1] However, various factors such as physical trauma from daily activities, injuries, burns, prolonged mechanical stress, and underlying diseases can compromise its integrity, leading to tissue damage or defects, collectively referred to as wounds.[2] Wounds are broadly categorized into acute and chronic types. Acute wounds, such as surgical incisions, burns, lacerations, and abrasions, typically heal in a predictable manner through the body's intrinsic regenerative mechanisms.[3] In contrast, chronic wounds, including diabetic foot ulcers, venous leg ulcers, and pressure sores, fail to progress through normal healing stages due to factors like ischemia, infection, or systemic disease.[4] These non-healing wounds pose significant medical and economic burdens, affecting 1–2% of individuals in developed nations, with over 6.5 million cases in the United States alone, and healthcare costs exceeding $25 billion annually. With the global rise in diabetes projected to affect over 400 million individuals by 2025, the prevalence of chronic wounds is expected to escalate, necessitating advanced therapeutic strategies.[5]

Wound healing process is a complex, highly coordinated biological cascade involving multiple cellular and molecular interactions. It progresses through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling.[6] Hemostasis is the immediate response to injury, marked by platelet aggregation and fibrin clot formation to prevent haemorrhage.[7] This is followed by the inflammatory phase, characterized by neutrophil and macrophage infiltration, which clears pathogens and necrotic debris while secreting cytokines and growth factors to regulate subsequent repair processes.[8] The proliferative phase involves fibroblast activation, extracellular matrix (ECM) synthesis, angiogenesis, and keratinocyte-driven re-epithelialization, culminating in tissue regeneration.[9] The final remodeling phase extends over months to years, involving collagen maturation and ECM remodeling to restore tensile strength (Fig. 1).[10] However, in chronic wounds, persistent inflammation, bacterial colonization, and dysregulated ECM impair normal healing, resulting in prolonged tissue damage and functional deficits.

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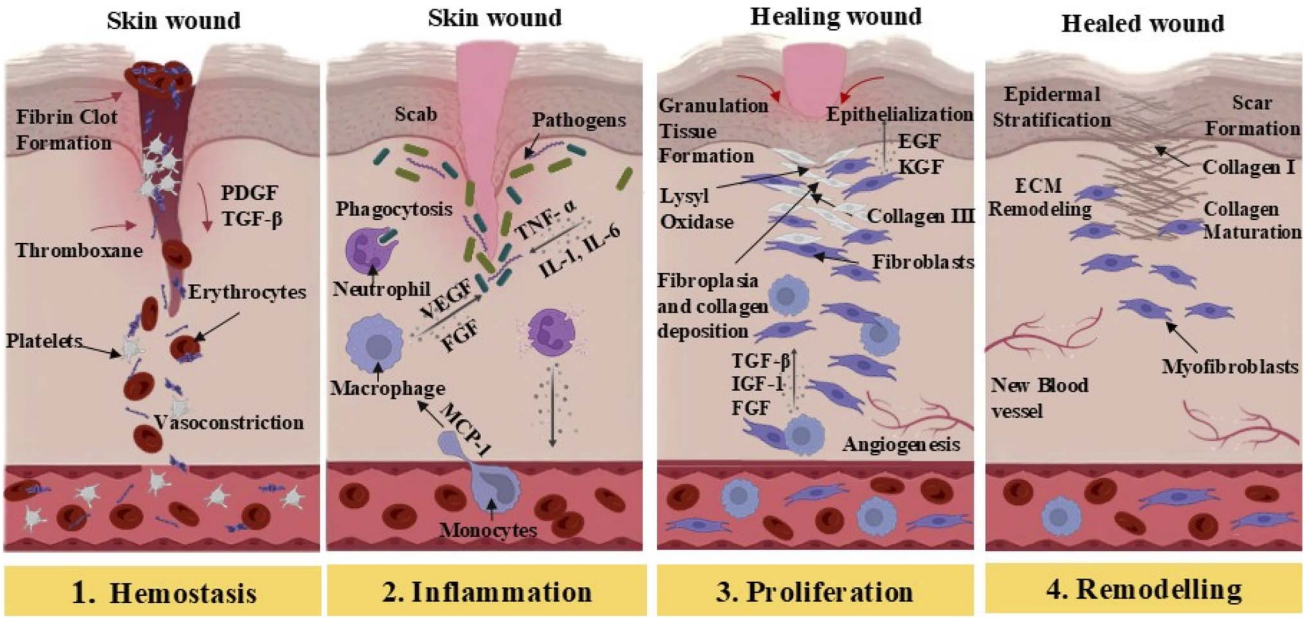

Fig. 1 Illustration of the four overlapping phases of the skin wound healing process: (1) Hemostasis with clot formation and vasoconstriction. (2) Inflammation with immune cell activation and cytokine release. (3) Proliferation involving fibroblast activity, collagen deposition, and angiogenesis, and (4) remodeling marked by ECM remodeling, collagen maturation, and scar formation (created with https://biorender.com).

To manage these chronic wounds, conventional wound care primarily relies on dressings such as gauze, hydrocolloids, foams, films, and alginate (ALG), which provide moisture balance, absorb exudate, and protect the wound from external contaminants.[11] These dressings play a fundamental role in wound management by creating a barrier against infections and facilitating a moist healing environment, which is crucial for optimal tissue regeneration.[12] However, traditional dressings have inherent limitations, including poor adhesion, inadequate antimicrobial properties, frequent replacements, and limited capacity for drug delivery. More critically, they are often insufficient in preventing bacterial colonization and biofilm formation, which significantly delays healing and increases the risk of infection-related complications.[13] Bacterial colonization of wounds exacerbates inflammation, prolongs the inflammatory phase, and contributes to chronic wound pathology.[14] This demonstrates the demand for innovative wound care solutions which led to significant market growth, with the global wound care market valued at over $20 billion, projected to expand further due to the rising prevalence of chronic wounds and advancements in biomaterial technologies.[15] Although systemic and topical antibiotics are commonly employed for infection control, their limited efficacy against biofilms and tendency to induce resistance necessitate advanced wound care approaches.[16]

To overcome these shortcomings, advanced wound care systems integrating biomaterials and nanotechnology have further revolutionized therapeutic approaches. Nanomaterials-based platforms, derived from both organic and inorganic sources, offer versatile strategies for wound healing. Organic nanomaterials and nanoparticles (NPs), such as polymeric NPs, liposomes, and dendrimers, are biocompatible and provide controlled drug delivery but often suffer from limited mechanical strength, insufficient antimicrobial activity, and rapid degradation. In contrast, inorganic nanomaterials, including metal and metal oxide NPs and ceramic-based NPs, exhibit structural stability and their sustained bioactive ion release, making them highly suitable for advanced wound healing applications.[17] In addition, the released bioactive ions can modulate the wound microenvironment by generating reactive oxygen species (ROS) and disrupting bacterial cell membranes, enhancing antimicrobial activity and preventing biofilm formation.[18]

In this review, we provide a comprehensive and critical evaluation of inorganic NP-based scaffolds as antimicrobial platforms for wound healing. We first outline the pathophysiology of chronic wounds and the evolution of current treatment strategies, followed by an in-depth discussion of the physicochemical properties and fabrication approaches of inorganic nanomaterials, along with their mechanisms of microbial inhibition. Special emphasis is placed on scaffold-based delivery systems incorporating NPs such as hydroxyapatite (HA), zinc oxide (ZnO), silica (Si), titanium dioxide (TiO_2) and bioactive glass (BG), highlighting their dual functionality in preventing infection and promoting tissue regeneration along with their preclinical outcomes. Furthermore, the review highlights challenges in clinical translation and future strategies to optimize scaffold design, emphasizing their potential as next-generation platforms for advanced wound healing.

2. Chronic wounds – pathophysiology and their current treatment strategies

Chronic wounds present a persistent clinical challenge due to their delayed healing and high susceptibility to infection.

Understanding the underlying pathophysiology is key to creating effective interventions. Over time, treatment strategies have evolved from simple protective dressings to advanced therapeutic approaches. These strategies aim not only to protect the wound but also to actively promote tissue regeneration and infection control.[19]

2.1 Pathophysiology of chronic wounds

Chronic wounds are characterized by sustained inflammation and impaired tissue remodeling, making them refractory to the natural healing process.[20] Unlike acute wounds, which typically resolve within weeks to months, chronic wounds exhibit dysregulated cellular signaling and aberrant tissue responses that disrupt the intricate cascade of wound repair.[21] Despite variations in their etiology, the fundamental pathophysiological mechanisms underlying chronic wound progression remain consistent. Following tissue injury, platelets rapidly aggregate at the wound site, initiating vasoconstriction and activating the coagulation cascade to establish a fibrin clot.[22] Under normal physiological conditions, the subsequent inflammatory phase is critical for pathogen clearance and cellular debris removal through phagocytosis, creating a pro-regenerative microenvironment that facilitates tissue repair.[23] However, in chronic wounds, this tightly regulated process becomes dysfunctional, perpetuating a cycle of inflammation and delayed healing. The excessive accumulation of pro-inflammatory cells, including macrophages and neutrophils, creates a hostile microenvironment that impedes the inflammatory phase transition to the proliferative phase.[24] This transition is crucial for resolving inflammation, stimulating angiogenesis, and facilitating ECM remodeling. The macrophage accumulation is further amplified by cytokine-driven activation of resident macrophages and the induction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NADPH oxidase 1 and NADPH oxidase 2), which promote monocyte differentiation into the M1 pro-inflammatory phenotype. Under homeostatic conditions, macrophages undergo phenotypic switching from M1 to the M2 reparative state.[25,26] However, in chronic wounds, this polarization is disrupted and the absence of M2 phenotype due to impaired efferocytosis of apoptotic neutrophils exacerbates the production of pro-inflammatory cytokines, chemokines, and dysregulated growth factors, ultimately hindering angiogenesis and tissue regeneration.[27]

Neutrophils play a pivotal role in delayed wound healing by driving excessive inflammation and tissue degradation.[28] They secrete proteolytic enzymes such as elastases and matrix metalloproteinases (MMPs), along with neutrophil extracellular trap-associated markers, which collectively disrupt the ECM and impair tissue regeneration. Additionally, the persistent accumulation of inflammatory cells leads to elevated ROS production, which exacerbates oxidative stress, inhibits epithelialization, and promotes tissue necrosis.[29] As inflammation persists, the overexpression of pro-inflammatory cytokines, including interleukin-1β and tumor necrosis factor-alpha, further upregulates MMP activity, accelerating ECM breakdown and impairing structural integrity.[30] The compromised wound bed creates a favourable niche for microbial

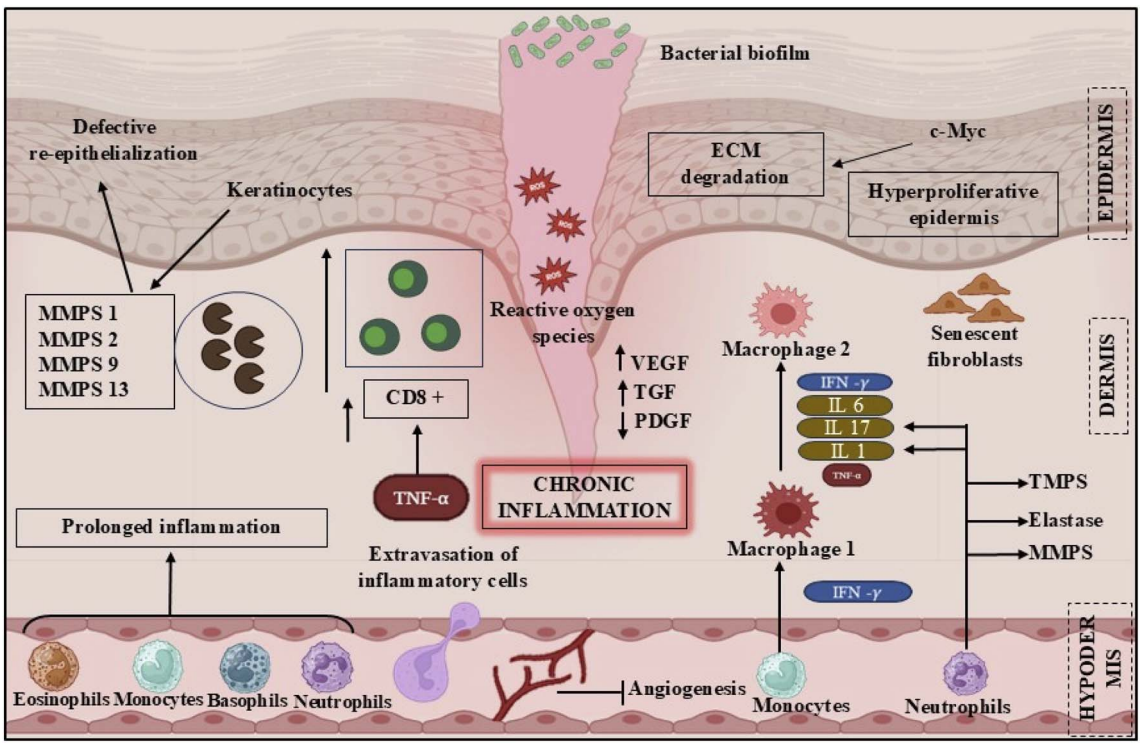

Fig. 2 Pathophysiology of chronic wounds outlining the multifactorial and complex biological mechanisms underlying delayed healing (created with https://biorender.com).

colonization and biofilm formation, resulting in two potential pathological outcomes: tissue necrosis or chronic inflammation, both of which disrupt immune homeostasis at the wound site.[31] This cascade of dysregulated processes contributes to a hyperproliferative yet non-advancing wound margin, where excessive cell proliferation fails to translate into effective wound closure. Further exacerbating the impairment, essential angiogenic factors such as platelet-derived growth factor and vascular endothelial growth factor (VEGF) are rapidly degraded by proteases, while the suppression of hypoxia-inducible factor 1-alpha (HIF-1α) further inhibits new blood vessel formation.[32] This disruption in vascularization deprives the wound of adequate oxygen and nutrients, further delaying tissue repair. Additionally, the crosstalk between keratinocytes and fibroblasts, which are crucial for the proliferative phase, becomes dysregulated leading to defective fibroblast function and impaired ECM remodeling.[33] A hallmark of chronic wounds is the failure to transition from type III collagen (early wound matrix) to type I collagen (scar tissue), which is essential for structural stability. This imbalance manifests as an absence of proper ECM remodeling or excessive collagen deposition, resulting in hypertrophic scar formation and fibrosis. Ultimately, chronic wounds arise from an intricate interplay of overlapping and interdependent factors, each reinforcing the pathological cycle of impaired healing (Fig. 2).[34] Given this complexity, a multifaceted therapeutic approach targeting inflammation, oxidative stress, angiogenesis, and ECM remodeling is essential to restore wound homeostasis and accelerate tissue regeneration.

2.2 Evolution of wound healing strategies and technologies

The evolution of chronic wound management has undergone substantial advancements, transitioning from conventional surgical interventions to sophisticated bioengineered approaches. The early 1900s marked the advent of debridement, a fundamental surgical procedure aimed at excising necrotic, infected, and non-viable tissue to minimize bacterial load and stimulate granulation tissue formation.[35] Despite its effectiveness in removing necrotic and infected tissue, it often necessitates successive intervention in chronic wounds, which can exacerbate inflammation and impede progression to the proliferative phase. Furthermore, debridement is inherently limited as it does not target the underlying pathophysiological mechanisms of chronic wounds, such as angiogenic insufficiency, dysregulated immune responses, and aberrant ECM remodeling.[35,36] To mitigate these challenges, hyperbaric oxygen therapy (HBOT) emerged as an adjunctive modality for chronic wound healing by 1960s which utilizes atmospheric pressure to enhance plasma oxygen solubility and improve oxygen perfusion in hypoxic tissues.[37] The therapeutic strategy fosters fibroblast proliferation, stimulates collagen deposition, and potentiates leukocyte-mediated bacterial clearance, collectively promoting angiogenesis and expediting re-epithelialization.[38] Additionally, negative effects like oxygen toxicity, barotrauma, and cell damage from oxidative stress make it harder to use HBOT.[39,40]

Recognizing the need for more accessible and targeted interventions, the 1970s marked a paradigm shift with the introduction of antibiotics and advanced wound dressings. Antibiotics addressed microbial colonization and maintained a moist microenvironment crucial for keratinocyte migration, regulated exudate levels and facilitated autolytic debridement thereby optimizing the repair dynamics.[41] Further, a localized delivery of these drugs facilitated the development of microneedle arrays (MNAs). MNAs are minimally invasive drug carrier systems that consist of needles in the microscale range, capable of promoting sustained drug release.[42] Xiang *et al.* developed a biodegradable Cu based zeolitic-imidazolate framework-8 encapsulated with polyethylene glycol diacrylate/CMC MNAs with strong antibacterial and pro-angiogenic properties for enhanced wound healing. These MNAs also demonstrated excellent biocompatibility and mechanical strength, along with a sustained release of Cu ions, which collectively contributed to enhanced epithelial regeneration and neovascularization.[43]

Biomaterials play a pivotal role in wound healing by offering structural support, enhancing cellular adhesion and migration,

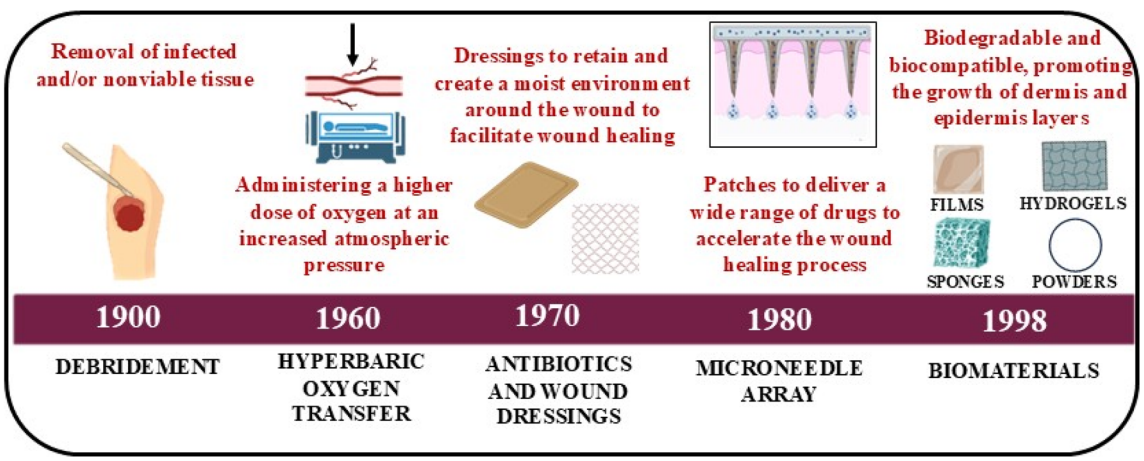

Fig. 3 Timeline illustrating the evolution of wound healing strategies and technologies, beginning with the empirical use of traditional treatments to systemic antibiotics and biomaterials, marking a significant improvement in infection control (created with https://biorender.com).

and facilitating tissue regeneration. To effectively fulfil these functions, biomaterials must exhibit precisely tuned mechanical properties tailored to the wound environment. Ideal biomaterials for skin regeneration should demonstrate optimized mechanical strength, flexibility, porosity, structural integrity, sustained biodegradability, and excellent biocompatibility.[44] Sufficient tensile strength ensures resilience against mechanical deformation, while flexibility enables conformation to wound contours, promoting better integration with surrounding tissues. Moreover, the mechanical characteristics of a biomaterial must be specifically engineered based on the wound's anatomical location and dimensions to optimize healing outcomes (Fig. 3).[45]

3. Inorganic nanomaterials – a versatile biomaterial

Inorganic NPs, including metals, metal oxides, and bioactive ceramics, possess distinct physicochemical properties that set them apart from bulk materials and render them highly effective in wound healing. Their high surface reactivity, controlled solubility, and catalytic activity modulate the wound microenvironment, simultaneously preventing microbial colonization, regulating oxidative stress, and promoting essential cellular processes such as fibroblast proliferation, keratinocyte migration, angiogenesis, and ECM remodeling.[46] Beyond their direct biological activity, they also function as reservoirs for sustained delivery of bioactive ions, which further enhance tissue repair and maintain a regenerative milieu.[47] When these NPs are incorporated into scaffold systems composed of natural or synthetic polymers, their properties are amplified, and the scaffolds provide structural support, mimic the ECM, and enable controlled and localized ion release, ensuring continuous stimulation of healing processes.[48] Various studies have successfully integrated inorganic NPs into polymeric scaffolds, demonstrating enhanced antimicrobial activity, accelerated re-epithelialization, and improved vascularization in preclinical wound models. For example, ZnO- or TiO_2-loaded polymeric nanofibers showed superior bacterial inhibition while promoting fibroblast proliferation, whereas BG-incorporated hydrogels enhanced collagen deposition and neovascularization *in vivo*.[49–51] These findings highlight the versatility of inorganic nanomaterials, not merely as passive components but as active biological cues that orchestrate multiple phases of wound healing, offering a multifunctional approach for advanced wound care strategies (Table 1).

3.1 Fabrication of inorganic nanoparticles incorporated composite scaffolds

Fabrication of scaffolds play a pivotal role in tissue engineering by serving as 3D templates that provide structural support, regulate cellular behaviour, and facilitate ECM deposition for functional tissue regeneration.[85] An ideal scaffold should possess a highly porous architecture to enable nutrient diffusion and vascularization while maintaining appropriate mechanical properties to withstand physiological loads.[86] Furthermore, the incorporation of inorganic NPs into these scaffolds has gained considerable attention, owing to its beneficial role in combating microbial infection in wound healing.[48] Several studies have demonstrated feasibility and versatility in fabricating inorganic NPs based composite scaffolds using advanced techniques such as gas foaming, electrospinning and fused deposition modelling (Fig. 4).

3.1.1 Electrospinning based scaffolds. Electrospinning has emerged as a highly efficient technique for fabricating scaffolds of submicron to nanoscale fibers with a high surface-area-to-volume ratio and offers precise control over fiber morphology, porosity, and mechanical characteristics. Therefore, these electrospun fibers replicate the structural and functional features of the native ECM in wound healing applications.[87] By incorporating bioactive NPs such as HA or BG into biodegradable polymeric matrices like polycaprolactone (PCL) or gelatin (Gel) and subjecting the solution to a high-voltage electrostatic field, ultrafine fibers were ejected and deposited as the nanofibrous matrix. They exhibited enhanced cellular interactions and accelerated wound healing.[88] Furthermore, NPs embedded within electrospun fibers undergo gradual disintegration, leading to the sustained release of bioactive ions, which in turn provide continuous biochemical cues essential for wound healing.[89] For instance, Khan *et al.* incorporated ZnO NPs into poly(lactide-*co*-glycolic acid) (PLGA)/silk fibroin (SF) nanofibrous membranes, which demonstrated enhanced tensile strength and thermal stability due to improved interfacial interactions within the polymer matrix and enhanced antibacterial property while promoting cell migration, re-epithelialization, and angiogenesis, making them highly relevant for wound healing.[90]

3.1.2 Gas foaming-based scaffolds. The gas foaming technique is a solvent-free fabrication strategy employed to produce scaffolds with high porosity, interconnected architecture, and favorable fluid absorption and mechanical stability.[91] In this approach, biodegradable polymers blended with NPs of HA, BG, Si, or zirconia (ZrO_2) are exposed to foaming agents like supercritical carbon dioxide or ammonium bicarbonate. The rapid expansion and subsequent dissipation of gas create uniform pores that promote oxygen diffusion and cellular infiltration.[92,93] The incorporation of these NPs further enriches the scaffolds with antimicrobial and immunomodulatory functions, extending their applicability to complex wound environments such as chronic wounds, diabetic ulcers, and burns.[92] Bianchi *et al.* developed pullulan-based nanofibers incorporated with cricket powder and HA, subsequently converted into 3D scaffolds using $NaBH_4$-mediated gas foaming. The scaffolds demonstrated excellent cytocompatibility with human dermal fibroblasts and mesenchymal stem cells, and *in vivo* studies in murine incisional and burn models confirmed their ability to support tissue regeneration and enhance wound healing.[94]

3.1.3 3D-printing based scaffolds. 3D-printing, known as additive manufacturing, is a transformative approach to industrial production that enables the fabrication of lightweight, mechanically robust scaffolds through a layer-by-layer deposition of biomaterials based on a digitally designed

Table 1 Types of Inorganic nanoparticles: Advantages and disadvantages across various applications

S. no	Nanoparticle category	Type of nanoparticle	Advantages	Disadvantages	Applications	Ref.
1	Oxide NPs	Al_2O_3	High surface area to volume ratio enhanced biomolecule adhesion	Induced oxidative stress by generation of ROS	Wound healing and skin regeneration	52–54
		ZrO_2	Resistance to plaque formation and tooth like appearance	Susceptibility to corrosion	Dental implants	55–57
		TiO_2	Photocatalytic activity led to effective killing of cancer cells	Lower drug loading capacity due to its crystalline structure	Drug delivery system for cancer therapy	58–60
		ZnO	Protected against harmful UV radiations	Induced allergic response and skin irritation	Skin barrier protection in dermatological products	61–63
2	Calcium-phosphate based NPs	Bioglass	Facilitated angiogenesis and promoted osteoblastic differentiation	Poor degradation rates compromised structural integrity during bone healing	Promoted bone regeneration	64–66
		HA	Enhanced protein adsorption and biomineralization	Exhibited brittleness and a slow resorption rate	Biomimetic scaffolds in bone tissue engineering	67–69
		Whitlockite	Promoted collagen deposition and reduced inflammatory expression	Whitlockite NPs did not match the mechanical strength of normal skin, hindering proper wound healing	Disinfection and treatment in bleeding wounds	70–72
3	Silicate based NPs	Akermanite	Promoted proliferation, migration and stemness of epidermal cells in wound healing	Decreased scaffold density and swelling properties	Promoted wound healing	73–75
		Calcium silicate (CaS)	Promoted migration and angiogenic capacity of human umbilical vein endothelial cells	High doses of CaS NPs caused cytotoxicity by releasing excessive ions, disrupting cell stability	Promoted wound healing	76–78
		Hardystonite	Stimulated cell migration, proliferation and promoted wound healing	High dissolution rate caused raise in the local pH, potentially becoming toxic to cells	Ideal candidate for tissue engineering and skin wound healing	79–81
		Zeolite	Zeolite's pH sensitivity enabled targeted ion release in acidic tumor environments, and promoted bone regeneration and inhibited tumor growth	Release kinetics from zeolite NPs varied widely with different drug formulations, risking toxicity or insufficient therapeutic effects	Aided in reconstructing bone defects post-cancer surgery and helped prevent cancer recurrence	82–84

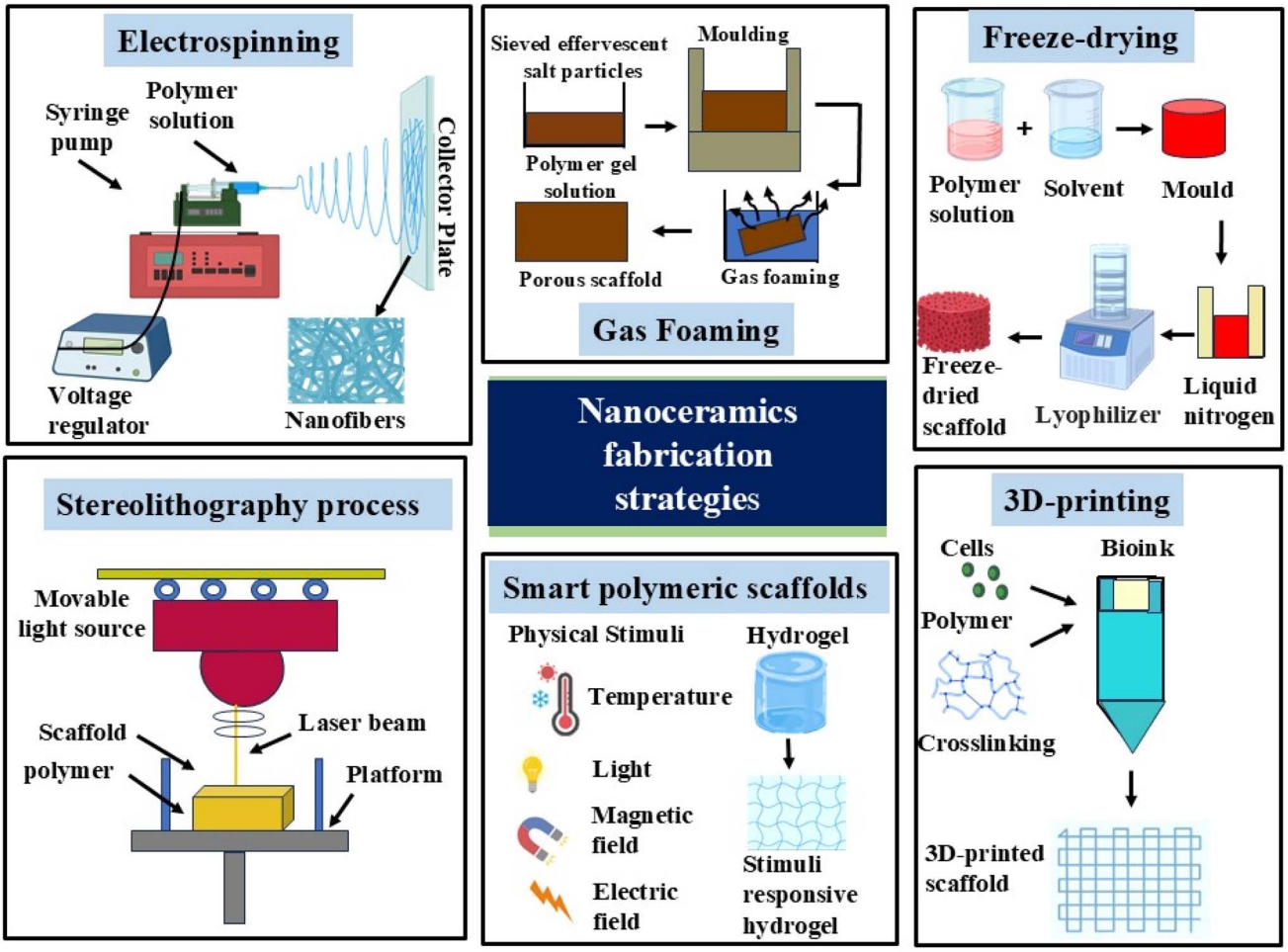

Fig. 4 Strategies of fabricating nanoceramic scaffolds with tailored architecture and responsiveness to support tissue regeneration such as electrospinning for nanofiber formation, gas foaming, and freeze–drying for creating porous structures, stereolithography and 3D-printing for precise scaffold design (created with https://biorender.com).

model.[95] 3D printing technology has enabled the precise fabrication of NPs incorporated 3D printed biocomposite scaffolds which demonstrate significant improvements in physicochemical and biological properties.[96] In particular, NPs integrated into various scaffold compositions address the challenges of wound healing application. The sodium alginate (Na-ALG)/poly(vinyl alcohol) (PVA) (3 : 1) 3D printed scaffolds loaded with copper (Cu)–silver (Ag) doped mesoporous bioactive glass nanoparticles (MBGNs) showed increased mechanical integrity, hydrophilicity with controlled swelling and degradation. Further, this scaffold showed *S. aureus* and *E. coli* inhibition, cytocompatibility, and angiogenic potential.[97]

3.1.4 Smart polymeric scaffolds. Smart polymeric scaffolds incorporated with inorganic NPs have emerged as a promising platform for advanced wound healing applications, and they offer stimuli-responsive behavior, enhanced mechanical properties, and controlled drug delivery.[98] The stimuli-responsive characteristics enable environmentally triggered therapeutic modulation, including pH-mediated drug release, thermally induced sol–gel transitions, and electroconductive signaling, facilitating precise regulation of wound healing processes.[99] Furthermore, the ions released from these NPs (*e.g.*, Cu, Ag, or Zn-doped BG) exhibit multifunctional bioactivity, conferring antibacterial efficacy, pro-angiogenic stimulation, and wound healing potential.[100] These bioactive properties synergistically enhance cellular proliferation, ECM synthesis, and neovascularization, ultimately optimizing the microenvironment for accelerated tissue regeneration.

3.1.5 Other fabricated scaffolds. The lyophilization technique or freeze–drying is a widely used method for fabricating highly porous bioactive scaffolds with a polymeric solution often incorporated with inorganic NPs, which is rapidly frozen at sub-zero temperatures leading to the formation of ice crystals that act as pore templates, followed by vacuum sublimation to achieve interconnected porous network.[101] For example, Raisi *et al.* fabricated carboxymethyl chitosan (CMC) and iron oxide (Fe_2O_3) NPs and they showed enhanced mechanical integrity of the CMC matrix along with its biocompatible nature.[102] Conventional scaffold fabrication techniques, such as solvent casting and particulate leaching, have also been utilized for the development of inorganic NPs-incorporated scaffolds in wound healing applications.[103] Notably, these techniques have unique

advantages and limitations, and further research is required to optimize their use in wound healing application.

3.2 Microbial inhibition pathways

Persistent microbial colonization and biofilm formation hinder wound healing by prolonging inflammation and impairing tissue repair.[104] Inorganic NPs incorporated into scaffolds counter these barriers by exerting localized and sustained antimicrobial effects through both surface contact and controlled ion release. In Gram-positive bacteria, the negatively charged teichoic acids in the thick peptidoglycan layer facilitate binding of cationic NPs or ions, and the porous nature of this layer allows partial penetration. In contrast, Gram-negative bacteria present an additional challenge with their lipopolysaccharide-rich outer membrane, which creates a strong negative surface charge that enhances electrostatic attraction but restricts penetration due to its compact bilayer structure. In both cases, interactions at the cell envelope compromise membrane integrity and increase permeability, enabling NPs and released ions to enter the cytoplasm.[105] Once internalized, metal ions such as Zn^{2+}, Ag^{+}, and Mg^{2+} bind strongly to phosphate, carboxyl, and sulfhydryl groups, destabilizing protein conformation, inactivating enzymes, and disrupting membrane-associated bioenergetics. These ions also interact with nucleic acids and ribosomal machinery, impairing transcription and protein synthesis and, in severe cases inducing DNA fragmentation or oxidative modifications. For instance, ZnO NPs have been shown to cause genomic breaks, whereas Ag NPs deregulate stress-response and metal-transport genes.[106,107] Through this multifaceted disruption of structural, metabolic, and genetic processes, inorganic NPs not only suppress bacterial growth but also attenuate virulence, thereby reducing microbial burden and supporting effective wound healing.

A key downstream consequence of NPs–bacteria interactions is the generation of ROS, which amplifies antimicrobial activity. The NPs or ions catalyze the production of ROS such as hydroxyl radicals, superoxide anions, singlet oxygen, and hydrogen peroxide.[108] This oxidative stress overwhelms the bacterial antioxidant defenses, leading to lipid peroxidation, protein oxidation, and nucleic acid damage.[109] By targeting enzymes essential for energy production (*e.g.*, ATP synthase, cytochrome oxidases) and biosynthesis (*e.g.*, fatty acid synthase, peptidoglycan synthesis enzymes, and DNA gyrase), these NPs or ions also reduce the ability of bacteria to establish resilient biofilms.[110] Collectively, these metabolic and biofilm-targeting actions position NPs as multifaceted agents that enhance scaffold-mediated antimicrobial efficacy and support effective wound healing.

4. Inorganic nanoparticle-based scaffolds as antimicrobial platforms for wound healing

Inorganic NP-based antimicrobial strategies represent a significant advancement in wound healing, harnessing their distinctive physicochemical properties to simultaneously prevent microbial colonization and stimulate tissue regeneration.[111] These NPs exhibit potent bactericidal effects for the inhibition of biofilm development.[112] Among them, HA, Zn, Si, and calcium phosphate NPs are extensively utilized in wound healing for their ability to promote cell adhesion, proliferation, and ECM remodeling.[113–116] When NPs are incorporated into scaffolds, they provide sustained and localized ion release, accelerating wound closure while also enhancing mechanical integrity and biocompatibility (Table 2). Importantly, scaffold-based systems help to mitigate cytotoxicity associated with excessive NPs loading.[117]

4.1 Hydroxyapatite

HA is widely employed in wound healing due to its remarkable bioactivity, biocompatibility, and structural similarity to the mineral component of human bone and hard tissues.[136] Its distinctive physicochemical properties make it an excellent scaffold for supporting cellular adhesion, proliferation, and ECM remodeling, effective for tissue repair.[137] The nano form of HA further amplifies its bioactivity by offering a high surface area-to-volume ratio, which facilitates the controlled release of calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions.[138] These ions play crucial roles in modulating cell signaling pathways, promoting angiogenesis, and accelerating wound healing process. For instance, Zhu *et al.* fabricated HA-ALG composite wound dressing that integrates an ultralong HA nanowire bio-paper with a calcium-ALG hydrogel matrix. Unlike conventional brittle HA-based bioceramics, the ultralong HA nanowires formed a highly flexible, interwoven structure, and they significantly enhanced the mechanical integrity. Their bioactive properties enabled sustained calcium ion release, biocompatibility, enhanced cell migration, stimulated angiogenesis, and exhibited enhanced antibacterial properties. Furthermore, *in vivo* wound models demonstrated their efficacy in accelerating wound closure, promoting collagen deposition, and inducing neovascularization.[139] Similarly, Tejaswini and coworkers synthesized HA from egg shell waste and developed an atorvastatin-loaded CS-HA composite that demonstrated excellent physicochemical properties and potent antibacterial activity. *In vivo* studies revealed a notable inflammatory response accompanied by fibrovascular proliferation, along with early epithelialization and fibroblastic proliferation at the wound site. Additionally, initial signs of normal skin regeneration were observed, indicating the composite's potential to accelerate wound healing.[140] The HA-based wound dressings exert antimicrobial effects *via* Ca^{2+} and PO_4^{3-} ion release, modulating the microenvironment and supporting angiogenesis. However, its intrinsic activity is modest, limiting bactericidal action.[141] To address this limitation, HA is frequently doped with Zn, Sr, Co, or Cu to introduces ROS generation, membrane disruption, and pro-angiogenic signaling, significantly enhancing antimicrobial and regenerative efficacy.

This integration of HA with metals like Zn, strontium, cobalt (Co), Cu *etc.*, has shown optimized functionality and improved antimicrobial resistance. For instance, Wojcik *et al.* fabricated

Table 2 A summary of inorganic nanoparticle-based scaffolds' antimicrobial and cytocompatibility evaluation for wound healing

S. no	Inorganic nanoparticle-based scaffolds	Inorganic nanoparticles	Antimicrobial studies	Cytotoxicity studies	Inferences	Ref.
1	Beta-glucan (BG)/ nanostructured ZnO films	ZnO	The minimum inhibitory concentration and minimum bacterial concentration for *Staphylococcus epidermidis* were 120 μg mL^{-1} and 480 μg mL^{-1}, respectively, while for *E. coli*, they were 480 μg mL^{-1} and 3750 μg mL^{-1}	—	The integration of BG with ZnO NPs, exhibited biocompatiblity and demonstrated notable antibacterial efficacy	118
2	Bimetallic (Ag and MgO) NPs, Aloe vera extracts loaded xanthan gum nanocomposite	Ag/MgO NPs	Zone of inhibition was observed to be 15.00 ± 0.12 mm for *Bacillus cereus* and 14.50 ± 0.85 mm for *E. coli*	Non-toxic and compatible NIH3T3 and HEK 293 cells	Wound closure after 48 h was 91.19 ± 1.87% in the nanocomposite treated group, compared to 68.68 ± 3.54% in the control group	119
3	ZnO biocomposite based on maleic anhydride modified bacterial cellulose membrane (BCM)	ZnO	5 wt% ZnO NP/BCM nanocomposite reduced bacterial growth by 78.64% against *S. aureus* and 37.67% against *E. coli*	Showed non-toxic effect to 5 wt% to L929 fibroblasts	The 5 wt% ZnO NP/BCM accelerated wound healing in BALB/*c* mice, with a closure time of 14.6 days, compared to 18.1 and 18.4 days for gauze and BCM, respectively	120
4	ZnO malachite (mlt) nanocomposites and its coating form with chitosan (CS)	ZnO	The inhibition zones were 25.25 ± 2.12 mm for *S. aureus* and 23.25 ± 1.41 mm for *P. aeruginosa* respectively	L929 cells showed nearly 100% viability to the ZnO/Mlt/CS nanocomposites	The nanocomposites effectively accelerated wound healing in a murine model of infected wounds, showing comparable performance to the standard polysporin ointment	121
5	Sodium carboxymethylated starch (CMS) hydrogel containing copper oxide (CuO) NPs	CuO	2 wt% and 4 wt% hydrogels demonstrated inhibition zones ranging from 20 mm to 32 mm against *P. aeruginosa*, *S. aureus*, *S. enterica*, *Y. enterocolitica*, and *Listeria monocytogenes*	2 wt% CuO demonstrated good biocompatibility while 4 wt% CuO showed cytotoxicity against human fibroblasts	Hydrogel achieved 94% wound healing in a rat model and showed superior wound healing efficacy *in vivo* compared to the pure CMS hydrogel	122
6	(Ce)-doped biotype Linde type A (LTA) zeolite NPs in pluronic F127/CS hydrogel	(Ce)-doped (LTA) zeolit	Hydrogel showed significant inhibition towards *E. coli and S. aureus* showed significant inhibition	There was no significant cytotoxicity towards human umbilical vein endothelial cells (HUVECs)	The Ce/LTA-NPs-F127/CS hydrogel promoted endothelial proliferation and enhanced neovascularization	123
7	Iron(II) oxide (FeO) synthesised from *Pinus densiflora* (PD) incorporated into CS/PVA nanocomposite sponge	FeO	Zone of inhibitions in *B. cereus* –22 ± 2 mm, *S. aureus* –21 ± 1 mm, *E. coli* – 20 ± 2 mm, and *Salmonella enterica* –22 ± 1.5 mm were observed	The CS/PVA-PD-FeO nanocomposite scaffold exhibited no significant cytotoxicity in HEK-293 cells	The CS/PVA-PD-FeO NPs nanocomposite supported essential wound healing functions, such as gaseous exchange, exudate absorption, and microbial inhibition, particularly beneficial for diabetic wounds	124

Table 2 (*Contd.*)

S. no	Inorganic nanoparticle-based scaffolds	Inorganic nanoparticles	Antimicrobial studies	Cytotoxicity studies	Inferences	Ref.
8	ZrO_2/HA/Graphene oxide (GO) encapsulated into nanofibrous scaffolds of PLA	ZrO_2 HA	The scaffolds exhibited inhibition rates of 69.2% for *E. coli* and 78.1% for *S. aureus*	The scaffolds were cytofriendly to HFB4 cells	The incorporation of HA, ZrO_2, and GO, into PLA nanofibers significantly enhanced its mechanical and biological properties	125
9	TiO_2 NPs incorporated gellan gum (GG)	TiO_2 NPs	Zone of inhibitions were found to be 9 ± 0.25 mm against *S. aureus* and 11 ± 0.06 mm against *E. coli*	The scaffolds exhibited cytocompatibility when tested on NIH 3T3 cells	*In vivo* studies on Sprague Dawley rats showed faster wound healing with the GG + TiO_2 NPs biofilm compared to the control and pure GG biofilm	126
10	Multifunctional injectable hydrogel loaded with Ce-containing BGN incorporated into gel methacryloyl	Ce-BGN	The hydrogel showed significant inhibition against *E. coli* and *S. aureus*	The hydrogel demonstrated cytocompatibility to L929 cells and HUVECs	Incorporating Ce-BGN in the hydrogel enhanced angiogenesis through improved HUVEC migration, tube formation, accelerated wound healing and skin tissue reconstruction	127
11	PVA hydrogel incorporated with Ag/TiO_2	Ag/TiO_2	The hydrogel incorporated with 1% and 5% Ag exhibited high bactericidal activity against *E. coli* and *S. aureus*	Endothelial cell viability was observed in 0.2% and 0.5% Ag/TiO_2 hydrogels, while 1% hydrogel exhibited cytotoxicity	0.5% Ag incorporated hydrogel demonstrated strong photocatalytic antibacterial activity, biocompatibility, and effective wound healing *in vivo*, without organ toxicity	128
12	Tannic acid (TA)-gel/oxidized Na-ALG hydrogel loaded with ZnO NPs	ZnO	The inhibition rates against *S. aureus* and *E. coli* were 97.8% ± 0.9% and 96.6% ± 1.2%, respectively	The hydrogel showed excellent biocompatibility on NIH 3T3 cells	The multifunctional hydrogel effectively accelerated wound healing and skin regeneration under infection and oxidative stress conditions	129
13	Polydimethylsiloxane (PDMS)/barium titanate ($BaTiO_3$) composite insoles (PDMS-BT)	$BaTiO_3$	*E. coli* and *S. aureus* were found to be inhibited to 44.7% and 24.0%, respectively	80% cell viability was observed in both HaCaT and L929 cells	The PDMS-BT ferroelectric insole accelerated wound healing by generating oxidative stress, reducing bacterial activity, and enhancing fibroblast migration and angiogenesis	130
14	Alpha lipoic acid (ALA) conjugated hexagonal boron nitride (hBN) and boron carbide (B_4C) NPs	hBN B_4C	At 50 μg mL^{-1}, the conjugate showed the highest bactericidal activity against *S. aureus* and *E. coli*	At the concentrations below 50 μg mL^{-1}, the NPs were cytofriendly towards human dermal fibroblasts (HDFs)	hBN-ALA and B_4C-ALA NPs showed strong potential for chronic wound healing, exhibiting regenerative, antimicrobial, and antioxidant properties	131
15	Levofloxacin (LV) loaded zirconium-based UiO-66-NH_2 metal–organic frameworks (MOFs)	UiO-66-NH_2 MOFs	At 100 μg mL^{-1}, the membranes showed 99.9% inhibition against *S. aureus* and *E. coli*	L929 cells exhibited a viability of 86.4% after 24 hours and 72.3% after 48 hours	The LV-loaded MOF membranes (LV/UiO-66-NH_2/PVA) accelerated wound healing in C57BL/6 mouse model	132

Table 2 (*Contd.*)

S. no	Inorganic nanoparticle-based scaffolds	Inorganic nanoparticles	Antimicrobial studies	Cytotoxicity studies	Inferences	Ref.
16	Microneedle with polydopamine (PDA) containing Fe_2O_3, glucose oxidase (GO_x), hyaluronic acid (HA) in the tips (Fe/PDA/GO_x/HA) and amine-modified mesoporous silica nanoparticles (MSNs) in the base	Fe_2O_3 NPs and amine modified MSNs	Fe/PDA/GO_x/HA showed inhibition against *S. aureus* and *E. coli* inhibition	95% cell viability was observed in endothelial and HaCaT cells	Fe/PDA/GO_x/HA significantly accelerated wound healing in *S. aureus*-infected models, reducing wound area to 7.8% under 660 nm laser irradiation through synergistic photothermal-chemodynamic therapy and anti-inflammatory effects	133
17	Na-ALG electrospun fibres blended with ZnO NPs	ZnO	At 2% of ZnO, the fibers showed 30% and 35% inhibition against *E. coli* and *S. aureus*, respectively	1% and 2% ZnO NPs showed good cell viability towards NIH-3T3 fibroblasts and HUVECs	*In vitro* and *in vivo* evaluations demonstrated superior epithelial regeneration, neovascularization, and microbial inhibition in ZnO-NP-loaded membranes compared to controls	134
18	A wound dressing containing CS and PVA with heparin (HP) functionalized ZnO NPs	ZnO NP	HP-ZnO NPs showed inhibition zones of 29 mm against *S. aureus* and *E. coli*	HP-ZnO NPs exhibited biocompatibility towards L-929 and HDF cells	*In vivo* studies confirmed the hydrogels' ability to accelerate wound healing by promoting re-epithelialization and collagen deposition	135

two curdlan based biomaterials, incorporating Zn-doped nano-HA and the other incorporating gentamicin. The Zn-doped HA exhibited a 99.9% reduction of *S. aureus*, while the gentamicin loaded biomaterial showed a strong bactericidal activity against both *S. aureus* and *P. aeruginosa*. The controlled release of Zn ions from the Zn-doped nano-HA biomaterial was effective in combating infections in wound site.[142] Among dopants, Cu and Zn remain the most widely explored for HA, with Cu providing potent bactericidal and angiogenic effects particularly suited for resistant infections, whereas Zn offers moderate antimicrobial efficacy alongside its role in enhancing keratinocyte proliferation and re-epithelialization. Furthermore, the integration of photothermal agents in wound healing also presents a promising strategy for both antimicrobial activity and tissue regeneration. These agents, upon near-infrared (NIR) irradiation, generate localized heat, effectively disrupting bacterial cell membranes, denaturing proteins, and inducing apoptosis, thereby eliminating infection at the wound site.[143,144] Tao *et al.* fabricated nanocomposites through a co-precipitation reaction between PDA-coated HA NPs-loaded with Cu^{2+}. The HA-Cu/PDA nanocomposites demonstrated a remarkable antibacterial efficacy of 91.0%, compared to HA-Cu (35.7%) and HA (8.5%). This enhanced bactericidal effect was attributed to the synergistic action of photothermal activation and Cu^{2+} release. The photothermal effect induced by NIR irradiation disrupted bacterial membrane integrity leading to ATP leakage and eventually bacterial lysis. Further, the scratch assay exhibited that HA-Cu/PDA nanocomposite reduced the wound area to 17.6% within 24 hours, compared to 64.5% in the control (Fig. 5). The HA-Cu/PDA nanocomposites along with NIR significantly accelerated *S. aureus*-infected wound healing, *via* anti-infection, anti-inflammation promoting cell migration, granulation tissue formation, collagen deposition, and angiogenesis.[145] Overall, the advancements in HA-based biomaterials, particularly through metal doping and photothermal integration, significantly progressed the wound care strategies.

4.2 Zinc oxide nanoparticles

ZnO NPs have demonstrated potent antimicrobial activity against both Gram-positive and Gram-negative bacteria, while also facilitating accelerated wound healing through enhanced

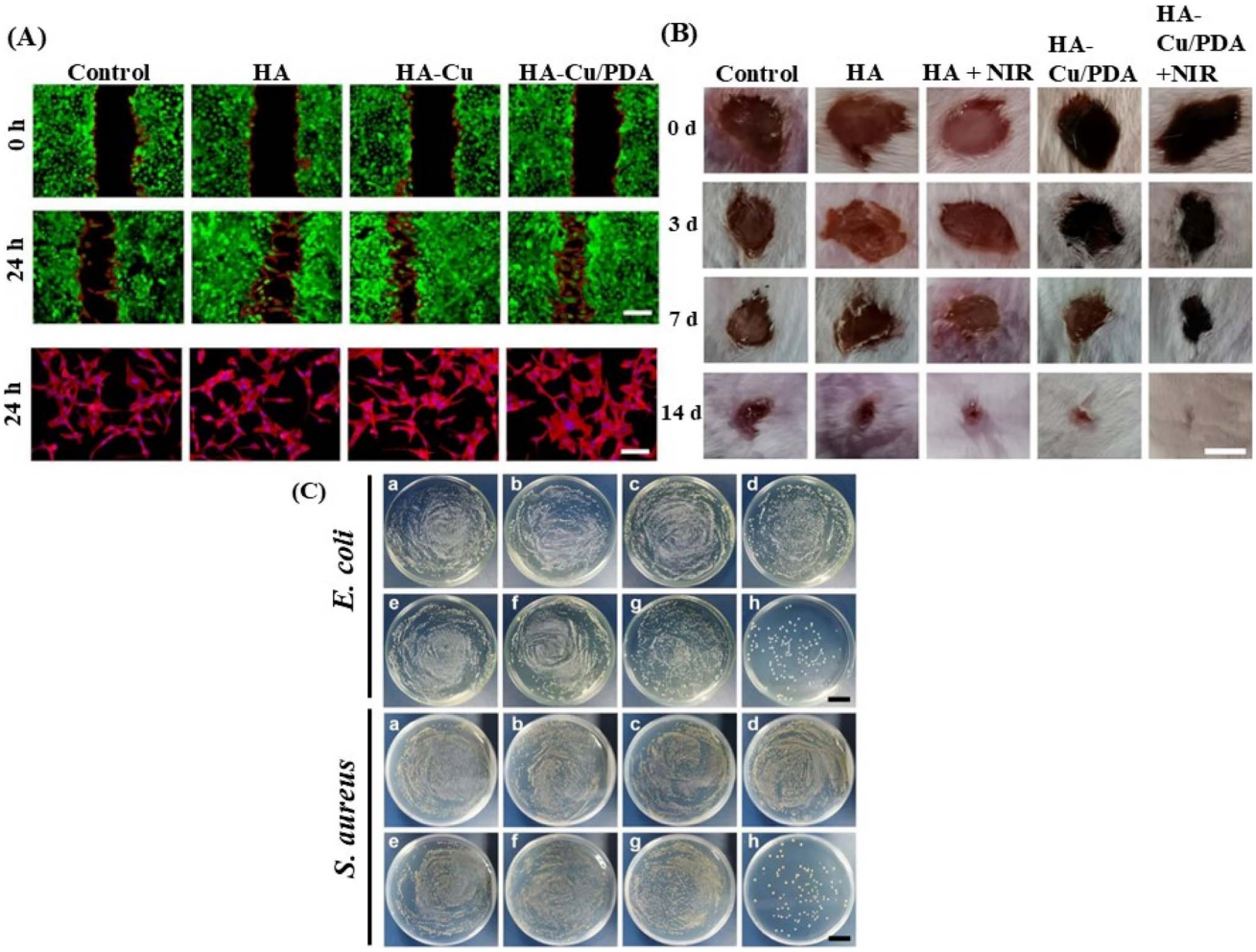

Fig. 5 (A) *In vitro* scratch assay and morphology of NIH-3T3 cells at different time. (B) Gross observation of wound area closure at day 0, 3, 7, and 14. (C) Antimicrobial activity against *E. coli* and *S. aureus*. Among them, (a) control, (b) HA, (c) HA-Cu, (d) HA-Cu/PDA, (e) control + NIR, (f) HA + NIR, (g) HA-Cu + NIR, and (h) HA-Cu/PDA + NIR. Adapted from Tao, *et al.* (ref. 145), with permission from Elsevier.

tissue regeneration.[146] The bactericidal mechanism of ZnO NPs operates through multiple pathways, including electrostatic interactions with bacterial membranes, and ROS generation.[147,148] The synthesis method of ZnO NPs significantly influences their effectiveness in wound healing. Green-synthesized ZnO NPs, derived from plant extracts, exhibit superior biocompatibility, reduced cytotoxicity, and enhanced biological activity, making them more suitable in promoting wound healing compared to chemically synthesized ZnO NPs.[149] It is evident that, compared to chemically synthesized counterparts, green-synthesized ZnO NPs not only enhance biocompatibility but also incorporate bioactive compounds that accelerate tissue regeneration, while modulating oxidative stress to prevent cellular damage and support wound-healing signaling pathways.[150] Despite advantages, widespread application is limited by poor standardization. Variations in plant metabolite composition, reaction conditions, and NPs stability reduce reproducibility and make cross-study comparisons difficult. To address these issues and improve functionality, ZnO NPs have been incorporated into polymeric scaffolds. For example, Khan *et al.* fabricated PLGA/SF nanofiber incorporated with ZnO NPs, which showed increased mechanical strength and antibacterial activity. The *in vivo* analysis showed a significant wound closure.[151] Similarly, Hamedi *et al.* developed a bioengineered hybrid wound dressing composed of schizophyllan (SPG)-modified bacterial cellulose polymers integrated with ZnO NPs. The ZnO-free scaffolds demonstrated limited antibacterial activity; whereas the incorporation of ZnO NPs markedly enhanced the bacterial inhibition rates. Additionally, the scaffolds exhibited biocompatibility and fibroblast proliferation, an important factor of wound healing.[152] These findings emphasize that the simultaneous application of SPG and ZnO NPs can be effective against burn wounds. These studies emphasize that the Zn^{2+} released from the scaffolds promoted increased fibroblast proliferation, keratinocyte migration, and collagen synthesis thereby enhancing angiogenesis at the wound site.[153]

Although ZnO NPs possess intrinsic antimicrobial activity through Zn^{2+} ion release, the incorporation of additional antimicrobial agents can further enhance its therapeutic efficacy, particularly in complex or infected wound environments.[154] Recent progress in nanomedicine has emphasized the strategic encapsulation of bioactive agents within ZnO NPs to augment complementary effects, particularly in wound healing applications.[155] Saddik *et al.* fabricated azithromycin (AZM)-loaded ZnO NPs, which showed superior antibacterial efficacy compared to free azithromycin. *In vivo* application of AZM loaded ZnO NPs embedded in a hydroxypropyl methylcellulose gel on wounded rats resulted in enhanced wound closure, improved epidermal regeneration, and a more organized tissue architecture, highlighting their potential as a dual-function therapeutic platform for infection control and tissue repair.[156]

4.3 Silica nanoparticles

Si NPs have emerged as promising materials in wound healing due to their unique physicochemical and biological properties.[157,158] Various forms including non-porous MSNs, hollow MSNs, and core–shell Si NPs-have been engineered to enhance wound healing efficacy.[159] In wound applications, Si NPs contribute by facilitating hemostasis, stimulating fibroblast proliferation, enhancing collagen synthesis, and accelerating re-epithelialization. The antibacterial activity is mainly ROS generation, and biofilm inhibition.[160] Abolghasemzade *et al.* reported the development of a multifunctional nanocomposite consisting of carbon quantum dots (CQDs), Si NPs, and SF, integrated into two wound dressing platforms: a bacterial cellulose structure *via* spray coating and PVA nanofibers *via* electrospinning. Antibacterial assessments demonstrated that the CQD/Si NP/SF composite exhibited enhanced efficacy due to Si NPs incorporation. *In vivo* wound healing studies in a murine model also showed that the Si NPs-incorporated PVA–CQD/SF nanofiber dressing achieved potent antibacterial and regenerative properties.[161] However, MSNs offer superior antimicrobial efficacy in wound healing applications compared to conventional Si NPs due to their unique structural characteristics, large pore volume, and tunable pore sizes, which allow MSNs to encapsulate and deliver a wide range of antimicrobial agents with high loading efficiency and controlled, sustained release at the wound site, combining stimuli-responsive drug release. Additionally, MSNs can be surface-functionalized with stimuli-responsive or targeting moieties, enabling site-specific delivery and enhanced therapeutic outcomes in infected or inflamed wounds. Zhu *et al.* developed a novel antibacterial nanoplatform, using Ag NPs-decorated and mesoporous silica ($mSiO_2$)-coated single-walled carbon nanotubes (SWCNTs), constructed *via* a *N*-[3-(trimethoxysilyl)propyl]ethylene diamine (TSD)-mediated method (SWCNTs/$mSiO_2$-TSD/Ag). The incorporation of Ag-decorated MSNs improved SWCNT dispersibility and increased bacterial contact. The SWCNTs/$mSiO_2$-TSD/Ag nanoplatform exhibited enhanced antibacterial performance due to the synergistic effect of $mSiO_2$ and Ag NPs, ensuring better bacterial inhibition at lower concentrations. Where, the $mSiO_2$ coating enhances SWCNT dispersibility, maximizing bacterial contact, while Ag NPs sustained Ag^+ release disrupts the cell membranes, impairing protein function, and inducing oxidative stress. Further *in vivo* study involving full-thickness skin wounds infected with multidrug-resistant *S. aureus* demonstrated significant reduction in wound area in the SWCNTs/$mSiO_2$-TSD/Ag group, compared to the SWCNTs/$mSiO_2$-TSD group, indicating their superior therapeutic efficacy with Ag NPs.[162]

Deaconu *et al.* developed a Zn-modified marine collagen porous scaffold incorporated with wild bilberry (Vaccinium myrtillus) leaf extract (WB) and encapsulated within functionalized MSNs. The WB/MSN system exhibited significantly improved antibacterial activity, compared to the free WB extract.[163] Li *et al.* engineered ROS-responsive drug delivery platform utilizing MSNs encapsulated with vancomycin (Van), and further functionalized with thioketal-linked methoxy poly (ethylene glycol) (mPEG-TK) to produce Van-mPEG-TK-MSNs. This functionalization in the presence of elevated ROS levels, commonly associated with infected and inflamed wound microenvironments, degrades the mPEG, thereby facilitating

targeted and controlled antibiotic release. The Van-mPEG-TK-MSNs exhibited a substantial bactericidal effect, achieving approximately 70% reduction in bacterial viability compared to control groups. Moreover, *in vivo* wound healing assessments revealed superior therapeutic outcomes, with the ROS-responsive nanocarriers markedly enhancing re-epithelialization and keratinocyte migration.[164] However, reliance on endogenous ROS is limited, as oxidative stress varies across wound types, causing inconsistent antibacterial outcomes. To address this challenge, light irradiation offers a controllable exogenous trigger, enabling consistent and reproducible activation of silica-based nanoplatforms.[165]

Light irradiation plays a crucial role in enhancing the antibacterial efficacy of SiO_2-based NPs through photodynamic and photothermal mechanisms. Upon activation by specific light wavelengths, these NPs generate ROS or localized hyperthermia, leading to bacterial membrane disruption, biofilm degradation, and increased bactericidal activity. In wound healing, silica-based NPs demonstrate intrinsic antimicrobial activity through ROS generation and membrane disruption, yet the therapeutic impact is considerably enhanced when integrated with additional agents or external triggers. Acting as multifunctional carriers, silica-based NPs stabilize therapeutic cargos, enable controlled release, facilitate targeted delivery, and promote deeper biofilm penetration, which broadens the scope of clinical applications.

4.4 Titanium dioxide nanoparticles

TiO_2 NPs have garnered significant attention in antimicrobial research due to their unique photocatalytic and physicochemical properties. Upon ultraviolet-A irradiation ($\lambda \leq 385$ nm), TiO_2 NPs undergo photoactivation, resulting in the generation of high-energy electron–hole pairs that catalyze the formation of ROS, including hydroxyl radicals ($\cdot OH$), superoxide anions (O_2^-), and hydrogen peroxide (H_2O_2). The cell wall is the initial target, where ROS disrupt peptidoglycan or chitin layers, exposing the underlying membrane to lipid peroxidation, increased permeability, and cell lysis. TiO_2 NPs also impair the mitochondrial respiratory chain, and induce DNA strand breaks. Additionally, they downregulate genes involved in iron and phosphate uptake, disturbing metabolic homeostasis, while inhibiting quorum sensing and biofilm formation. The nanoscale size enhances the surface interaction and cellular penetration, enabling broad-spectrum efficacy against bacteria, fungi, and multidrug-resistant strains. These multifactorial mechanisms position TiO_2 NPs as a promising antimicrobial platform for chronic wound management.[166]

TiO_2 NPs can be synthesized through chemical and green methodologies but the TiO_2 NPs synthesized through green methods exhibited superior photodegradation efficiency, enhanced antibacterial activity against pathogens such as *S. aureus*, *E. coli*, and *K. pneumonia*, and notable wound-healing potential.[167] Although TiO_2 NPs are widely recognized for their antimicrobial properties through various mechanisms, their large bandgap prevents activation under visible light, which limits photocatalytic efficiency and reduces antimicrobial effectiveness. However, this limitation can be overcome through structural modifications or by incorporating TiO_2 into nanocomposites, thereby enhancing their bioactivity and therapeutic potential.[168]

Nikpasand *et al.* developed a TiO_2/Gel nanocomposite and it significantly reduced bacterial colonization. Under *in vivo* conditions, there were the synergistic antimicrobial and regenerative properties conferred by the TiO_2/Gel nanocomposite.[169] Li *et al.* engineered a multifunctional nanocomposite by incorporating TiO_2NPs into a heparin–polyvinyl alcohol hydrogel matrix (H-PVA/TiO_2) *via* freeze–drying. This hydrogel-based nanocomposite bandage exhibited potent antimicrobial activity and favourable cytocompatibility. *In vivo* wound healing studies in Kunming mice revealed that wounds treated with the H-PVA/TiO_2 nanocomposite achieved nearly complete closure within 14 days.[170] Whereas the addition of TiO_2 into PCL nanofibers slightly improved the mechanical strength from 1.044 MPa in pure PCL to 1.78 MPa in the composite. The nanofibers showed very strong antimicrobial efficacy against *E. coli* and *S. aureus*. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and DAPI (4′,6-diamidino-2-phenylindole) staining showed biocompatibility of the PCL/TiO_2 scaffolds towards cells. This dual role of enhancing scaffold mechanics while exerting strong antimicrobial action underscores TiO_2's distinctive functionality in wound healing applications.[171] Furthermore, the subsequent study has explored the multifunctional designs of TiO_2 with other bioactive components, not to substitute but to synergize its bactericidal potential. For example, a multifunctional nanofibrous wound dressing by integrating GO, TiO_2, and curcumin into a cellulose acetate (CA) matrix was prepared and tested. The nanofibrous matrix showed potent antimicrobial activity against *E. coli*, *S. aureus*, *P. aeruginosa*, and *E. faecalis*. Biocompatibility assessments *via* MTT assay confirmed enhanced fibroblast viability and favourable, stress-free cell morphology.[172] Collectively, these studies underscore the versatility of TiO_2-based nanomaterials as potent antimicrobial and wound regenerative agents.

4.5 Bioactive glass nanoparticles

Bioactive glass nanoparticles (BGNs) are multifunctional materials widely recognized for their excellent biocompatibility, regenerative capacity, and broad applicability in wound healing and antimicrobial therapies.[173] BGNs are primarily composed of SiO_2, sodium oxide, calcium oxide, and phosphorus pentoxide, imparting distinct physicochemical characteristics.[174] The release of bioactive molecules from BGNs increases local pH and osmotic pressure, hence providing antimicrobial effects, while simultaneously facilitating angiogenesis, collagen production, and tissue regeneration.[175] Furthermore, BGNs play a pivotal role in immunomodulation by facilitating macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory and tissue-regenerative M2 phenotype. This transition mitigates excessive inflammation while promoting a microenvironment conducive to tissue repair and regeneration.[176] Its effectiveness in diabetic wound healing has been

demonstrated by the studies conducted by Sharaf *et al.* fabricated CA nanofibers incorporated with BGNs; the incorporation of 3% BGNs exhibited better inhibitory effects against *S. aureus*, *E. coli*, *S. typhimurium*, *B. subtilis* and *B. cereus*. Further, the incorporation of 3% BGN in the CA nanofibers accelerated the wound healing potential in diabetic rat model.[177] Yuan *et al.* synthesized poly(L-lactide-*co*-glycolide)/Gel nanofibers incorporated with BGNs and they facilitated cell migration, tubule-like network formation in HUVECs, and upregulated the expression of VEGF, FGF, EGF, Col1 genes in diabetic rat models, thereby fostering angiogenesis and collagen synthesis. Given these translational characteristics, BGN-loaded scaffolds could be strategically advanced for clinical application in diabetic wound management.[178]

The therapeutic efficacy of BGNs in antimicrobial and wound healing applications can be substantially enhanced through the incorporation of functional dopants such as Ag, Zn, Cu, boron (B), cobalt (Co), cerium (Ce), and gold (Au).[179] Among these, Ag-doped BGNs have garnered considerable attention due to their potent and broad-spectrum antibacterial activity.[180] The sustained release of Ag^+ ions from the BGN matrix not only facilitates the concurrent release of critical network modifiers such as Ca^{2+} and Si^{4+}, but also induces pronounced antimicrobial effects by compromising bacterial membrane integrity, disrupting vital metabolic and protein synthesis pathways, and effectively inhibiting biofilm formation which is critical for preventing infection and promoting accelerated tissue repair.[181] In another study, Sharifi *et al.* fabricated Gel, CS, and polyethylene oxide (PEO) nanofibers incorporated with Ag-doped BGNs and these nanofibers exhibited enhanced antibacterial properties. *In vivo* studies in BALB/*c* mice showed that wounds treated with Ag/BGNs-Ch/PEO/Gel scaffolds promoted thicker epidermal layers, enhanced epithelialization, increased collagen synthesis, and stimulated angiogenesis.[182] However, Ag^+ ions often exhibit burst-release kinetics, resulting in an initial surge in ion concentration that may compromise long-term antimicrobial efficacy and biocompatibility.

The incorporation of ZnO-doped BGNs in a hydrogel matrix consisting of succinyl CS/oxidized ALG exhibited nearly 100% bacterial lethality towards *S. aureus* and *E. coli*, which was attributed to the synergistic interaction between CS and ZnO-BGNs. Moreover, the controlled release of therapeutic ions from biocomposite supported macroscopic skin regeneration and stimulated cellular secretion of key angiogenic markers, such as CD31 and α-SMA, thereby promoting vascularization and tissue remodeling.[183] Collectively, these findings demonstrate that doped BGNs represent adaptable platforms for wound care, with Ag conferring potent antimicrobial protection, Cu and Co stimulating angiogenesis, and Zn integrating antibacterial and immunoregulatory functions. Such multifunctional properties enable tailored scaffold design aligned with wound severity and type, thereby harmonizing infection control with vascular and regenerative demands.

However, silicate-based BGN are characterized by slower degradation in physiological environments, resulting in suboptimal ion release kinetics that may impede the activation of cellular signalling pathways essential for wound healing. To overcome this, borate-based bioactive glass nanoparticles (BBGNs) have emerged as a compelling alternative to traditional silicate glasses. Unlike silicate glasses, BBGNs exhibit faster dissolution, allowing for more rapid ion release, which can stimulate key cellular activities associated with wound healing.[184] The degradation of BBGNs releases boron ions (B^{3+}), which have been shown to promote angiogenesis, collagen deposition, and fibroblast proliferation.[185] Moreover, BBGNs possess intrinsic antibacterial properties attributed to the elevated pH and osmotic pressure resulting from its ion exchange dynamics.[186] Altogether, BGN based scaffolds provide a versatile platform for wound healing, where tailored degradation and therapeutic ion release enable simultaneous infection control, angiogenesis, and tissue repair, underscoring its potential for effective clinical translation.

4.6 Other nanoparticles

Transition metal oxide-based NPs have been increasingly recognized as a distinct class of biofunctional materials, exhibiting considerable potential in therapeutic biomedical applications, particularly in the context of wound repair and regeneration. Metal oxide-based NPs such as yttrium oxide (Y_2O_3), vanadium(III) oxide (V_2O_3), magnesium oxide (MgO), cerium oxide (CeO_2), and alumina (Al_2O_3) have garnered increasing interest for their therapeutic utility in wound healing, owing to their distinctive lattice structures, redox behaviour, and surface chemistry. The antibacterial activity of these NPs arises from diverse physicochemical interactions that collectively disrupt microbial integrity and biofilm formation. Among these, Y_2O_3 NPs demonstrated notable bactericidal and angiogenic properties. The positively charged surface of Y_2O_3 NPs facilitated strong electrostatic interactions with the negatively charged bacterial membranes, resulting in membrane disruption and increased permeability. These interactions also contributed to the inhibition of biofilm formation, which is critical in preventing recurrent infections in chronic wounds.[187]

V_2O_3 NPs exhibit intrinsic oxidase-mimetic activity, undergoing cyclic redox transitions between V^{3+}, V^{4+}, and V^{5+} states. This redox cycling promotes efficient electron transfer, which in turn drives the catalytic conversion of molecular oxygen into ROS with strong antimicrobial effects.[188] Furthermore, this controlled ROS levels act as secondary messengers, modulating redox-sensitive pathways that upregulate pro-regenerative genes involved in fibroblast proliferation, angiogenesis, and matrix remodeling.[189] Similarly, MgO NPs eradicate bacteria through ROS generation but also establish a mildly alkaline microenvironment that suppresses microbial survival while supporting cell proliferation and matrix deposition.[190] Alongside these effects, MgO actively promotes VEGF-induced angiogenesis and drives macrophage polarization toward a regenerative M2 phenotype, creating a coordinated cellular and molecular response that culminates in effective wound closure.[191,192]

Additionally, Al_2O_3 and CeO_2 NPs known for their structural stability and biocompatibility, exhibit pronounced antimicrobial properties.[193] CeO_2 NPs, capable of redox-switching between Ce^{3+} and Ce^{4+}, exhibit potent antioxidant and antimicrobial properties.[194] Thus, it is evident that the metal oxide-based NPs have the

Table 3 Overview of emerging metal oxide nanoparticle-based scaffolds in wound healing

S. No	Inorganic nanoparticles	Emerging inorganic nanoparticle-based scaffolds	Microbial models	*In vitro* models	Inferences	References
1	Y_2O_3 NPs	PVA/L-lysine/Y_2O_3 NPs nanofibers	*E. coli*, *S. aureus*, *P. aeruginosa*	L929 cells	Y_2O_3 incorporation enhanced bactericidal and antibiofilm efficacy while maintaining fibroblast compatibility suitable for wound healing	195
		Polyurethane nanofibrous mats incorporated with *Azadirachta indica* leaf extract, clindamycin hydrochloride, and Y_2O_3 NPs	*E. coli*, *S. aureus*, *P. aeruginosa*	—	Synergistic action of Y_2O_3 with antibiotic agents provided broad-spectrum of antibacterial activity and accelerated wound closure in diabetic models	196
2	MgO	PCL/Gel/MgO	*E. coli*, *S. aureus*, *S. epidermidis*	NIH 3T3 fibroblasts and HUVECs	The optimized MgO loading produced strong antimicrobial activity and favorable cell proliferation for infected wounds	197
		PCL/poly-L-lactic acid-gel-MgO bilayer nanofibers	*E. coli* and *S. aureus*	NIH 3T3 fibroblasts and HUVECs	The bilayer configuration enabled sustained antibacterial response and biocompatibility, reflecting a balance between antimicrobial potency and cytocompatibility	198
3	CeO_2 NPs	PVA/CS/CeO_2 NPs	Methicillin resistant *S. aureus* (MRSA)	Human dermal fibroblasts	CeO_2 nano-oxidative behavior conferred selective antibacterial effect, maintained fibroblast compatibility, thus, demonstrating their therapeutic potential for chronic wounds	199
		CS/ALG/CeO_2 NPs	*E. coli* and *S. aureus*	NIH3T3 fibroblasts	Integration of CeO_2 improved mechanical integrity, biocompatibility, and antimicrobial response, enabling multifunctional wound healing performance	200
4	Al_2O_3	PVP/Al_2O_3 NPs	*S. aureus* and *E. coli*	L929 fibroblast cells	Al_2O_3 NPs imparted durable antibacterial functionality with fibroblast viability and surface features favorable for tissue restoration	201
5	Vanadium(V) oxide (V_2O_5)	PCL/CuO/V_2O_5 nanofibers	*E. coli* and *S. aureus*	Normal human cells	V_2O_5 addition improved surface wettability and porosity, thus, enhancing bacterial inhibition and biocompatibility essential for effective wound repair	202

therapeutic potential towards wound healing when they are incorporated into to suitable scaffold systems (Table 3).

4.7 Comparative evaluation of inorganic nanoparticles in wound healing

Each class of inorganic NPs exhibits distinct profiles of ion release, antimicrobial activity, angiogenic stimulation, and cellular migration. Comparative evaluation of these profiles is essential for aligning inorganic NP-based systems with the pathological features of different wound types and ensuring that their functional contributions meet clinical requirements. In acidic wound microenvironments, ZnO and CuO quickly release Zn^{2+} and Cu^{2+}. This kills a wide range of pathogens, including *E. coli*, *P. aeruginosa*, *S. aureus*, MRSA, and *Candida albicans*.[203] Their regenerative effects, including fibroblast migration and angiogenesis, are dose-dependent, observed predominantly at lower concentrations, while higher doses induce oxidative stress or excessive early inflammation, making it suitable for highly infected wounds.[204] While TiO_2 contributes primarily *via* modest ROS-driven antibacterial activity against *E. coli* and *S. aureus* with minimal angiogenic and migratory effects, which can be enhanced *via* photoactivation, making it suitable for superficially infected wounds.[205] In contrast, MgO, as an emerging inorganic NP, releases Mg^{2+} in a sustained manner to stabilize the wound while moderating inflammatory cytokine activity.[206] MgO demonstrates moderate antimicrobial coverage against Gram-negative (*E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae*), Gram-positive (*S. aureus*, MRSA, *Enterococcus faecalis*), and opportunistic fungi (*Candida albicans*, *Candida tropicalis*), thereby improving their ability to promote regeneration in chronic or ischemic wounds.[207]

Mineral-derived NPs, including HA, bioglass, and Si NPs, exhibit ion-driven bioactivity. HA dissolves slowly, releasing Ca^{2+} and PO_4^{3-} ions to support matrix organization and fibroblast migration, but offering minimal antimicrobial action. Bioglass dissolves more rapidly, enhancing endothelial activation, angiogenesis, and granulation, with moderate antimicrobial suppression of *S. aureus*, *E. coli*, and *P. aeruginosa*; doping with Ag, Zn, or Cu further expands antimicrobial coverage to MRSA and *Candida albicans* and its angiogenic potential.[208] Si NPs release silicate ions gradually, modulating inflammation and supporting structured matrix deposition, with modest antimicrobial activity that improves when doped or surface-functionalized.[209]

Furthermore, redox-active NPs, including CeO_2 and vanadium dioxide (VO_2) rely on valence-state-mediated redox regulation rather than ion dissolution. CeO_2 promotes fibroblast migration and granulation, making it particularly suited for chronic or inflammation-impaired wounds.[210] VO_2 demonstrates stronger antimicrobial activity against *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, and occasionally Candida species, making it more suitable for infected wounds. However, the therapeutic window for these NPs is narrower due to their dose-dependent cytotoxicity.[211] The redox-active NPs stabilize chronic inflammation, support neovascular organisation, and facilitate collagen deposition, and wound closure outcomes are highly formulation- and dose-dependent, and their angiogenic stimulation is moderate at sub-toxic concentration.[212,213] Across these inorganic NP classes, fabrication challenges commonly arise from maintaining particle size uniformity, preventing agglomeration, and ensuring stable dispersion within polymeric matrices, all of which influence consistent ion release or redox activity. Overall, the therapeutic performance of the inorganic NPs in the scaffold largely depends on specific wound conditions, as the wound microenvironment ultimately governs the inorganic NP stability, bioavailability, and biological response in the scaffold.

5. Preclinical to clinical translation

Even though NP- based scaffolds have emerged as highly promising biomaterials in regenerative medicine, as evidenced by the *in vitro* studies, *in vivo* models or preclinical studies are indispensable for comprehensively evaluating the therapeutic efficacy of NPs within complex biological environments. These studies yield critical mechanistic insights into antimicrobial performance, immunomodulatory responses, and the regulation of cellular processes essential for effective tissue remodelling and wound resolution. The preclinical evaluation conducted by Qianqian *et al.* involved in analysing the inorganic NP-based hydrogel composed of nanohydroxyapatite, CS, and tilapia skin-derived peptides (TP) using partial-thickness burn wound model with the New Zealand rabbits. The NHA/CS/TP-II hydrogel exhibited superior wound healing efficacy, with complete scab detachment and visible hair regrowth by day 21, indicating substantial epithelial and follicular regeneration. Furthermore, biochemical analyses and immunohistochemical staining indicated the hydrogel's ability to promote angiogenesis and tissue regeneration.[214] Similarly, Zhang *et al.* developed a multifunctional bioactive hydrogel combining aldehyde-functionalized pluronic F127 and alendronate sodium-modified Si–Ca–Cu nanoglass (BGNCu/AL) for wound healing. The *in vivo* assessment in normal and MRSA-infected full-thickness skin wounds in murine models demonstrated rapid wound healing with 75% closure in normal wounds and 70% closure in MRSA-infected wounds, approximately three times faster than the untreated control. This hydrogel also exhibited enhanced epidermal thickness, collagen organization, vascularization, and anti-inflammatory microenvironment.[215]

Furthermore, the therapeutic potential of inorganic NP-based scaffolds has also been reported in the clinical trials. For example, the therapeutic efficacy of calcium ALG dressings loaded with ZnO (CAZnODs) was evaluated for treating diabetic foot ulcers in type 2 diabetes patients. A total of 26 patients were randomized into two groups: 16 received the NPs-infused dressings (experimental group), and 10 received standard calcium ALG dressings (control group). Over a 10 weeks treatment period, both groups demonstrated progressive wound healing; however, the experimental group exhibited significantly improved wound closure. Collectively, the study demonstrated that CAZnODs accelerated wound healing, exhibited biocompatibility, and represented a safe and effective therapeutic option for managing diabetic foot ulcers in diabetic

populations.[216] Collectively, these findings emphasize the transformative potential of inorganic NP-based scaffolds in wound care, providing not only accelerated healing but also a safe and effective alternative to conventional treatments. To fully harness its therapeutic potential and refine its application across varied patient populations and wound types, further clinical trials and long-term studies are essential. While such clinical outcomes highlight the therapeutic potential of inorganic NPs-based scaffolds, their broader clinical implementation remains limited due to complex regulatory pathways, manufacturing challenges, and incomplete understanding of long-term biosafety.

6. Challenges and future perspectives

Inorganic NP-based wound healing platforms continue to gain significant momentum because of the convergence between nanotechnology and regenerative medicine. The global inorganic NPs market, valued at USD 2.5 billion in 2022, is projected to reach approximately USD 7.9 billion by 2030, representing a compound annual growth rate of 15.4%.[217] This rapid expansion is primarily driven by the increasing demand for advanced antimicrobial wound care solutions and the widening scope of nanomaterials in biomedical engineering, especially within tissue regeneration and infection control. Numerous NP-based formulations have demonstrated potent antimicrobial activity and favourable biocompatibility, leading to the development of promising commercial products. For instance, megaNANO^2 Gel (Zuventus Healthcare Ltd, India) which is incorporated with Ag NPs, has been utilized for managing wound infections, while NanoSALV, a catalytic advanced wound care treatment (NanoTess Inc, Canada) has shown efficacy in treating advanced, non-healing wounds. These developments underscore the translational potential of inorganic NP systems, particularly in accelerating wound closure, enhancing tissue regeneration, and improving infection resolution.

Despite progress, inconsistent safe dose ranges continue to limit the clinical translation of NPs, with some studies reporting toxicity at concentrations considered non-toxic. These discrepancies arise from variations in particle size, surface chemistry, and testing methods. Standardized evaluation criteria are therefore essential to ensure reliable safety assessments.[218] Refinement of inorganic NP formulations is essential to optimize dosing, exposure duration, and controlled release, minimizing off-target effects and improving safety. Heterogeneity in wound types, microenvironments, and patient comorbidities complicates standardization, while long-term biocompatibility remains a concern due to potential delayed inflammatory or fibrotic responses. Current studies are limited by small sample sizes, short-term evaluations, and lack of multicenter trials, highlighting the need for robust, longitudinal *in vivo* research to validate safety, immunocompatibility, and functional efficacy in chronic wounds. Standardized preclinical models and adherence to specific regulatory frameworks, including Food and Drug Administration guidance on nanotechnology in drug products and European Medicines Agency guidelines on nanomedicinal products, will be critical for clinical translation. On the technological front, integrating inorganic NPs into stimuli-responsive hydrogels, biodegradable films, or hydrocolloids, combined with wearable biosensors, offers the potential for adaptive, personalized wound care with precision-controlled therapeutic release.

From a manufacturing perspective, high costs and technical complexity in NP synthesis limit scalability. Conventional methods often require energy-intensive conditions or rare precursors, prompting exploration of eco-friendly approaches such as plant-based or microbial-assisted green synthesis. Advances in additive manufacturing and AI-driven modeling offer the potential for patient-specific, biologically functional scaffolds. Clinical translation must comply with internationally recognized safety standards, including ISO 10993, which guides biological evaluation of medical devices. Part 1 of the standard emphasizes structured risk assessment and testing before *in vivo* or clinical application.[219] However, within the ISO 10993 framework, long-term implantation and genotoxicity assessments are particularly important for NPs, since standard assays may not fully account for its persistence or nanoscale interactions. In addition, hemocompatibility and degradation studies must be tailored to wound types to ensure a reliable safety profile. Navigating these regulatory pathways demands early engagement with approval bodies, harmonization of testing protocols, and interdisciplinary collaboration to facilitate commercialization while ensuring patient safety and clinical efficacy.

7. Conclusions

Inorganic NP-based scaffolds in wound healing offer a highly versatile platform integrating antimicrobial functionality with regenerative bioactivity. Through mechanisms such as localized ion exchange, redox modulation, and biointerface-mediated cell signaling, inorganic NPs have demonstrated efficacy in promoting fibroblast migration, angiogenesis, collagen deposition, and biofilm disruption. The integration of NPs into engineered constructs including electrospun nanofibers, injectable hydrogels, and 3D biocomposites has enabled site-specific, sustained delivery of therapeutic agents while concurrently providing structural support and biomimetic cues for tissue regeneration. Even though the inorganic NP-based therapies show great promise, optimizing biocompatibility, ensuring consistent performance under physiological conditions, and establishing standardized long-term safety protocols remain important for their broader clinical adoption. Advances in green synthesis, stimuli-responsive architectures, and patient-specific scaffold engineering *via* computational modelling and additive manufacturing present promising avenues to overcome these current limitations. Furthermore, advancing clinical success will require not only material innovation but also the incorporation of predictive *in vitro* platforms, real-time biosensing, and responsive scaffold designs to precisely regulate therapeutic ion delivery and orchestrate cellular behaviour. With continued interdisciplinary innovation and regulatory alignment, inorganic NP-based systems are poised to become pivotal in the next generation of targeted, intelligent wound care therapies.

Abbreviations

Ag	Silver
Ag NPs	Silver nanoparticles
Al_2O_3	Alumina
α-SMA	Alpha-smooth muscle actin (α-SMA)
ALA	Alpha lipoic acid
ALG	Alginate
AZM	Azithromycin
B_4C	Boron carbide
$BaTiO_3$	Barium titanate
BBGNs	Borate based bioactive glass nanoparticles
BCM	Bacterial cellulose membrane
BG	Bioactive glass
BGNs	Bioactive glass nanoparticles
BS	*Boswellia serrata*
CA	Cellulose acetate
CaS	Calcium silicate
CD31	Cluster of differentiation 31
Ce	Cerium
CeO_2	Cerium oxide
CMC	Carboxymethyl chitosan
CMS	Carboxymethylated starch
Co	Cobalt
CQDs	Carbon quantum dots
CS	Chitosan
Cu	Copper
Cu-MBGNs	Copper containing mesoporous bioactive glass
CuO	Copper oxide
DAPI	4′,6-Diamidino-2-phenylindole
ECM	Extracellular matrix
Fe_2O_3	Iron oxide
FeO	Iron(II) oxide
Gel	Gelatin
GG	Gellan gum
GO	Graphene oxide
GO_x	Glucose oxidase
HA	Hydroxyapatite
hBN	Hexagonal boron nitride
HBOT	Hyperbaric oxygen therapy
HDF	Human dermal fibroblasts
HIF-1α	Hypoxia-inducible factor 1-alpha
H-PVA	Heparin-polyvinyl alcoholPVA
HUVEC	Human umbilical vein endothelial cells
LTA	Linde type A
LV	Levofloxacin
MBGNs	Mesoporous bioactive glass nanoparticles
MgO	Magnesium oxide
Mlt	Malachite
MMP	Matrix metalloproteinases
MNA	Microneedle array
mPEG-TK	Thioketal-linked methoxy poly(ethylene glycol)
MRSA	Methicillin-resistant *Staphylococcus aureus*
$mSiO_2$	Mesoporous silica
MSNs	Mesoporous silica nanoparticles
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
Na-ALG	Sodium alginate
NADPH	Nicotinamide adenine dinucleotide phosphate
NIR	Near infrared
NPs	Nanoparticles
PCL	Polycaprolactone
PD	*Pinus densiflora*
PDA	Polydopamine
PDMS	Polydimethylsiloxane
PEO	Polyethylene oxide
PLGA	Poly(lactide-*co*-glycolic acid)
PVA	Poly(vinyl alcohol)
PVP	Polyvinylpyrrolidone
ROS	Reactive oxygen species
SF	Silk fibroin
Si	Silica
Si NPs	Silica nanoparticles
SPG	Schizophyllan
SWCNTs	Single-walled carbon nanotubes
TA	Tannic acid
TiO_2	Titanium dioxide
TSD	*N*-[3-(trimethoxysilyl)propyl] ethylene diamine
VO_2	Vanadium dioxide
V_2O_3	Vanadium(III) oxide
V_2O_5	Vanadium(V) oxide
Van	Vancomycin
VEGF	Vascular endothelial growth factor
WB	Wild bilberry
Y_2O_3	Yttrium oxide
Zn	Zinc
ZnO	Zinc oxide
ZrO_2	Zirconia

Author contributions

Anand Varsha: writing of the original manuscript, visualization, investigation. Arumugam Bharathraj: writing of the original manuscript, visualization, investigation. Kumar Shivanee: writing of the original manuscript, visualization, investigation. Rajan Kalpana Sahana: writing of the original manuscript, visualization, investigation. Sushma Babu: writing – review & editing, supervision, conceptualization, investigation. Nagarajan Selvamurugan: writing – review & editing, supervision, conceptualization, investigation, formal analysis.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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