International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Silicon-Based Nanomaterials in Chronic Wound Healing: Mechanisms, Therapeutic Applications, and Clinical Prospects

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Abstract: Silicon-based nanosystems are emerging as promising nanotherapeutic platforms in the biomedical field, particularly for the treatment of chronic wounds. These materials possess several advantageous features. They offer excellent drug-loading capacity, controlled and stimuli-responsive drug release, and highly customizable structures and functions. These characteristics make them well-suited for personalized therapeutic approaches.This review provides a comprehensive summary of recent advances in the application of silicon-based nanosystems in wound healing. It highlights their mechanisms of action and discusses future development directions. We begin by outlining the clinical significance and complex pathophysiological characteristics of chronic wounds. A detailed classification of silicon-based nanomaterials is then provided, including mesoporous silica nanoparticles and silicon-based composites. The review emphasizes their key roles in modulating inflammation, reducing oxidative stress, and promoting angiogenesis and tissue regeneration. In addition, we summarize recent findings from in vitro and in vivo studies, as well as updates from relevant clinical research. The biocompatibility and safety profiles of these systems are also comprehensively evaluated. Future research should focus on optimizing the synthesis of these materials and improving their long-term biosafety. Efforts should also aim to integrate multifunctional therapeutic strategies to enhance efficacy and translational potential. Moreover, large-scale, rigorously designed clinical trials are urgently needed. These studies will help build robust clinical evidence and support the practical application of silicon-based nanosystems in advanced wound care. In conclusion, silicon-based nanosystems represent a next-generation approach for wound therapy. However, further interdisciplinary research is essential to fully realize their clinical value.

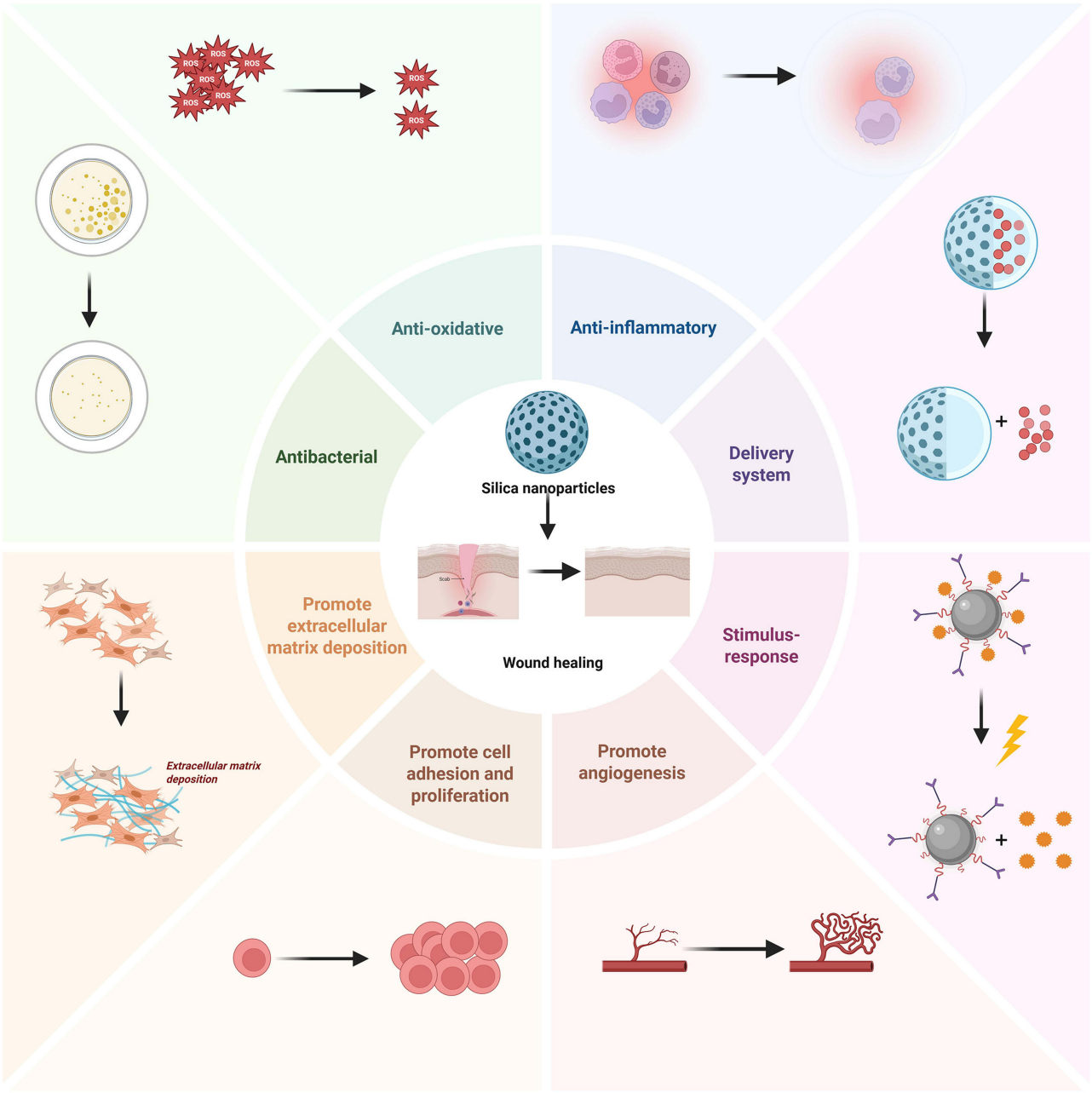
Keywords: silicon, nanomaterial, chronic wound healing, wound healing, silicon-based nanosystems

Introduction

The skin is an important organ that covers the human body and interacts directly with the outside world. It plays a key role in immunity, feeling, and protection.[1,2] In recent years, the prevalence of chronic wounds has sharply increased, primarily due to the growing population of individuals with diabetes and obesity, in addition to external physical damage.[3,4] Under normal conditions, wound healing is a complex, dynamic process supported by numerous cellular events, tightly coordinated to repair damaged tissues effectively.[5] However, in certain situations such as diabetes, wound infection, inflammation, and vascular or neural dysfunction, the normal wound healing process becomes disrupted, leading to the development of chronic wounds.[6,7] In the United States, chronic wounds affect approximately 10.5 million

Received: 15 March 2025
Accepted: 18 September 2025
Published: 30 September 2025

Graphical Abstract



Medicare beneficiaries (an increase of 2.3 million since 2014), with annual treatment costs exceeding $25 billion.[8,9] Despite advancements, promoting rapid and high-quality skin wound healing remains a significant challenge.

In recent years, silica nanoparticles (SNPs) and their multifunctional carriers have gained considerable attention due to their significant advantages in drug delivery.[10–12] These advantages include their hydrophilic surface, diverse surface functionalization options, tunable shapes, and sizes, biocompatibility, ease of large-scale synthesis, and low production costs,[10,13–15] making them highly promising therapeutic carriers. Among these, mesoporous silica nanoparticles (MSNs), with pore sizes ranging from 2 to 50 nanometers, have been extensively studied. MSNs have been applied in targeted

drug delivery and tissue engineering,[11,16] and their surfaces can be modified with stimuli-responsive molecules and various therapeutic macromolecules, enabling on-demand and localized controlled drug release.[17] Additionally, capping strategies endow MSNs with intelligent drug delivery properties, allowing them to respond to various stimuli (eg, PH changes, photothermal, and photodynamic effects) and release therapeutic cargo for targeted applications.[18] The development of silica-based nanosystems has shown significant potential in biomedicine, demonstrating their utility in clinical practice[19–23] (Figure 1).

Over the past few decades, advancements in nanotechnology have led to the emergence of various nanomaterials and nanomaterial-based drug delivery systems, which have been applied to wound repair and regeneration.[24] The quantum size and surface effects of different nanomaterials impart unique physicochemical properties and functionalities, enabling them to carry and release bioactive drugs in controlled and sustained manners.[25] These functionalized nanoparticles promote wound healing by modulating the microenvironment through antibacterial, anti-inflammatory, antioxidant, and pro-angiogenic properties.[26–31] This review discusses different types of SNPs and their surface engineering, elucidating their mechanisms and potential roles in improving wound healing, while also exploring their biocompatibility and safety profiles.

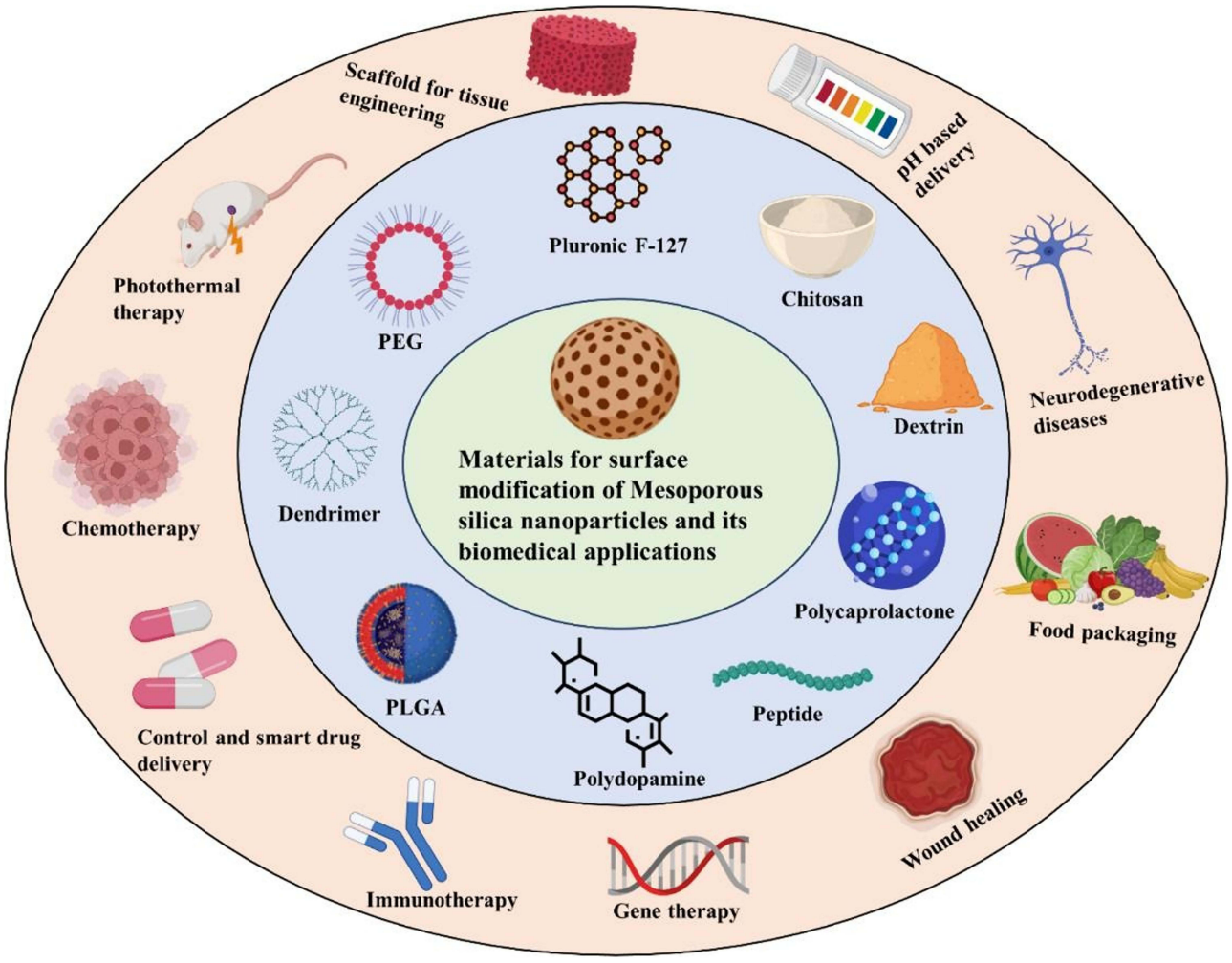


Figure 1 Applications of polymer-coated MSNs in various therapeutic fields, including photodynamic therapy (PDT), photothermal therapy (PTT), chemotherapy, RNA delivery, wound healing, tissue engineering, food packaging, and the treatment of neurodegenerative diseases. Reprinted from Nair A, Chandrashekhar H R, Day CM, et al. Polymeric functionalization of mesoporous silica nanoparticles: biomedical insights. *Int J Pharm*. 2024;660:124314. Creative Commons.[19]

https://doi.org/10.2147/IJN.S528531

Wound Classification and Pathophysiology of Injury Repair

Skin wounds are defined as disruptions or damage to the structure and function of the skin caused by various factors, including trauma, burns, and physiological or medical conditions.[32,33] In such cases, the anatomical structure of the skin is compromised, leading to a loss of its physiological functions. Based on the healing timeline, wounds are generally classified into two categories: acute wounds and chronic wounds. Acute wounds are often caused by mechanical injury or exposure to extreme temperatures, radiation, electrical shocks, or corrosive chemicals.[34] With proper wound management, acute wounds restore skin integrity within weeks or a month through the normal and orderly stages of tissue repair.[35,36] Chronic wounds, however, are often complications of specific conditions such as diabetes, vascular diseases, or pressure ulcers, although wound-specific factors like infection, inflammation, and radiation also contribute.[37] Systemic factors, including malnutrition, immunosuppression, aging, and other complications, can further delay wound healing.[38,39] Wounds can also be classified based on their depth: superficial wounds (involving only partial epidermal loss), partial-thickness wounds (affecting the epidermis and deeper dermis), and full-thickness wounds (damaging subcutaneous fat and deeper tissues).[40]

Following injury, damaged skin initiates a complex repair process involving the interplay of various cell types, cytokines, and biological mediators. Under normal conditions, this process progresses through distinct stages, including hemostasis, inflammation, proliferation, and remodeling (Figure 2).[33,41–43]

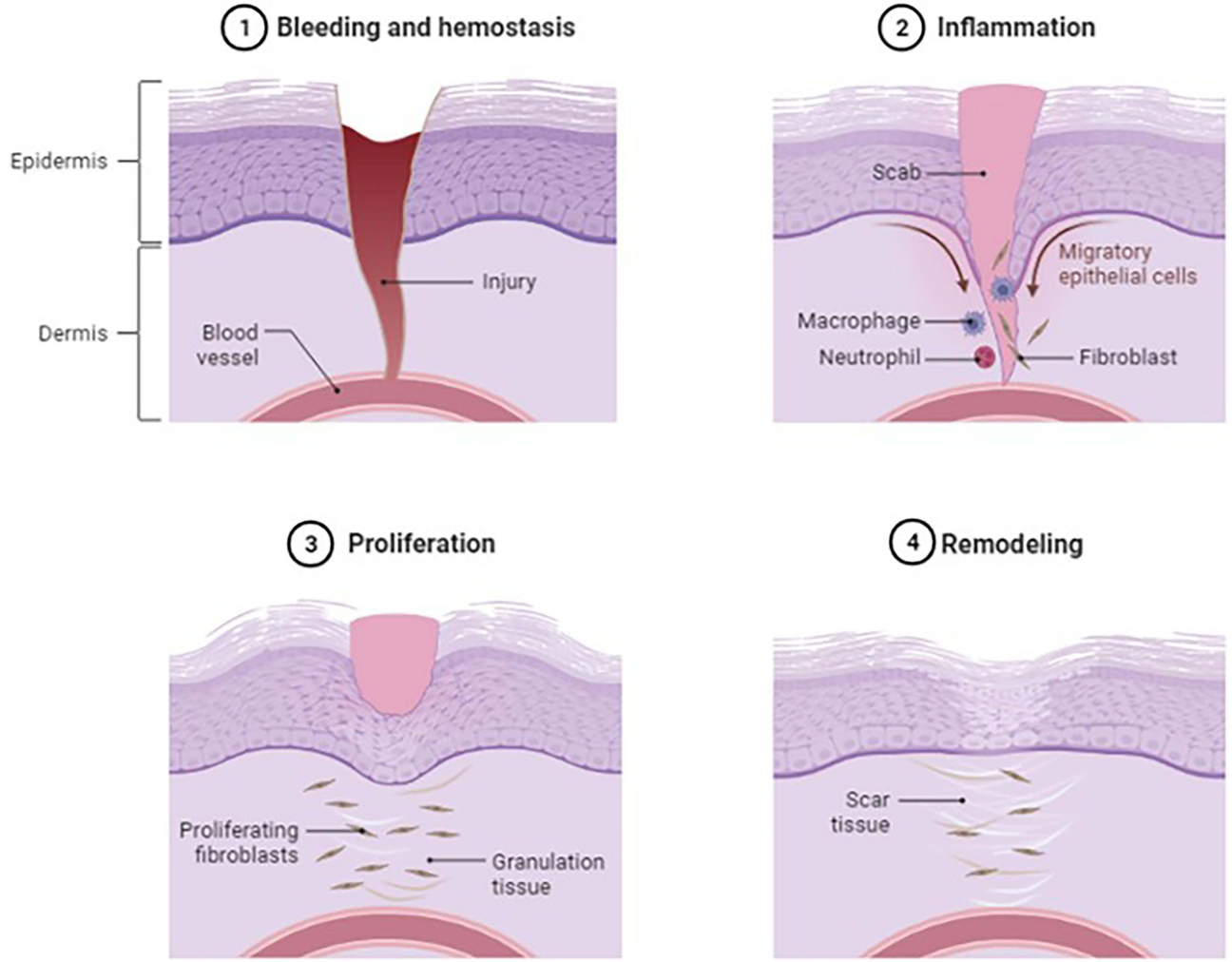


Figure 2 Damaged skin initiates a complex repair process involving the interaction of multiple cell types, cytokines, and biological mediators. Under normal conditions, this process undergoes a series of stages, including hemostasis, inflammation, proliferation, and remodeling. Adapted from from Cioce A, Cavani A, Cattani C, Scopelliti F. Role of the Skin Immune System in Wound Healing. *Cells*. 2024; 13(7):624. Creative Commons.[44]

Hemostasis

Immediately after injury, the body triggers hemostatic responses to minimize blood loss. Local blood vessels constrict via smooth muscle contraction to limit blood flow, and both intrinsic and extrinsic coagulation pathways are activated.[45,46] The fibrin clot formed by platelets and coagulation factors not only prevents bleeding but also provides a temporary scaffold for cell adhesion and migration.[47–49]

Inflammation

The inflammatory phase typically occurs from day 2 to day 5 post-injury. During this phase, platelets activated by thrombin release various growth factors, including epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factors (TGF-α and TGF-β).[50,51] These factors serve as biological signals that attract neutrophils, monocytes, leukocytes, and macrophages to the wound site, mediating inflammation, protecting the skin from infection, and secreting additional growth factors to accelerate healing.[40,52,53]

Proliferation

From 3 days to 2 weeks post-injury, the wound enters the proliferative phase, characterized by cell proliferation and migration.[40] Angiogenesis and capillary formation occur under the influence of pro-angiogenic factors such as PDGF released by platelets and inflammatory cells.[54] Simultaneously, fibroblast migration is stimulated by PDGF and FGF, resulting in granulation tissue formation.[55,56] Fibroblasts accumulate and proliferate, producing a new extracellular matrix (ECM) composed of collagen, proteoglycans, and elastin. Some fibroblasts differentiate into myofibroblasts, contributing to wound contraction.[57] Additionally, activated keratinocytes at the wound edges migrate to the injured area, completing re-epithelialization.[58]

Remodeling

The remodeling phase involves structural reorganization and cellular reduction. Type III collagen in the granulation tissue is gradually replaced by type I collagen, the primary matrix component of the dermis. The rearrangement, cross-linking, and alignment of collagen fibers involve the dynamic synthesis of collagen and matrix metalloproteinases (MMPs), leading to ECM strengthening and contraction, and ultimately the formation of mature scar tissue. This phase typically lasts from 3 weeks to 2 years.[59,60] Wound repair is a highly organized and complex pathological process. Disruptions at any stage can lead to wound pathologies, such as hypertrophic scars, keloids, or chronic wounds.[61,62]

If the normal healing process is disrupted, wounds may become chronic. Chronic wounds fail to heal in a timely and orderly manner. Clinically, diabetic foot ulcers (DFUs), pressure ulcers (PUs), and venous leg ulcers (VLUs) are common types of chronic wounds.[37,39,63] Despite varying etiologies, these wounds share common characteristics, including excessive exudate, infection, tissue necrosis, insufficient re-epithelialization, reduced angiogenesis, and elevated levels of reactive oxygen species (ROS).[64,65] Diabetes and hyperglycemia also contribute to peripheral neuropathy and peripheral vascular disease, significantly increasing the risk of DFUs and VLUs.[66,67] Vascular damage leads to hypoxia, promoting the formation of avascular, non-viable tissue that creates an environment conducive to bacterial growth and biofilm formation. Biofilms exacerbate inflammation, hinder ECM deposition, and impair tissue repair.[68] Unlike acute wounds, chronic wounds are influenced by multifactorial elements, including dysfunction of inflammatory cells; limited bioavailability of growth factors and cytokines; overexpression of proteases, persistent infection, reduced angiogenesis, and inadequate nutrient supply.[53,69] These factors often interrupt the wound healing process, leaving it stalled in the inflammatory phase.

Diabetes significantly impacts all stages of wound repair, creating a pro-inflammatory environment characterized by elevated levels of pro-inflammatory cytokines such as TNF-α and reduced concentrations of healing-promoting mediators like IL-10 and TGF-β. This imbalance can lead to tissue necrosis and chronic wound formation.[70] Additionally, the wound microenvironment after infection becomes pro-inflammatory, with prolonged presence of

myeloid cells (eg, macrophages and neutrophils) and reduced levels of skin dendritic cells (DCs), Langerhans cells (LCs), and eosinophils, perpetuating the inflammatory state.[64,71,72]

Systemic or localized pathological factors often impair immune cells' ability to eliminate pathogens, creating a vicious cycle that exacerbates the hostile wound microenvironment.[73] Moreover, failure in signal transduction, weakened keratinocyte migration, and proliferation, and delayed re-epithelialization further contribute to chronic wound progression.[71,74] Excessive ECM degradation, partly induced by the imbalance of MMPs and their inhibitors, hinders proper ECM deposition.[75,76] In wounds with neuropathy, reduced neuropeptides and neurotrophic factors also impede critical healing mechanisms.[76]

Classification and Structural Characteristics of SNPs

The main synthesis methods of silicon-based nanomaterials include chemical vapor deposition (CVD), sol-gel method, solvothermal method, hydrothermal method, reverse microemulsion method, and self-assembly method.[77–79] Due to their versatility in synthesis, size and shape regulation, surface functionalization, and biocompatibility, various types of silica nanoparticles (SNPs) have been developed for biomedical applications,[77–80] including non-porous, mesoporous, hollow, core-shell, yolk-shell, and Janus architectures.[81] Typically, SNPs are classified into two classic types—non-porous and mesoporous—based on their porosity (Figure 3). The term "mesoporous" generally refers to materials with pore sizes ranging from 2 to 100 nm.[82] Non-porous SNPs lack special surface structures, while mesoporous silica nanoparticles (MSNs) feature tunable mesopores. The most notable difference between the two is the orderly, porous structure of MSNs.[83] Characterization analysis shows that both types exhibit an amorphous, near-spherical morphology.

Amorphous SNPs not only provide drug-loading capabilities and enable precise regulation of pharmacokinetics through porous channels but also possess two critical functional surfaces: cylindrical pore surfaces and external particle surfaces. Both surfaces can be functionalized according to specific requirements. On the one hand, pore surfaces can be specifically functionalized to precisely control drug release rates and mechanisms; on the other hand, external particle surfaces can bind to targeting ligands to achieve specific drug delivery.[84] According to assembly strategies, specific nanostructured composites can be obtained, and MSNs are categorized into five types[16] (Figure 3):

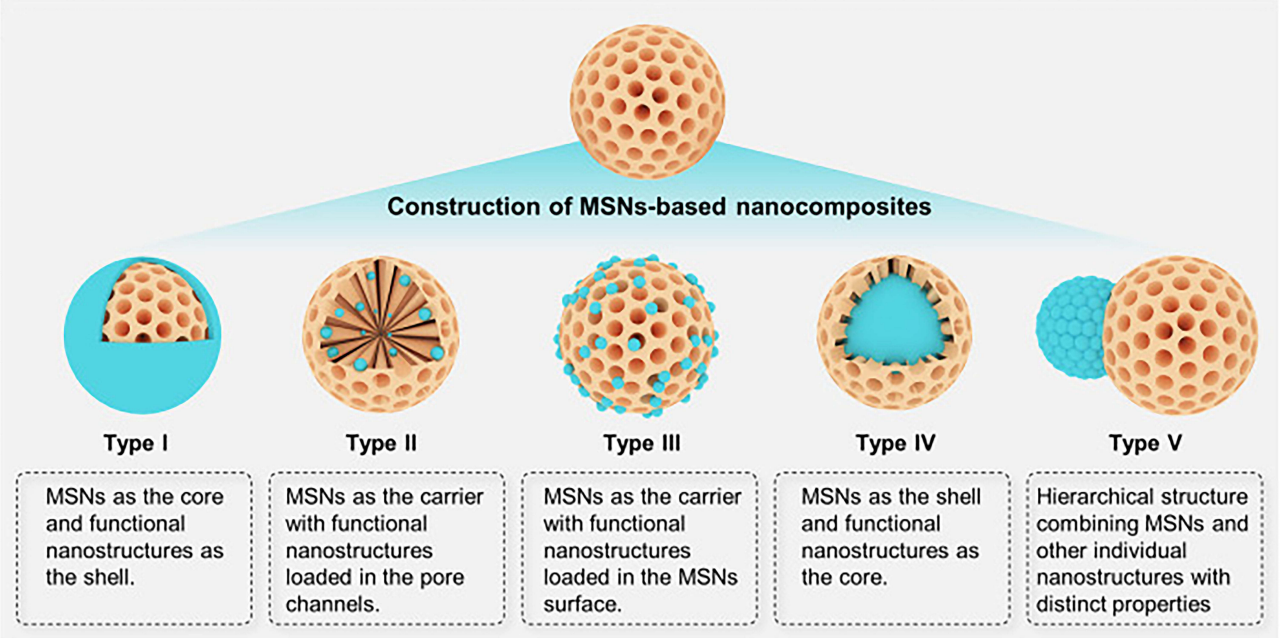


Figure 3 Silica MSNs-based nanocomposites developed in the biomedical field. Various nanostructured MSN-based nanocomposites. Depending on the assembly process, the functional nanostructures can be introduced as the shell (Type (**I**) or core (Type IV), loaded in the pore channels (Type II) or surface (Type III), or form Janus-type hierarchical structures (Type V). Reprinted from Xu B, Li S, Shi R, et al. Multifunctional mesoporous silica nanoparticles for biomedical applications. *Signal Transduct Target Ther.* 2023;8(1):435. Creative Commons.[16]

1. **Type I**: Core-shell structures where MSNs act as the core, and functional components serve as the shell. Functional nanocoatings of specific sizes can be easily achieved by manipulating MSNs as hard templates.
2. **Type II**: Small functional components are directly loaded into MSN pores. Common functional components, such as carbon quantum dots and black phosphorus quantum dots, are often encapsulated in this form. In such structures, MSNs enable the slow and controlled release of small functional components.
3. **Type III**: Functional components are loaded onto MSN surfaces or pore peripheries through covalent bonds or electrostatic adsorption. This approach avoids masking the active sites of functional components, thereby ensuring catalytic stability.
4. **Type IV**: Core-shell structures where MSNs act as the shell, and functional components serve as the core. This structure prevents the aggregation of exposed inorganic functional components, enhancing the stability of nanocomposites and reducing physiological toxicity.
5. **Type V**: Janus-type architecture. Janus-type nanocomposites feature biphasic geometric shapes with distinct compositions or anisotropic structures. Unlike the Type I–IV nanocomposites, the physicochemical properties of individual components in Janus structures remain largely unaffected.

Using these unique structures, researchers have developed numerous silicon-based hybrid nanomaterials with distinctive properties through surface functionalization, such as silicon-drug polymers, silicon-nucleic acid hybrids, silicon-protein hybrids, and silicon-magnetic composites. Additionally, silica can hybridize with peptides, amino acids, gold nanomaterials, and quantum dots to meet the demands of complex biomedical applications.[85,86]

In recent years, experts have continually proposed new insights into the design principles of silica nanostructures,[87] such as engineering pore geometry, surface topology, and asymmetry to enhance the efficiency of drug, gene, and protein delivery.[87,88] Innovations include altering surface roughness to improve cellular uptake and adhesion, as well as hollow MSNs (HMSNs) with mesoporous shells and hollow interiors. Another class of innovative mesoporous silica materials has been designed to overcome the limitations of traditional MSNs in delivering large-volume drugs like proteins by exhibiting advanced mass diffusion properties and high storage capacities.[88–90] Additionally, novel SNPs have been designed as biological modulators to regulate intracellular microenvironments and cell signaling, such as oxidative stress and glutathione levels, thereby enhancing therapeutic anticancer effects and mRNA transfection in specific cell lines[91] (Figure 4). Thus, silicon-based nanomaterials are becoming increasingly diverse in terms of morphology and functionality, finding widespread applications in biomedical fields, including targeted drug delivery, tissue engineering, biosensing, bioimaging, and more.[92]

Potential Regulatory Mechanisms of Silicon-Based Nanomaterials in Wound Healing

Silicon-based nanoparticles (SNPs) have shown immense potential in tissue regeneration, particularly in wound healing. Silicon-based nanostructured composites exhibit promising roles, either individually or synergistically, in promoting wound healing through antibacterial/anti-inflammatory effects, antioxidation, and tissue regeneration.[93,94] Below, we elucidate their potential regulatory mechanisms with illustrative examples.

Antibacterial Effects

After skin injury, bacteria easily migrate from the surface to non-resident areas, leading to wound infection and significantly disrupting the healing process.[37] Wound exudates, as a hallmark of chronic wounds, contain corrosive components that exacerbate extracellular matrix (ECM) degradation. Matrix metalloproteinases (particularly MMP-9) have been identified as key destructive factors, and the increase in bacterial load is closely associated with elevated MMP-9 levels.[95] Furthermore, biofilm formation provides bacteria with protection, enhances their proliferation, and increases their resistance to antibacterial treatments, which is a major cause of chronic wound infections.[96] With the growing prevalence of bacterial antibiotic resistance, effectively treating chronic infections and promoting wound healing has become increasingly challenging. Silicon-based nanocomposites have garnered significant attention in wound healing

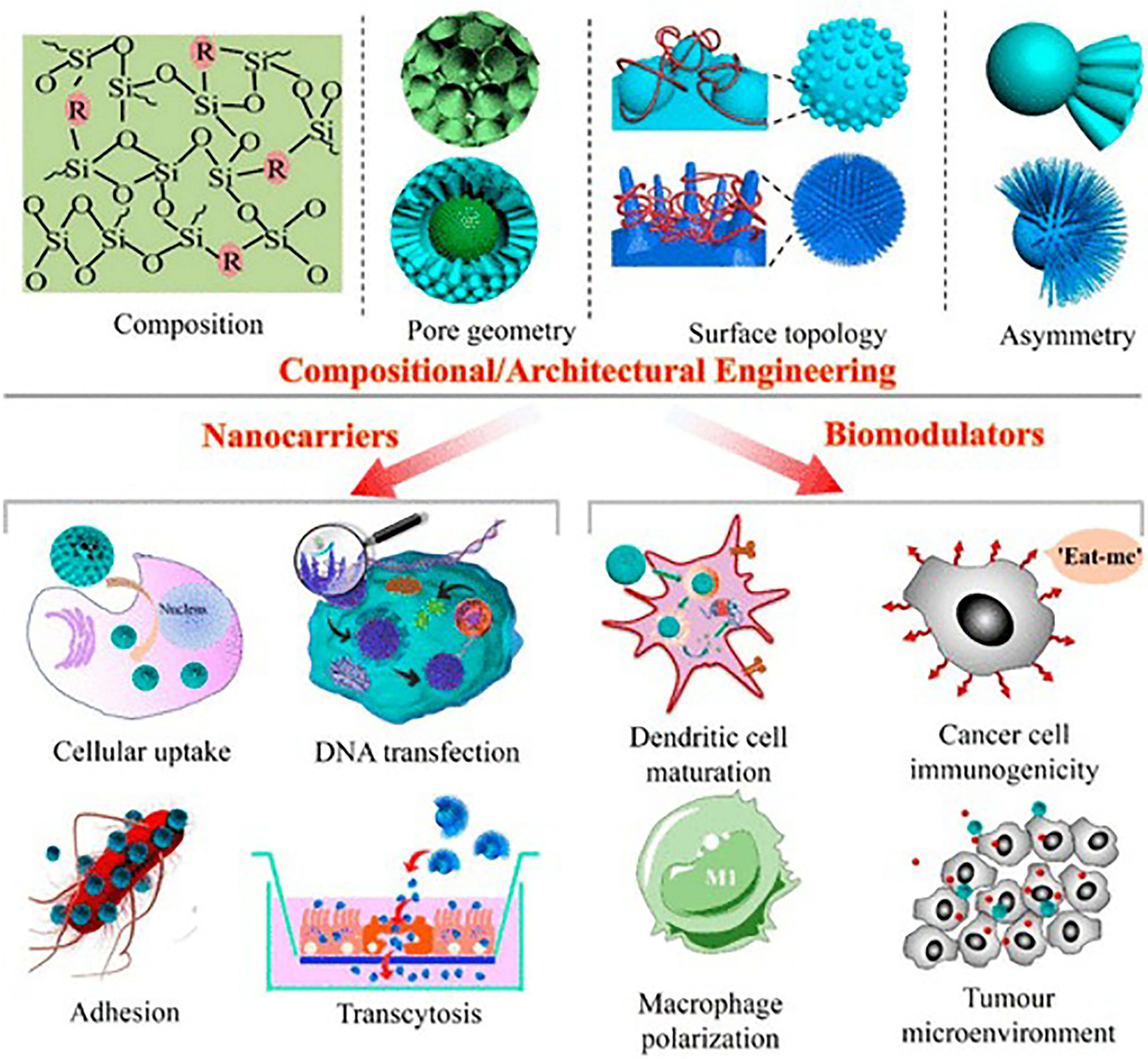


Figure 4 Schematic illustration of the composition and architecture of engineered silica-based nanoparticles with diverse appealing properties as nanocarriers and biomodulators for biomedical applications. Reprinted from Fu JY, Gu Z, Liu Y, et al. Bottom-up self-assembly of heterotrimeric nanoparticles and their secondary Janus generations. *Chem Sci.* 2019;10(44):10388–10394. Creative Commons.[91]

due to their excellent antibacterial properties. Their antibacterial and anti-infection effects are primarily attributed to two mechanisms: serving as physical barriers and releasing antibacterial active substances.[97,98]

Silicon-based nanosystems are commonly used as multifunctional delivery platforms to load and release antibacterial active substances to inhibit pathogen growth. For example, Ni et al successfully loaded vancomycin and nanosilver onto pollen-shaped silica nanoparticles. The unique spiked morphology of the silica carrier enhanced nanoparticle adhesion to bacterial surfaces, thereby promoting local drug release for bacterial eradication. This dual delivery of vancomycin and nanosilver demonstrated enhanced bactericidal activity[98] (Figure 5I and II). Additionally, Cao et al constructed mesoporous silica nanoparticles loaded with silver-bismuth nanoparticles (Ag-Bi@SiO2NP). The high-temperature effect of bismuth nanoparticles accelerated the release of Ag ions, exhibiting excellent antibacterial performance against methicillin-resistant *Staphylococcus aureus* (MRSA)[99] (Figure 5III). Rasool et al developed functionalized silica-ceria nanocomposites (FSC), which combined mesoporous silica nanoparticles with ceria's inherent antibacterial activity, effectively inhibiting biofilm formation.[100]

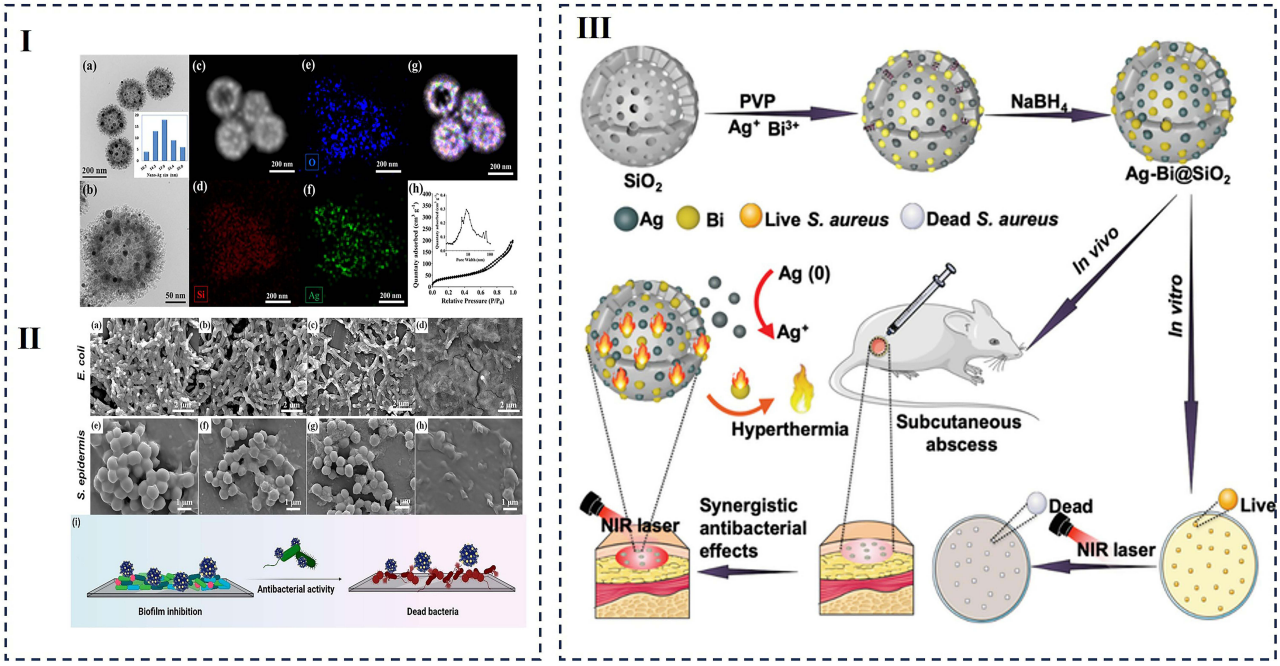


Figure 5 (**I**) TEM images (a and b), with the nano-Ag particle size distribution shown in the inset of (a), dark field image (c), corresponding elemental mapping for silicon (d), oxygen (e), silver (f), Si-Ag-O merged image (g), nitrogen sorption isotherm (h), and the inset showing pore size distribution for SiNPs-Ag. (**II**) SEM images of *E. coli* (a–d) and *S. epidermidis* (e–h) after treatment with vancomycin (a, e), SiNPs-Van (b, f), SiNPs-Ag (c, g), and SiNPs-Ag-Van (d, h), along with a schematic illustration of antibacterial activity (i). Reprinted from Ni C, Zhong Y, Wu W, et al. Co-Delivery of Nano-Silver and Vancomycin via Silica Nanopollens for Enhanced Antibacterial Functions. *Antibiotics*. 2022;11(5):685. Creative Commons.[98] (**III**) Schematic description of the preparation of Ag-Bi@SiO2 NPs and their synergistic antibacterial effects. Reprinted from Cao CY, Ge W, Yin J, et al. Mesoporous Silica Supported Silver-Bismuth Nanoparticles as Photothermal Agents for Skin Infection Synergistic Antibacterial Therapy. Small. 2020;16(24). © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[99]
Note: The original figure contains a spelling error "quantaty", which is retained as published.

The smart-responsive properties of silicon-based nanomaterials further enhance their antibacterial efficacy. For instance, Li et al developed a silicon-based nanocomposite hydrogel scaffold with biomimetic elastic mechanics, self-healing behavior, and broad-spectrum antibacterial activity. This scaffold significantly enhanced the vitality and angiogenic capability of endothelial progenitor cells (EPCs) in vitro and promoted collagen deposition and vascular network reconstruction by enhancing HIF-1α/VEGF expression in vivo, thereby accelerating full-thickness wound healing[22] (Figure 6I). Moreover, specific nanostructure designs of silicon-based materials, such as sharp nanoblades, microspheres, and nanoflower-like structures, further improve their antibacterial effects. Huang et al synthesized silver dendritic nanoforests (Ag-DNFs/Si) on silicon substrates. The sharp nanoblade structures exhibited superior antibacterial efficiency, showing significant bactericidal effects against *Escherichia coli* and *Staphylococcus aureus*[101] (Figure 6II and III).

Silicon-based nanoparticles can also be specifically designed to meet diverse needs. Khan et al prepared silica microspheres loaded with nitrofurazone (NFZ) and lidocaine (LD). The successful incorporation of drugs into the microspheres avoided drug-drug interactions and effectively addressed pathological skin infections. In-vitro and *in-vivo* experiments demonstrated good antibacterial activity and biocompatibility.[102] Hashemikia et al prepared hybrid nanofibers of chitosan/polyethylene oxide/silica, incorporating ciprofloxacin into the electrospun mixture. The nanofibers absorbed moisture during degradation and gradually released ciprofloxacin, exhibiting excellent antibacterial activity against *E. coli* and *S. aureus*.[103] Gwon et al synthesized antibacterial silicon-based nickel nanoflowers (Si@Ni) using microfluidics and photopolymerization techniques and encapsulated them in methacryloyl gelatin (GelMA) to construct uniform microscale hydrogel spheres (Si@Ni-GelMA). Due to nickel's antibacterial effects against *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and MRSA, the injectable Si@Ni-GelMA demonstrated superior antibacterial activity with negligible cytotoxicity.[104] By acting as physical barriers, releasing antibacterial active substances, and leveraging smart-responsive properties, silicon-based nanomaterials not only address antibiotic resistance but also significantly accelerate wound healing. Additionally, their customizable designs for various drug metabolism needs make them ideal materials for wound repair applications (Table 1).

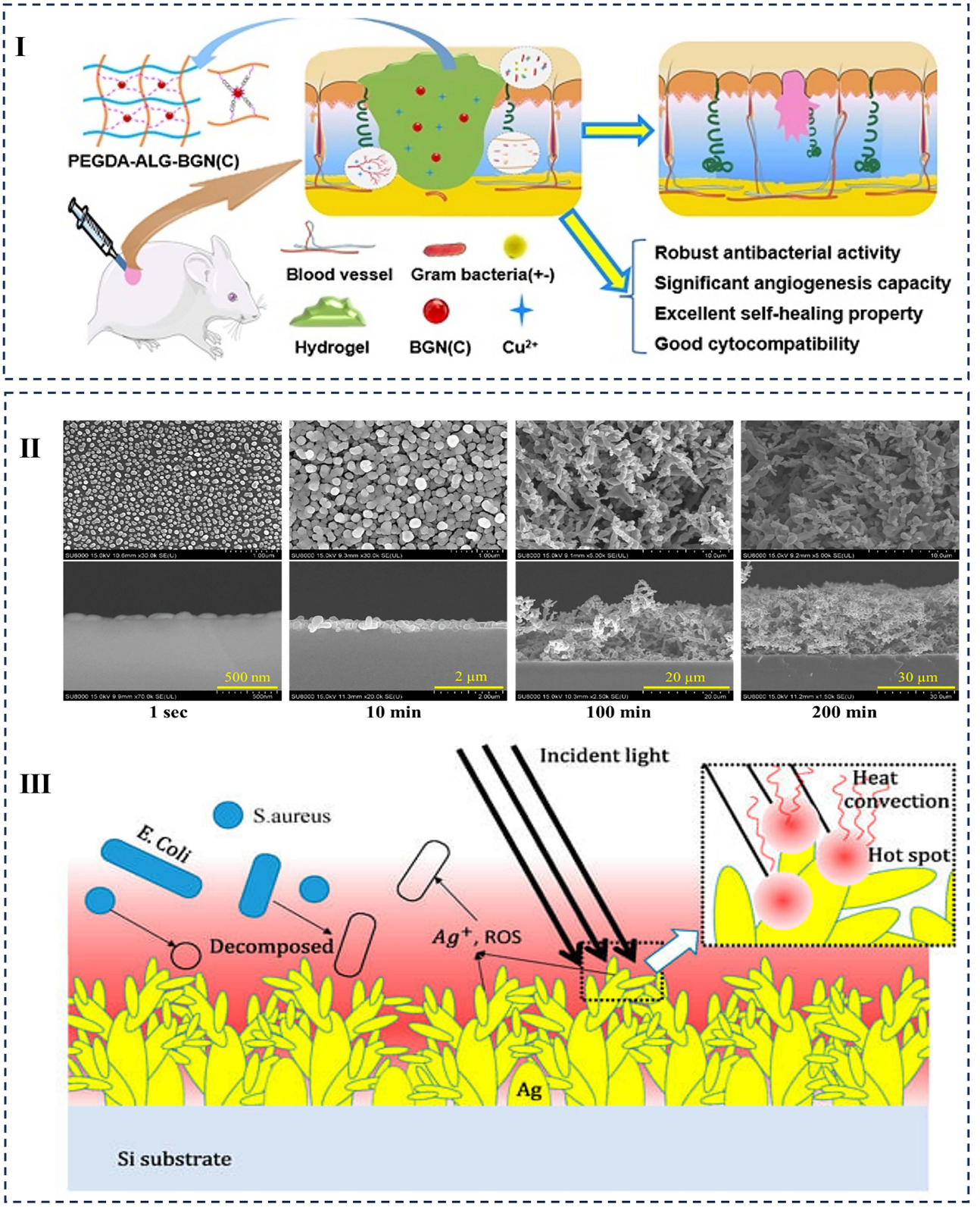


Figure 6 (**I**) Silicon-based Ag dendritic nanoforests for light-assisted bacterial inhibition. Reprinted from Li Y, Xu T, Tu Z, et al. Bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair. *Theranostics*. 2020;10(11):4929–4943. Creative Commons.[22] (**II**) Top- and side-view SEM images of Ag-DNFs/Si synthesized at various times. (**III**) Schematic of plasmonic-assisted bacterial inhibition. Reprinted from Huang HJ, Chang H-W, Lin Y-W, et al. Silicon-Based Ag Dendritic Nanoforests for Light-Assisted Bacterial Inhibition. *Nanomaterials*. 2020;10(11):2244. Creative Commons.[101]

Table 1 Application of Silicon-Based Materials in Antibacterial Therapy

Application Direction	Material/Constructed System	Mechanism/Features	Target Bacteria or Pathogen	Ref.
Antibacterial Drug Delivery	Pollen-like silica nanoparticles loaded with vancomycin + silver nanoparticles	Spiky surface enhances bacterial adhesion, localized drug release, synergistic bactericidal effect	Broad-spectrum (bacterial surfaces)	[98]
Photothermal-Assisted Antibacterial	Ag-Bi@SiO_2 mesoporous silica loaded with Ag-Bi nanoparticles	Bismuth generates heat to promote Ag^+ release, excellent activity against MRSA	MRSA	[99]
Anti-Biofilm	Functionalized silica-ceria composite (FSC)	Cerium has intrinsic antibacterial activity; combined with mesoporous SiO_2 to inhibit biofilm formation	Biofilm-associated bacteria	[100]
Smart-Responsive Antibacterial	Biomimetic, elastic, self-healing silica-based hydrogel scaffold	Broad-spectrum antibacterial, enhances EPC activity and angiogenesis, promotes HIF-1α/VEGF expression and collagen deposition	Wound microbiota	[22]
Structural Antibacterial	Silver dendritic nanoforests (Ag-DNFs/Si) grown on silicon substrate	Sharp "nano-blade" structures physically destroy bacteria, high killing efficiency	E. coli, S. aureus	[101]
Combined Drug Release Antibacterial	NFZ + lidocaine (LD) @ silica microspheres	Synergistic drugs, isolated loading to avoid interaction, suitable for complex infectious skin conditions	Bacterial skin infections	[102]
Biodegradable Antibacterial	Chitosan/PEO/silica composite nanofibers doped with ciprofloxacin	Absorbs moisture and degrades to slowly release drug, prolonged antibacterial effect	E. coli and S. aureus	[103]
Injectable Antibacterial	Si@Ni nanoflower + GelMA microsphere hydrogel	Nickel nanoflowers show strong killing effect against P. aeruginosa, K. pneumoniae, MRSA; injectable and low cytotoxicity	Multidrug-resistant bacteria	[104]

Inflammation Regulation

Inflammation is a critical stage of wound healing; however, excessive or persistent inflammation, often accompanied by microbial recruitment and biofilm formation, leads to chronic wound formation. Regulating inflammatory responses to maintain immune balance is one of the key strategies for promoting wound healing.[105,106] In recent years, silicon-based nanomaterials have demonstrated significant advantages in regulating chronic wound inflammation due to their unique structural properties and functionalization potential as drug carriers for inflammatory modulators (Table 2).

Table 2 Application of Silicon-Based Materials in Anti-Inflammatory Therapy

Application Direction	Material/Constructed System	Mechanism/Features	Target Cells/Factors	Reference
Integrated Anti-inflammatory and Antibacterial	Carboxylated norfloxacin or ibuprofen-functionalized silica nanoparticles (SNPs)	Drugs covalently linked via amide bonds to simultaneously regulate inflammation and bacterial infection	Inflammatory cells / Bacteria	[107]
Drug Carrier for Anti-inflammation	Silica/calcium carbonate nanocomposite loaded with quercetin	Plant-derived quercetin exerts anti-inflammatory effects via silica carriers, optimizing wound microenvironment	Inflammatory microenvironment	[108]

(*Continued*)

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Table 2 (Continued).

Application Direction	Material/Constructed System	Mechanism/Features	Target Cells/Factors	Reference
Macrophage Polarization Modulation	Hydrogel loaded with mesoporous silica nanoparticles (MSNs)	Inhibits pro-inflammatory M1 macrophages and promotes anti-inflammatory M2 polarization, improving tendon repair	Macrophages (M1 → M2)	[109]
Ion-Mediated Anti-inflammation	Electrospun magnesium-doped SiO_2 bioactive glass composite membrane	Releases Mg^{2+} to suppress IL-6 and TNF-α expression, reduce M1 polarization, and enhance anti-inflammatory effects	IL-6, TNF-α, M1 macrophages	[110]

Single silicon-based monomers containing carboxylated antibiotics, specifically norfloxacin, and anti-inflammatory agents, such as ibuprofen, were developed. Liu et al covalently linked silicon nanoparticles (SNPs) derived from these single silicon-based monomers with the anti-inflammatory and antibacterial drugs through amide bonds. This process resulted in the synthesis of bifunctional SNPs that exhibit both inflammation-regulating and antibacterial activities.[107] Additionally, quercetin, a plant-derived anti-inflammatory drug, was loaded onto calcium carbonate/silica nanocomposites to exert anti-inflammatory effects and improve wound healing rates.[108] These silicon-based nanosystems function as drug carriers to modulate inflammatory responses, thereby optimizing the wound healing environment.

Moreover, macrophages play a crucial role in wound healing, with their polarization states determining the progression of inflammation and the efficiency of tissue repair. During the early inflammatory stage, M1 macrophages function to clear pathogens, but their overactivation can delay healing. In the later repair stage, M2 macrophages accelerate tissue regeneration by secreting anti-inflammatory factors (eg, IL-10) and pro-repair factors (eg, VEGF).[111] Scholars have designed various silicon-based composites to effectively promote macrophage polarization from M1 to M2. For example, MSN-loaded hydrogels significantly inhibited pro-inflammatory M1 macrophages while promoting anti-inflammatory M2 macrophages, accelerating tendon healing and reducing inflammatory responses[109] (Figure 7I). Liu et al fabricated magnesium-doped SiO2 bioactive glass composite membranes using electrospinning technology. The release of magnesium ions significantly suppressed the expression of the pro-inflammatory factors IL-6 and TNF-α while inhibiting M1 macrophage polarization, thereby enhancing anti-inflammatory effects[110] (Figure 7II).

Through the release of anti-inflammatory factors, inhibition of pro-inflammatory signals, regulation of macrophage polarization, or synergistic mechanisms, silicon-based nanomaterials demonstrate significant potential in inflammation regulation, making them promising candidates for research and applications in chronic wound healing.

Antioxidant Effects

Reactive oxygen species (ROS) play a dual role in the wound healing process. At physiological levels, ROS act as signaling molecules to regulate cell migration, angiogenesis, and immune responses. However, in chronic wounds or infected wounds, excessive ROS can induce oxidative stress, damage cellular structures and functions, and lead to the oxidative modification of proteins, lipids, and DNA, further exacerbating tissue inflammation and damage.[112–114] This persistent oxidative stress inhibits the proliferation of fibroblasts and keratinocytes, thereby delaying wound healing.[115] Thus, eliminating excessive ROS and providing sustained antioxidant protection are critical for accelerating wound repair.

Silicon-based nanomaterials, owing to their unique structures and bioactivity, are widely applied in ROS scavenging (Table 3). On one hand, silicon-based nanomaterials can act as drug carriers with antioxidant effects. For instance, tannic acid-modified silicon nanoparticles (TA-SNPs) have demonstrated significant free radical scavenging potential in antioxidant experiments. Additionally, TA-SNPs exhibit efficient intracellular ROS scavenging ability[117] (Figure 8I). On the other hand, silicon ions themselves possess antioxidant properties. For example, silicon ions at optimal concentrations enhance ROS metabolism and scavenging under oxidative stress conditions in C2C12 cells, protecting them from oxidative damage and promoting skeletal muscle cell regeneration.[116] Furthermore, silicon ions released from

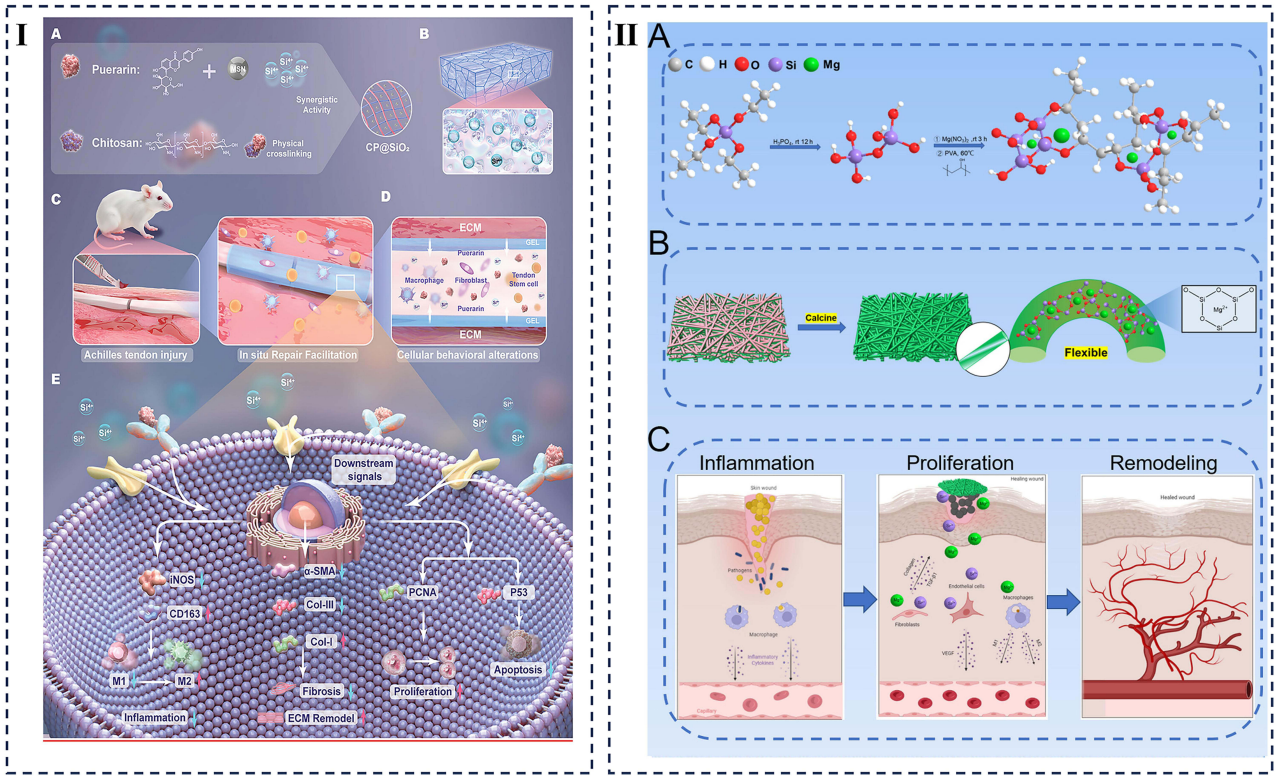

Figure 7 (**I**) (A) Preparation of CP@SiO_2 composite by combining puerarin, chitosan, and SiO_2 nanoparticles. (B) Structure of CP@SiO_2 hydrogel showing uniform distribution of SiO_2 within the network. (C) Application in Achilles tendon injury to achieve in situ repair. (D) Regulation of extracellular matrix (ECM) and cellular behaviors, including macrophage polarization and fibroblast activity. (E) Schematic mechanism showing CP@SiO_2-mediated signaling pathways that regulate inflammation, fibrosis, proliferation, and apoptosis. Reprinted from Wan R, Luo Z, Nie X, et al. A Mesoporous Silica-Loaded Multi-Functional Hydrogel Enhanced Tendon Healing via Immunomodulatory and Pro-Regenerative Effects. *Adv Healthc Mater.* 2024;13(26):e2400968. © 2024 Wiley-VCH GmbH.[109] (**II**) (A) Synthesis scheme of precursor solutions for electrospinning. (B) Synthesis and chemical structure of flexible inorganic SiO2/MgO nanofiber membranes. (C) Electrospun flexible SiO2/MgO nanofiber membranes inhibit *S. aureus* infection and promote the healing of infected wounds. Reprinted from Liu MY, Wang X, Cui J, et al. Electrospun flexible magnesium-doped silica bioactive glass nanofiber membranes with anti-inflammatory and pro-angiogenic effects for infected wounds. *J Mat Chem B.* 2023;11(2):359–376. © Royal Society of Chemistry 2023.[110]

amorphous silicon nitride surfaces can enhance superoxide dismutase (SOD1) activity and significantly promote collagen matrix formation by increasing antioxidant expression.[120]

Moreover, the functionalization of silicon-based nanomaterials can further enhance their antioxidant activity. Ashraf et al synthesized MnS2-SiO2 nano-heterojunction photocatalysts with varying MnS2 contents, demonstrating antioxidant activity through DPPH radical scavenging.[118] Additionally, silicon-based nanocomposites with combined antioxidant and antibacterial properties have been reported to promote wound healing more effectively. For instance, functionalized silicon nanoparticles conjugated with antioxidants such as glutathione or vitamin C enhance their antioxidant effects, creating an optimal microenvironment for wound healing. Researchers have used glutathione (GSH) to modify biosilica nanoparticles, forming GSH@SNPs, which can target bacterial surfaces and biofilms. By loading resveratrol onto GSH@SNPs, they developed ResGSH@SNPs, which bind to bacterial surface receptors, disrupt membrane potential, induce excessive ROS production, cause membrane damage and DNA disruption, and ultimately exhibit antibacterial activity[119] (Figure 8II).

The application of silicon-based materials in oxidative stress management for wound healing is progressing toward multifunctionality and intelligence. Enhancing material stability and achieving sustained release of antioxidant components through structural optimization remain key challenges to address.

Promoting Angiogenesis

Angiogenesis is an indispensable biological process in wound healing. In chronic wounds, insufficient local angiogenesis often leads to hypoxia and limited nutrient supply, thereby delaying tissue repair and regeneration. Thus, stimulating

Table 3 Application of Silicon-Based Materials in Combating Oxidative Stress

Application Direction	Material/System Description	Mechanism/Features	Key Targets or Pathways	Reference
Intrinsic Antioxidant Activity of Silicon Materials	Silica ions (eg, Si^{4+}) at optimal concentrations	Enhance ROS metabolism, scavenge excess free radicals under oxidative stress, protect C2C12 myocytes	ROS clearance, increased SOD1 activity	[116]
Antioxidant Drug Carrier Based on Silica	Tannic acid-modified silica nanoparticles (TA-SNPs)	Exhibit strong radical scavenging capacity, effectively remove intracellular ROS	Radical scavenging, intracellular ROS metabolism	[117]
Photocatalyst-Enhanced Antioxidant Effect	MnS_2-SiO_2 heterojunction nano-photocatalyst	MnS_2 content modulates antioxidant activity; effective in scavenging DPPH radicals and relieving oxidative stress	DPPH radical scavenging, enhanced antioxidant activity	[118]
Composite Antioxidant and Antibacterial Effect	Resveratrol-loaded, glutathione-modified SNPs (ResGSH@SNPs)	Damage bacterial membrane potential, induce ROS accumulation, and offer antioxidant protection	ROS modulation, bacterial membrane damage, antioxidation	[119]
Silicon Ion Release Promoting Tissue Repair	Silicon ion (S^{4+}) release from silicon nitride surface	Upregulates antioxidant gene expression, promotes collagen matrix synthesis, accelerates wound healing	Collagen synthesis, antioxidant gene regulation	[120]
Functional Composite Antioxidant Carrier	Functionalized silica nanoparticles loaded with antioxidants (eg, GSH, Vitamin C)	Enhance antioxidation, regulate ROS levels, support wound healing microenvironment, promote cell survival	ROS regulation, cell survival, antioxidant protection	[117, 119]
Dual Antioxidant and Antibacterial Function	Silicon-based composites combined with antioxidants (eg, glutathione)	Synergistic effect: ROS scavenging, bacterial inhibition, and sustained wound protection	ROS elimination, bacterial suppression, antioxidation	[116, 118]

angiogenesis at the wound site is considered a crucial strategy for treating chronic wounds. Silicon-based composite nanomaterials, with their unique bioactivity and tunable physicochemical properties, exhibit significant potential in promoting angiogenesis and accelerating wound healing (Table 4).

Studies have shown that appropriate concentrations of silicon ions (Si^{4+}) can significantly enhance angiogenesis by upregulating pro-angiogenic factors such as vascular endothelial growth factor (VEGF), CD31, and α-smooth muscle actin (α-SMA).[121,122] Wang et al prepared short SiO2 nanofibers via electrospinning and blended them with varying proportions of tricalcium phosphate (TCP) to fabricate TCPx@SSF aerogel scaffolds. These scaffolds released Si^{4+}, significantly upregulating VEGF and α-SMA expression, thereby promoting angiogenesis[123] (Figure 9I). Li et al designed a dual-network silica-based nanocomposite hydrogel scaffold that, without the addition of any bioactive factors, significantly enhanced early angiogenesis and promoted diabetic wound healing.[22]

Furthermore, the functionalized design of silicon-based materials is particularly notable Functionalized silicon-based materials can carry pro-angiogenic factors (eg, VEGF, FGF) or nucleic acids (eg, miRNA) for precise release. Wang et al functionalized mesoporous silica nanoparticles (MSNs) with polyethyleneimine (PEI) and modified their surface with a pentapeptide (YIGSR) capable of recognizing endothelial cells. This system delivered miR-146a inhibitors with high precision, significantly enhancing angiogenesis[124] (Figure 9II). Combining silicon nanoparticles with other biomaterials can further enhance their pro-angiogenic properties. For example, hollow silica nanoparticles (HSNs) loaded with RL-QN15 peptide and incorporated into a zinc alginate (ZA) hydrogel formed HSN@RL-QN15/ZA hydrogels. These hydrogels effectively regulated angiogenesis, significantly reduced inflammation, and accelerated epithelial regeneration and granulation tissue formation, thereby promoting rapid healing of chronic wounds.[125]

In summary, silicon-based nanomaterials demonstrate great potential in promoting angiogenesis and accelerating wound healing through silicon ion release, loading of pro-angiogenic factors, and optimizing material microstructures.

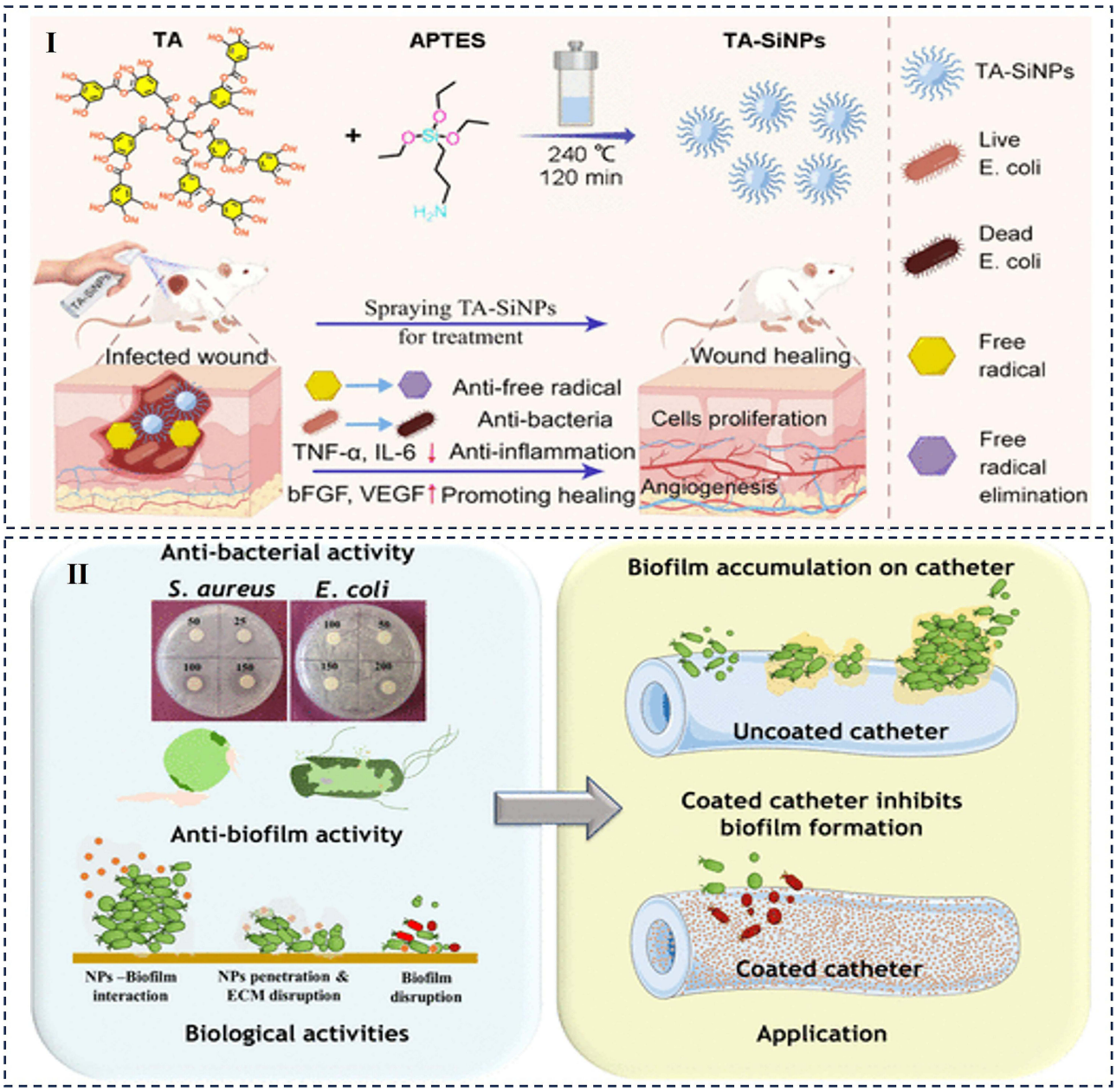

Figure 8 (**I**) Nanoparticles demonstrated multifunctional therapeutic effects by disrupting biofilms, eradicating *E. coli*, neutralizing reactive oxygen species (ROS), stimulating fibroblast growth, and enhancing angiogenesis. Additionally, they suppressed inflammatory cytokines while upregulating factors involved in cell proliferation and vascular formation, ultimately facilitating wound repair in experimental models. Reprinted from Shen Y, Jia T, Zeng J, et al. Broad-Spectrum Bactericidal Multifunctional Tiny Silicon-Based Nanoparticles Modified with Tannic Acid for Healing Infected Diabetic Wounds. *ACS Appl Mater Interfaces*. 2024;16(46):63241–63254. Copyright © 2024 American Chemical Society.[117] (**II**) Res_GSH@SNP exerts antibacterial effects by binding to bacterial surface receptors, disrupting membrane potential, inducing ROS production, causing membrane damage, and leading to DNA degradation. Reprinted from Verma M, Nisha A, Bathla M, et al. Resveratrol-Encapsulated Glutathione-Modified Robust Mesoporous Silica Nanoparticles as an Antibacterial and Antibiofilm Coating Agent for Medical Devices. ACS Appl Mater Interfaces. 2023;15(50):58212–58229. Copyright © 2023 American Chemical Society.[119]

Their multifunctional design not only improves therapeutic efficiency but also provides new strategies for the comprehensive treatment of chronic wounds.

Promoting Cell Adhesion, Migration, and Proliferation

The proliferation phase of wound healing is characterized by cell proliferation and migration. During this phase, angiogenic factors actively promote new blood vessel formation, which further supports the proliferation and migration of fibroblasts. These fibroblasts accumulate and act at the wound site, producing new extracellular matrix (ECM) that eventually forms

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Table 4 The Role of Silicon-Based Materials in Promoting Angiogenesis

Application Direction	Constructed Material/System Description	Mechanism/Features	Main Targets or Pathways	Reference
Silicon Ion-Induced Angiogenesis	Silicon ions (Si^{4+})	Appropriate concentrations of Si^{4+} upregulate angiogenic factors (VEGF, CD31, α-SMA), promoting angiogenesis	VEGF, CD31, α-SMA	[121, 122]
Silica Nanofibers Promote Angiogenesis	Silicate (SiO_2) nanofibers combined with tricalcium phosphate (TCP)	Si ion release significantly enhances expression of VEGF and α-SMA, facilitating angiogenesis	VEGF, α-SMA	[123]
Double-Network Hydrogel for Angiogenesis	Silicon-based double-network nanocomposite hydrogel	Enhances early-stage angiogenesis and diabetic wound healing without addition of bioactive factors	Angiogenesis, diabetic wound healing	[22]
Functionalized Silica for Vascular Targeting	Polyethyleneimine (PEI)-modified mesoporous silica nanoparticles (MSNs)	Functionalized with YIGSR peptide to target endothelial cells and deliver miR-146a inhibitors, enhancing angiogenesis	Endothelial cells, miR-146a	[124]
Silica-Biomaterial Composite for Angiogenesis	Hollow silica nanoparticles (HSNs) and RL-QN15 peptide-loaded zinc alginate hydrogel (ZA)	Promotes angiogenesis, reduces inflammation, accelerates epithelial regeneration and granulation tissue formation	Angiogenesis, epithelial regeneration, granulation tissue	[125]

granulation tissue.[54,126] A subset of fibroblasts differentiates into myofibroblasts, playing a crucial role in wound contraction.[57] Additionally, keratinocyte proliferation and migration are essential for epidermal regeneration.[127,128]

Cell adhesion is a prerequisite for proliferation and migration, directly impacting wound healing efficiency. Studies have shown that functionalized silicon-based nanomaterials significantly enhance cell adhesion. For example, Zhang et al investigated the effects of glycine-aspartic acid (RGD)-functionalized mesoporous silica nanoparticles (MSNs-RGD) on stem cell adhesion and differentiation. Results indicated that when the total RGD density increased from 1.06 to 5.32 nmol/cm², cell adhesion and spreading significantly improved, suggesting that MSNs-RGD could serve as drug carriers to promote cell adhesion and proliferation[129] (Figure 10I). Furthermore, Motealleh et al incorporated bifunctional nanomaterials into glass and polydimethylsiloxane surfaces, creating a hybrid nanocomposite material. This material significantly enhanced cell adhesion and proliferation while inhibiting bacterial biofilm formation, demonstrating excellent antibacterial properties and biocompatibility.[130]

In tissue engineering research, cell migration ability is a critical indicator of cell proliferation and its role in wound repair. Silicon-based nanomaterials have been shown to promote cell migration, thereby supporting wound healing. For instance, TA-SNP exhibited outstanding efficacy in treating full-thickness wounds in diabetic mice infected with *E. coli*. At a TA-SNP concentration of 100 μg/mL, the cell migration rate increased from 9.19% to 18.21%, further rising to 30.98% at a concentration of 500 μg/mL. This significant effect is attributed to the positive impact of silicon nanoparticles on cell proliferation, migration, and wound repair.[117] Silicon-based materials also support cell proliferation through various pathways. Shie et al found that appropriate concentrations of Si ions significantly promoted the proliferation of osteoblast-like cells while inducing specific biological responses through bone-specific protein synthesis in MG63 cells. Cells maintained normal morphology and proliferated well under these conditions, further validating the excellent biocompatibility of silicon-based materials.[133,134]

The structure and micro-morphology of scaffolds are critical for cell adhesion, migration, and proliferation. Gao et al successfully developed silica-SFO-P scaffolds using extrusion-based 3D printing and validated their performance through direct cell biocompatibility tests. The porous structure of the scaffold significantly supported L929 cell adhesion and proliferation, with cells demonstrating robust growth on the scaffold surface and within its pores after three weeks of culture[131] (Figure 10II). Ren et al fabricated a directional porous composite membrane (DS-PL), a polylactic acid (PLLA) directional electrospun fiber membrane containing mesoporous silica nanoparticles (DS). By loading the drug dimethyloxalylglycine (DMOG), controlled release of DMOG and Si ions was achieved. The combined directional

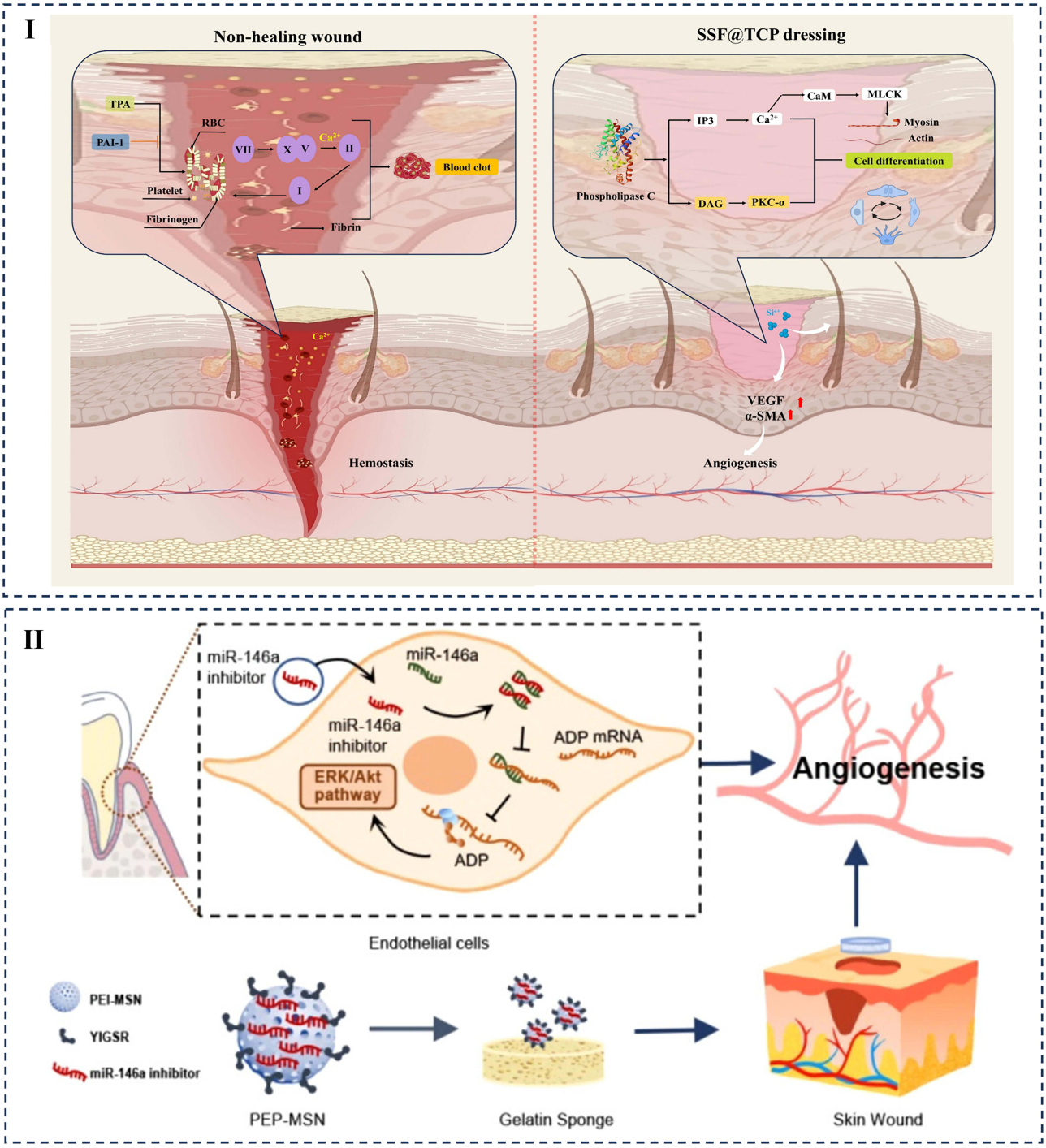

Figure 9 (**I**) Schematic representation of the interactive and dynamic healing mechanisms of TCPx@SSF dressings during wound repair. Reprinted from Wang XY, Yuan Z, Shafiq M, et al. Composite Aerogel Scaffolds Containing Flexible Silica Nanofiber and Tricalcium Phosphate Enable Skin Regeneration. *ACS Appl Mater Interfaces*. 2024;16 (20):25843–25855. Copyright © 2024 American Chemical Society.[123] (**II**) Mesoporous silica nanoparticles (MSNs) modified with polyethyleneimine (PEI) and functionalized with the endothelial-recognition pentapeptide YIGSR enable precise delivery of miR-146a inhibitors, significantly boosting angiogenesis. Reprinted from Wang Y, Wu J, Feng J, et al. From Bone Remodeling to Wound Healing: an miR-146a-5p-Loaded Nanocarrier Targets Endothelial Cells to Promote Angiogenesis. *ACS Appl Mater Interfaces*. 2024;16 (26):32992–33004. Copyright © 2024 American Chemical Society.[124]

porous structure and functional components synergistically promoted the proliferation, migration, and expression of angiogenesis-related genes in human umbilical vein endothelial cells (HUVECs), rapidly stimulating angiogenesis in diabetic wound beds, offering a novel therapeutic strategy for efficient diabetic wound healing[132] (Figure 10III). In summary, silicon-based nanomaterials systematically enhance cell adhesion, migration, and proliferation by optimizing

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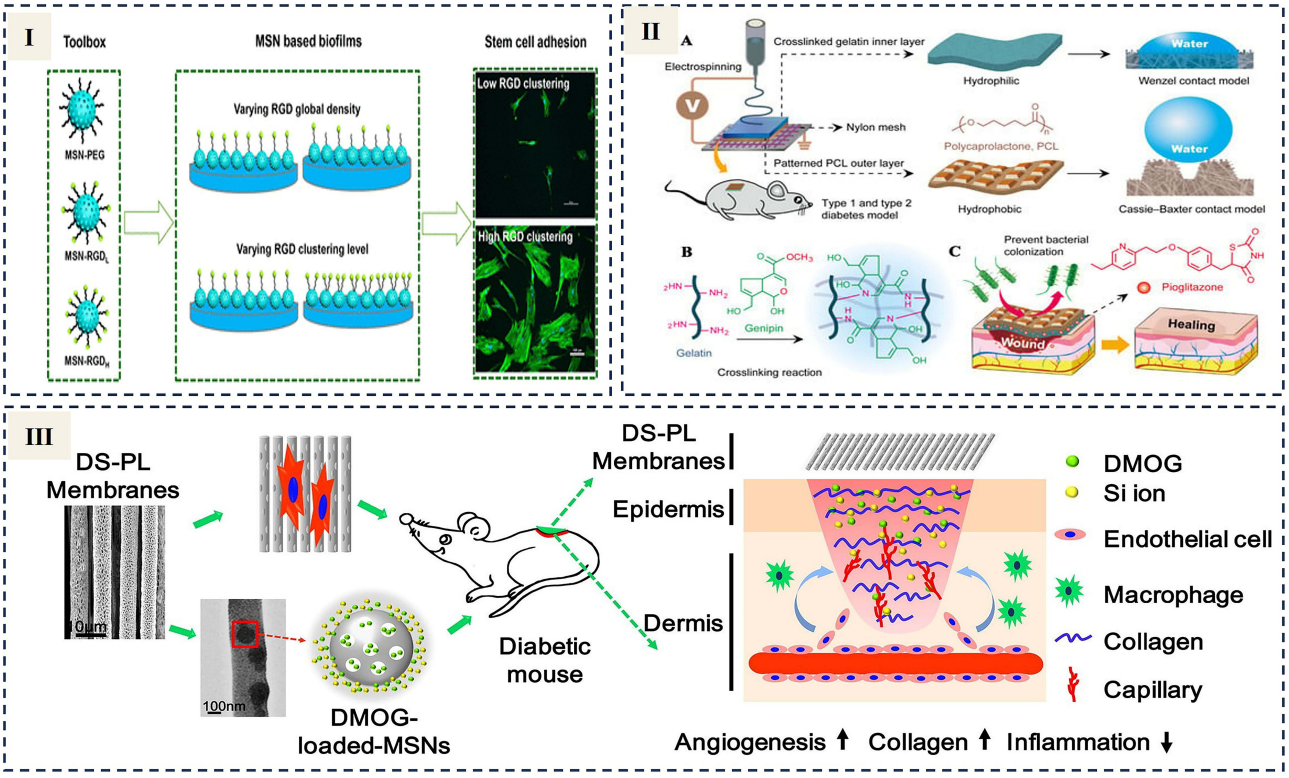

Figure 10 (**I**) Fabrication of mesoporous silica nanoparticle-based films with adjustable densities and clustering levels of arginine–glycine–aspartate peptides to investigate stem cell adhesion and differentiation. Reprinted from Zhang X, Karagöz Z, Swapnasrita S, et al. Development of Mesoporous Silica Nanoparticle-Based Films with Tunable Arginine–Glycine–Aspartate Peptide Global Density and Clustering Levels to Study Stem Cell Adhesion and Differentiation. *ACS Appl Mater Interfaces.* 2023;15(32):38171–38184. Creative Commons.[129] (**II**) (A) Illustration of the preparation process for PCL/Gel-Pio nanofiber membranes. (B) Mechanistic depiction of the genipin-induced cross-linking reaction in the fiber membrane. (C) Mechanism by which the fiber membrane enhances diabetic wound healing. Reproduced from Gao ZJ, Wang Q, Yao Q, et al. Application of Electrospun Nanofiber Membrane in the Treatment of Diabetic Wounds. *Pharmaceutics.* 2022;14(1):6. Creative Commons.[131] (**III**) A directional porous composite membrane (DS-PL) was developed using polylactic acid (PLLA) electrospun fibers incorporating mesoporous silica nanoparticles (DS) loaded with dimethyloxalylglycine (DMOG). The system facilitates controlled DMOG and silicon ion release, enhancing HUVEC proliferation, migration, and angiogenesis-related gene expression, which accelerates vascularization in diabetic wound environments. Reprinted from *Acta Biomater.* Volume 70. Ren XZ, Han Y, Wang J, et al. An aligned porous electrospun fibrous membrane with controlled drug delivery - An efficient strategy to accelerate diabetic wound healing with improved angiogenesis. 140–153, copyright 2018, with permission from Elsevier.[132]

surface chemical properties, functional design, and regulating biological signals in the local microenvironment, thereby promoting wound healing (Table 5).

Promoting Extracellular Matrix Deposition

The extracellular matrix (ECM) is an indispensable structural and functional unit in wound healing, primarily produced and organized by myofibroblasts. ECM serves as both a structural scaffold for cells and a reservoir of cytokines and growth factors, interacting with surrounding cells to regulate critical behaviors during their life cycle, including migration, growth, proliferation, differentiation, and morphogenesis.[135,136] Major ECM components include interstitial collagen and elastic fibers, non-collagenous proteins (eg, fibronectin and laminin families), glycosaminoglycans (GAGs), and proteoglycans (PGs). These molecules collectively provide mechanical support to cells while regulating cellular behavior. Silicon, as a component of certain GAGs and PGs, participates in GAG synthesis. By binding to polysaccharide matrices, silicon acts as a biological crosslinker, enhancing the structure and elasticity of connective tissues and further promoting ECM deposition.[137]

During the remodeling phase of wound healing, collagen deposition plays a pivotal role in enhancing tissue strength and supporting wound contraction. Studies have shown that silicon-based materials significantly promote collagen deposition, thereby accelerating wound repair. For example, Jiang et al designed an electrospun scaffold with uniformly distributed silicon-doped amorphous calcium phosphate nanoparticles (Si-ACP/PM) approximately 40 nm in size. This

Table 5 The Role of Silicon-Based Materials in Promoting Cell Adhesion, Migration, and Proliferation

Application Direction	Constructed Material/ System Description	Mechanism/Features	Main Targets or Pathways	Reference
Promotion of Cell Adhesion	RGD-functionalized mesoporous silica nanoparticles (MSNs-RGD)	Increasing the density of RGD peptides significantly enhances cell adhesion and spreading, thereby promoting proliferation	Cell adhesion, cell proliferation	[129]
Enhanced Cell Adhesion and Proliferation with Antibacterial Properties	Dual-functional nanomaterials (glass and PDMS surface)	Improves cell adhesion and proliferation while inhibiting bacterial biofilm formation, exhibiting good antibacterial properties and biocompatibility	Cell adhesion, proliferation, antibacterial activity	[130]
Promotion of Cell Migration	Tannic acid-modified silica nanoparticles (TA-SNPs)	TA-SNPs significantly enhance cell migration, promoting full-thickness wound healing in diabetic mice	Cell migration, wound healing	[117]
Promotion of Cell Proliferation	Silicon ions	Appropriate concentrations of silicon ions significantly promote osteoblast-like cell proliferation and induce protein synthesis via specific biological responses	Osteoblast proliferation, protein synthesis	[133, 134]
Scaffold Optimization to Promote Cell Proliferation	Silicon-based SFO-P scaffold	3D-printed porous scaffolds support cell adhesion and proliferation; cells grow well on both surfaces and within pores	L929 cell adhesion, proliferation	[131]
Directional Porous Composite Membrane Enhancing Cell Proliferation and Migration	Electrospun polylactic acid (PLLA) fiber membrane with mesoporous silica nanoparticles	Directional porous structure combined with functional components promotes cell proliferation, migration, and angiogenesis-related gene expression	HUVECs, angiogenesis	[132]

scaffold continuously released silicon ions, promoting collagen deposition and re-epithelialization in diabetic wound beds, effectively accelerating wound healing[138] (Figure 11I). Through functionalization, silicon-based nanocomposites demonstrate multifunctionality in promoting ECM deposition and wound repair. For instance, Masson staining revealed that diabetic wounds treated with double-network silica-based nanocomposite hydrogel scaffolds exhibited excellent collagen deposition and tissue remodeling, along with effective vascular network repair.[22] Additionally, Xue et al developed a hydrogel based on gelatin methacrylate (GelMA)/hyaluronic acid methacrylate (HAMA) and mesoporous silica nanoparticles (MSNs), with artemisia extract (AE) loaded for sustained release. This GelMA/HAMA/MSNs@AE hydrogel accelerated wound healing by promoting re-epithelialization and collagen deposition[139] (Figure 11II). In summary, silicon-based materials offer significant advantages in promoting collagen deposition and improving chronic wound repair, providing innovative ideas for developing efficient wound repair materials (Table 6).

Multimechanism Synergy

The pathological causes of refractory wounds are often complex and diverse. Thus, leveraging the overlapping and synergistic effects of two or more functions of silicon-based nanomaterials—including antibacterial properties, antioxidation and anti-inflammation, angiogenesis promotion, cell proliferation and migration promotion, and tissue remodeling promotion—can significantly accelerate the wound healing process. For instance, Xi et al developed biodegradable bioactive elastic multifunctional PPCP nanofiber scaffolds. The optimized assembly and combination of the multifunctional elastomer polylactic acid/polysiloxane citrate/curcumin endowed PPCP scaffolds with inherent multifunctionality. PPCP significantly promoted normal and infection-induced wound healing through infection prevention, reduction of proinflammatory factors, upregulation of CD31 and VEGF growth factors, stimulation of collagen deposition, and promotion of dermal and skin appendage formation.[103]

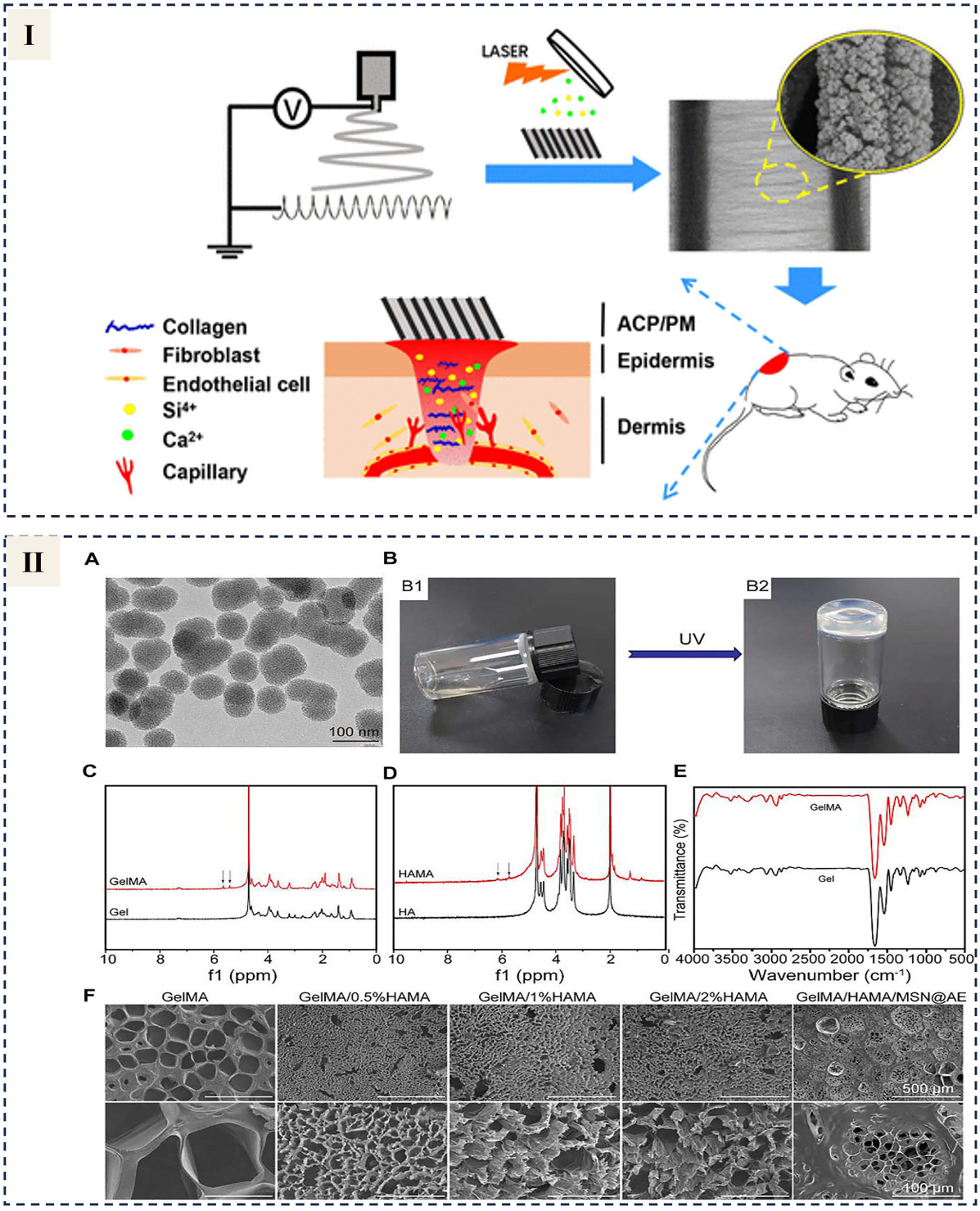

Figure 11 (**I**) Jiang et al designed an electrospun scaffold featuring uniformly distributed silicon-doped amorphous calcium phosphate nanoparticles (Si-ACP/PM, ~40 nm diameter). The scaffold released silicon ions gradually, enhancing collagen deposition and re-epithelialization in diabetic wound models. Reprinted from Jiang Y, Han Y, Wang J, et al. Space-Oriented Nanofibrous Scaffold with Silicon-Doped Amorphous Calcium Phosphate Nanocoating for Diabetic Wound Healing. *ACS Appl Bio Mater.* 2019;2(2):787–795. Copyright © 2019 American Chemical Society.[138] (**II**) (A) TEM visualization of MSNs. (B) Photograph showing the UV cross-linked GelMA/HAMA. Hydrogel.flowing liquid (B1) before cross-linking and gradually changed into a solid phase after the UV curing (B2). (C) ^{1}H NMR analysis of Gel and GelMA. The distinctive double peaks (δ = 5.4 and 5.6 ppm), marked by the black arrows, were observed in GelMA. (D) ^{1}H NMR analysis of HA and HAMA. The distinctive double peaks (δ = 5.7 and 6.1 ppm), marked by the black arrows, were observed in HAMA. (E) FTIR spectra comparing Gel and GelMA. (F) SEM images of GelMA/HAMA hydrogels prepared with varying HAMA concentrations. Reprinted from Xue LY, Deng T, Guo R, et al. A Composite Hydrogel Containing Mesoporous Silica Nanoparticles Loaded With Extract for Improving Chronic Wound Healing. *Front Bioeng Biotechnol.* 2022;10:825339. Creative Commons.[139]

Table 6 The Role of Silicon-Based Materials in Extracellular Matrix Deposition

Application Direction	Constructed Material/ System Description	Mechanism/Features	Main Targets or Pathways	Reference
Promotion of Collagen Deposition	Silicon-doped amorphous calcium phosphate nanoparticles (Si-ACP/PM)	Sustained release of silicon ions promotes collagen deposition and epithelialization, improving diabetic wound healing	Collagen deposition, epithelialization, wound healing	[138]
Collagen Deposition and Tissue Remodeling	Dual-network silicon-based nanocomposite hydrogel scaffold	Enhances collagen deposition and tissue remodeling while effectively restoring vascular networks	Collagen deposition, tissue remodeling, vascular repair	[22]
Collagen Deposition and Wound Healing	GelMA/HAMA hydrogel incorporated with mesoporous silica nanoparticles (MSNs)	Sustained release of Artemisia extract (AE) promotes epithelialization, collagen deposition, and wound healing	Epithelialization, collagen deposition, wound healing	[139]

Yu et al designed soluble microneedle (MN) patches made of γ-PGA with multiple arrays loaded with core-shell-structured nanoparticles (NPs) called Ag@MSNs@CeO2. These MN tips induced the formation of multiple regeneration sites at different points, enabling antibacterial effects, reduced reactive oxygen species, macrophage niche regulation, enhanced angiogenesis, and promoted collagen deposition, thereby significantly accelerating the healing of infectious diabetic wounds (DW) (Figure 12I).[140] Additionally, Lv et al successfully prepared a nanofiber composite scaffold (NAG-PL) containing partial silicate bioceramic particles using co-electrospinning technology. *In-vivo* and in-vitro studies showed that this scaffold significantly activated epithelial-mesenchymal transition (EMT) and endothelial-mesenchymal transition (EndMT) pathways, inducing angiogenesis, collagen deposition, and epithelial regeneration in diabetic mouse models while suppressing inflammation, thereby accelerating the repair of diabetic wounds (Figure 12II).[141] Through the synergistic effects of multiple mechanisms, silicon-based nanomaterial systems demonstrate greater potential and application prospects in wound repair (Table 7).

Clinical Trials of Silicon-Based Nanomaterials

Silicon-based nanosystems have demonstrated significant potential in wound treatment due to their excellent biocompatibility, tunable porosity, and multifunctional properties. Colloidal silica, as a material, has been used as a flow aid in tablet production for decades and is recognized as safe by the US Food and Drug Administration (FDA).[142] Currently, several silicon-based nano-products have reached clinical or preclinical stages of application[143] (Table 8).

To date, more than ten clinical trials on silica nanoparticles have highlighted their favorable safety profiles. Oral delivery systems exhibited good tolerance, with no severe adverse effects, and significantly improved the bioavailability of hydrophobic drugs. In a clinical trial involving 12 adults, lipid-ceramic hybrid silica nanoparticles were used to enhance the pharmacokinetics of simvastatin. Compared to a commercial simvastatin formulation (Sandoz), these nanoparticles improved bioavailability by 3.5 times (ACTRN12618001929291). Similarly, in another clinical study involving 12 healthy adults, mesoporous silica nanoparticles increased the bioavailability of fenofibrate by 54% compared to the commercial formulation (Lipanthyl), demonstrating their advantage in drug delivery and bioavailability enhancement.

In addition to drug delivery applications, silica nanoparticles have been explored in fields such as plasmonic therapy and thermal ablation treatment. For instance, in a Phase I clinical trial, Fe_3O_4 magnetic core-shell silica-gold nanoparticles (90–150 nm in diameter) were used in plasmonic therapy to significantly reduce coronary atherosclerosis (NCT01270139). Compared to traditional stent implantation, this treatment method reduced the risk of atherosclerosis and cardiovascular disease-related mortality with acceptable safety. In photothermal ablation therapy, gold-shell silica nanoparticles (eg, Aurolase and Auroshell) have been applied in clinical trials for malignant tumors of the head, neck, and prostate (NCT00848042, NCT04240639, NCT02680535, NCT04656678). These nanoparticles preferentially accumulate at tumor sites through enhanced permeability and retention (EPR) effects, converting near-infrared light into heat

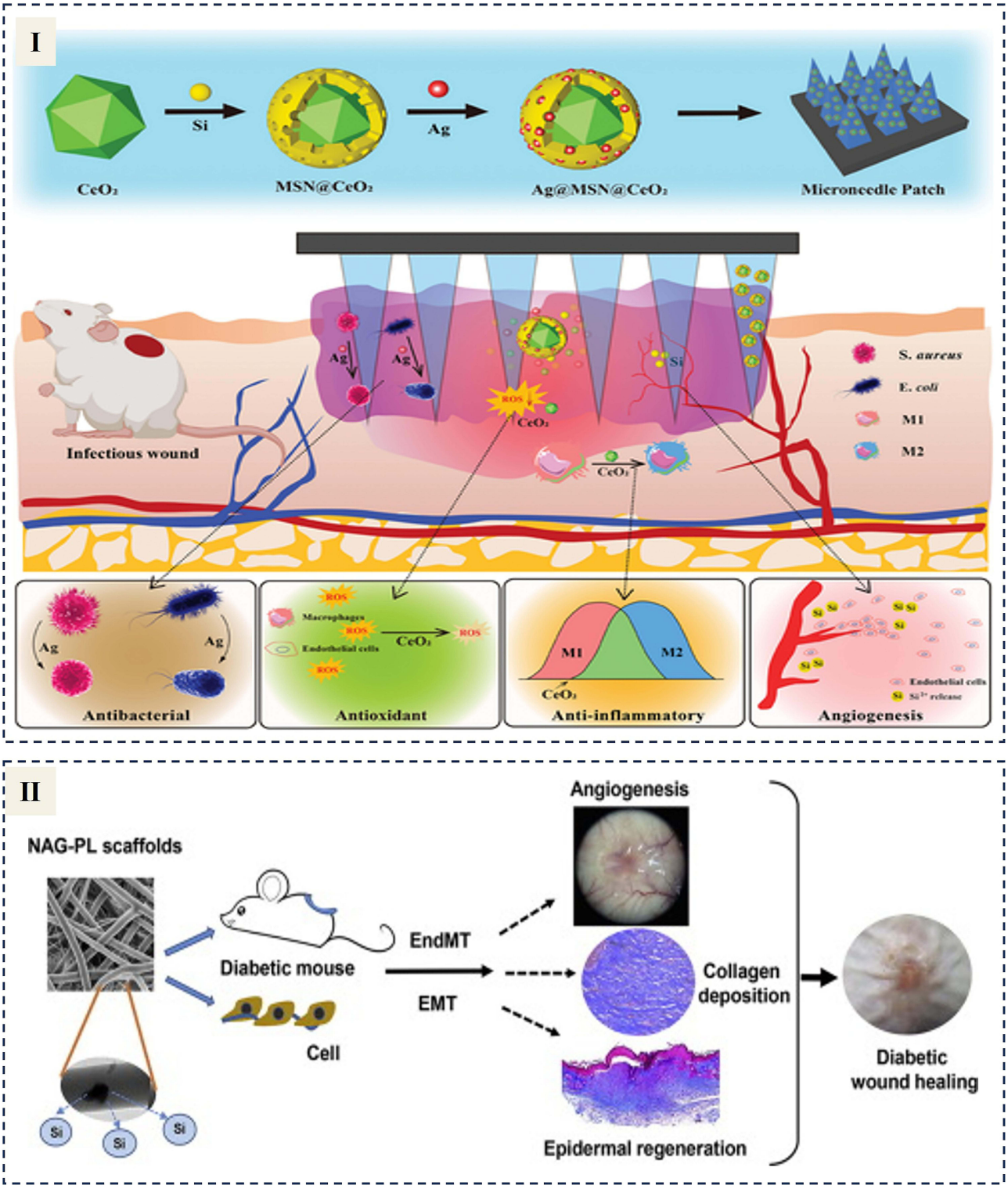

Figure 12 (**I**) A multifunctional MN@Ag@MSN@CeO2 patch was developed to promote healing in infected diabetic wounds (DW) through its antibacterial, antioxidant, anti-inflammatory, and angiogenic properties. Reprinted from Yu D, Chen L, Yan T, et al. Enhancing Infected Diabetic Wound Healing through Multifunctional Nanocomposite-Loaded Microneedle Patch: inducing Multiple Regenerative Sites. *Adv Healthc Mater.* 2024;13(20):e2301985. © 2024 Wiley-VCH GmbH.[140] (**II**) A conductive nanofibrous composite scaffold incorporating silicate-based bioceramic particles (Nagelschmidtite, NAGEL, Ca7P2Si2O16) was fabricated via co-electrospinning. Biological assessments confirmed that NAGEL particles activated epithelial-to-mesenchymal transition (EMT) and endothelial-to-mesenchymal transition (EndMT) pathways, both in vitro and in vivo. Reprinted from Acta Biomater. Volume 60. Lv F, Wang J, Xu P, et al. A conducive bioceramic/polymer composite biomaterial for diabetic wound healing. 128–143, copyright 2017, with permission from Elsevier.[141]

Table 7 Multimechanism Synergy of Silicon-Based Materials

Application Direction	Constructed Material/ System Description	Mechanism/Features	Main Targets or Pathways	Reference
Anti-infection and Wound Healing	Polylactic acid/polysiloxane citrate/curcumin (PPCP) nanofiber scaffold	Prevents infection, reduces pro-inflammatory factors, upregulates CD31 and VEGF, stimulates collagen deposition and skin appendage formation	Infection prevention, collagen deposition, angiogenesis, skin appendage formation	[103]
Accelerated Diabetic Wound Healing	γ-PGA dissolvable microneedle patch loaded with Ag@MSNs@CeO_2 core–shell nanoparticles	Antibacterial, reduces reactive oxygen species (ROS), modulates macrophage microenvironment, enhances angiogenesis and collagen deposition	Diabetic wound healing, antibacterial, collagen deposition, angiogenesis	[140]
Angiogenesis and Wound Repair	Nanofibrous composite scaffold containing partial silicate bioceramic particles (NAG-PL)	Activates epithelial–mesenchymal transition (EMT) and endothelial–mesenchymal transition (EndMT) pathways, induces angiogenesis, collagen deposition, epithelial regeneration, and inhibits inflammation	Angiogenesis, collagen deposition, epithelial regeneration, inflammation inhibition	[141]

Table 8 A Summary of the Current Clinical Research and Applications of Silica-Based Nanomaterials

Application Field	Research	Clinical Research/Trials	Advantages
Drug Delivery	Silica nanoparticles for improving the bioavailability of hydrophobic drugs.	Lipid-ceramic hybrid silica nanoparticles increased the bioavailability of simvastatin by 3.5 times (ACTRN12618001929291). Mesoporous silica nanoparticles enhanced the bioavailability of fenofibrate by 54% compared to Lipanthyl.	Improved drug bioavailability, good oral tolerance, and no severe adverse effects.
Plasmonic Resonance Therapy	Fe_3O_4 magnetic core-shell silica-gold nanoparticles for treating coronary atherosclerosis.	Phase I clinical trial showed reduced risks of atherosclerosis and cardiovascular disease mortality (NCT01270139).	Higher safety and significant efficacy compared to traditional stent implantation
Photothermal Ablation Therapy	Gold-shell silica nanoparticles for tumor photothermal therapy	Applied in head and neck tumors and prostate cancer (NCT00848042, NCT04240639, NCT02680535, NCT04656678)	Utilizes enhanced permeability and retention (EPR) effect, efficiently converts light to heat for tumor ablation
Tumor Imaging	Ultra-small silica nanoparticles (Cornell dots) for tumor diagnosis and staging	Used for melanoma and brain tumor diagnosis (NCT03465618, NCT01266096, NCT02106598). - PET and fluorescence imaging for diagnosis (NCT01266096).	High tumor targeting, strong fluorescence intensity, excellent photostability, avoids accumulation in the body.
Dental Treatment	Silicate biomaterials widely applied in treating dental issues.	Extensively used in clinical practice	High biocompatibility, excellent safety.
Wound Dressings	Silica gel fiber (SGF) dressings and silicate wound dressings for accelerated wound healing.	SGF dressings reduced dressing frequency for venous leg ulcers.[144] DermFactor® dressings accelerated post-anal rectal surgery wound healing.[145]	Effectively Accelerates wound healing, convenient to use, suitable for various wound types.

to achieve tumor ablation. In a pilot study involving 16 prostate cancer patients, gold-shell silica nanoparticles successfully performed photothermal ablation with fewer side effects compared to traditional local ablation therapies.

Ultrasmall silica nanoparticles (Cornell dots, 6–10 nm in diameter) have shown remarkable potential in tumor imaging. These nanoparticles have been utilized for the diagnosis and staging of melanoma and malignant brain tumors

(NCT03465618, NCT01266096, NCT02106598). Due to their size being below the renal clearance threshold of 10 nm, Cornell dots can be excreted through the kidneys, avoiding the risk of accumulation in the body. Functionalized with RGDY peptides and fluorescent dye Cy5.5, Cornell dots exhibit enhanced tumor targeting and act as efficient imaging agents. In a first-in-human clinical trial, 124I-labeled Cornell dots were used for PET and fluorescence-guided tumor diagnosis and staging (NCT01266096). Results showed that these particles were stable, well-tolerated, with no significant side effects, and had a plasma half-life of 8.7 hours. Furthermore, Cornell dots have been employed to detect and locate sentinel lymph nodes in head and neck melanoma patients (NCT02106598), significantly improving biopsy accuracy. Compared to traditional radio-guided methods, they demonstrated higher sensitivity, enhanced fluorescence intensity, and improved photostability.

Currently, commercial products derived from silicate biomaterials are widely used in clinical settings to address dental-related issues.[144–146] Silica gel fiber (SGF) dressings, a bioabsorbable inorganic silica gel fiber patch, consist of a network of hydroxyethoxy-siloxane polymers with the molecular structure H[Si8O12O(OH) x(OC2H5)6-x]nOH. In a study involving 130 patients with leg venous ulcers, participants were randomly divided into two groups to receive four weeks of local care with either SGF dressings or alginate dressings, followed by follow-up until the 8th week. Results showed that SGF dressings reduced dressing change frequency while maintaining equivalent therapeutic efficacy.[147]

In a randomized study, the effects of silicate wound dressings (DermFactor®) were evaluated in post-anorectal surgery wound treatment. A total of 328 patients were randomly assigned to a control group (routine dressing changes) and an observation group (routine dressing changes + DermFactor®). The observation group exhibited significantly shorter average wound healing times (mixed hemorrhoids: 19.04 days; anal fistula: 23.72 days; anal fissure: 21.14 days) compared to the control group (23.25 days, 27.76 days, and 24.32 days, respectively), along with a higher effective rate (80.4% vs 70.4%). These findings indicate that DermFactor® dressings effectively accelerate wound healing, making them a valuable adjunctive tool for post-anorectal surgery treatment.[148]

Although some silicon-based nano-products have reached clinical trial stages, challenges such as long-term biosafety, production feasibility, and individualized treatment remain to be addressed. With the integration of multidisciplinary technologies, silicon-based nanosystems are expected to become key technologies in wound treatment, driving the development of personalized and efficient therapies.

Prospects and Challenges

Silicon-based nanosystems hold immense promise in wound treatment, with development directions including personalized and intelligent therapies, combination therapy strategies, novel material development, and multicenter clinical studies. In personalized therapy, intelligent dressings integrated with sensor technology can monitor wound environments in real time and dynamically release drugs as needed, achieving efficient and precise treatment. Combined with wireless technologies, these systems support remote management. For instance, infected sites and bacterial biofilms exhibit microenvironments distinct from normal tissues, such as low PH, elevated local temperatures, and altered redox potentials, which can be exploited for nanosystem targeting.[149] Endogenous stimulus-responsive nanosystems successfully deliver lower doses of antimicrobials to infection sites, reducing systemic distribution and minimizing side effects on normal organs and tissues.[150]

In combination therapies, silicon-based nanomaterials can carry photosensitizers, antimicrobials, and tissue regeneration promoters, synergizing with photothermal or photodynamic therapy to effectively control infections and accelerate wound healing. For example, polydopamine and curcumin exhibit excellent near-infrared photothermal and anticancer properties. Researchers have synthesized multifunctional nanofiber matrices through surface functionalization, achieving photothermal chemotherapy for skin tumors and wound healing induced by infections.[93]

The size of nanoparticles plays a critical role in their in-vivo transport due to physiological size thresholds and size-dependent biological effects. It has been widely observed that nanoparticle size significantly influences their cellular uptake efficiency and mechanisms. Additionally, protein corona adsorption varies significantly with particle size.[151] Therefore, optimizing the physicochemical properties of nanoparticles, such as pore size, can enhance drug delivery and therapeutic performance.

Multicenter clinical studies validate the efficacy and safety of silicon-based nanosystems through large-scale trials, promoting their standardization and commercialization. These efforts lay a solid foundation for the broad application of silicon-based nanosystems in complex wound treatment, facilitating their transition from laboratory research to clinical practice.

However, clinical translation of silicon-based nanosystems for wound treatment faces multiple challenges, including safety, biocompatibility, applicability to complex wound models, multifunctional integration, and scalable production. Although their preliminary safety has been validated, long-term toxicity and potential impacts of chronic exposure require further investigation, especially under high-dose or repeated-use conditions. The diverse characteristics of complex wounds, such as chronic inflammation and impaired angiogenesis in diabetic ulcers or antimicrobial needs in burns, necessitate tailored functional strategies for specific pathologies, validated through clinically relevant 3D wound models or organ-on-chip technologies.

Materials with single functions are insufficient to meet the diverse needs of complex wounds, making multifunctional integration a research trend. However, verifying the combined efficacy of such systems remains challenging. Additionally, the complex fabrication processes of silicon-based nanosystems lead to significant batch-to-batch variability, affecting quality stability and clinical efficacy consistency. To achieve scalable production, industrial technologies must be developed, and stringent quality control standards established to ensure reproducibility and material performance consistency. Addressing these issues will pave the way for clinical application of silicon-based nanosystems.

Conclusion

Silicon-based nanomaterials, with their unique physicochemical properties and biological advantages, exhibit tremendous potential in wound healing applications. These materials feature high specific surface area, excellent mechanical and chemical stability, low toxicity, and superior biocompatibility, enabling precise drug delivery. In wound healing, silicon-based nanosystems synergistically enhance repair through multiple mechanisms, including antimicrobial, anti-inflammatory, and antioxidant activities, as well as promoting angiogenesis and cell proliferation.

Although studies have demonstrated their good biocompatibility, only a few silicon-based nanoproducts have entered clinical trials. Challenges such as long-term biosafety, production feasibility, and personalized treatment strategies remain unresolved. Future research on silicon-based nanosystems should focus on personalized and intelligent therapies, combination treatment strategies, novel material development, and multicenter clinical studies. These efforts aim to provide more efficient, safe, and comprehensive solutions for wound treatment, ultimately improving patient experiences and clinical outcomes.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Acknowledgments

The authors would like to thank Qinxin Liu for her assistance during the revision stage of the manuscript.

Funding

This study was supported by grants from Hubei Provincial Natural Science Foundation of China (No. 2023AFB825,2023AFB216) and Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. 2023A15).

Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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