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REVIEW

The Trilogy of Skin Regeneration via Metal-Organic Frameworks Nanomedicine: Precision Management of Refractory Wounds, Pathological Scarring, and Hair Follicle Reactivation

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Abstract: Diabetic infected wounds represent a formidable clinical challenge characterized by persistent hyperglycemia-induced pathological cascades that disrupt normal healing processes through multiple mechanisms including chronic inflammation, oxidative stress, and microvascular dysfunction. As prototypical chronic wounds, they exhibit severely impaired tissue regeneration due to this multifaceted dysfunction in both skin architecture and biological function. Metal-organic frameworks (MOFs) have emerged as promising next-generation therapeutic platforms owing to their exceptional structural tunability, multifunctional properties, and precise spatiotemporal drug delivery capabilities. This review examines several critical aspects: (1) fundamental MOF classifications and advanced synthesis methodologies; (2) metal-specific (Zn^{2+}, Cu^{2+}, Ag^{+}, etc.) therapeutic mechanisms against diabetic wound infections; (3) extended applications in pathological scar modulation and hair follicle regeneration through targeted molecular pathway regulation; and (4) the integrated "healing-scar suppression-functional restoration" treatment paradigm. We further elucidate critical unresolved challenges in MOF-based skin regeneration, including long-term biosafety and large-scale production issues while providing a comprehensive theoretical framework for future translational research. By uniting prior MOF studies on scar and hair regeneration with pro-healing paradigms, this discussion frames design principles for concurrent structural and functional repair, guiding MOF research from healing to regeneration.

Keywords: metal-organic framework, diabetic wound, infected wound, scar, hair regeneration

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Introduction

Diabetic wounds affect approximately 2.2% of the global population and represent the leading cause of hospitalization and amputation among diabetic patients, with about 20% of moderate-to-severe infected wounds ultimately requiring amputation.[1,2] The high recurrence rate (reaching 50% within 5 years) and mortality rate (5-year survival rate of only ~50%) underscore the severe clinical challenges in management.[2,3] As a prototypical chronic wound, its refractory nature stems from pathological cascades triggered by a hyperglycemic microenvironment. Persistent hyperglycemia induces vascular endothelial damage, neuropathy, and immune dysfunction, impairing wound microcirculation and causing local ischemia-hypoxia, which progresses to chronic wounds.[4] In this process, wound infections (eg, *Staphylococcus aureus, Pseudomonas aeruginosa*) further exacerbate tissue damage.[5] Pathogenic biofilm formation evades host immune clearance, while sustained inflammatory responses release excessive reactive oxygen species (ROS) and pro-inflammatory factors (eg, tumor necrosis factor (TNF)-α, interleukin (IL)-6), leading to overactivation of matrix metalloproteinases (MMPs) and disruption of extracellular matrix (ECM) homeostasis, creating a vicious "inflammation-infection" cycle.[6] Concurrently, hyperglycemia and infection synergistically suppress fibroblast proliferation/migration, reducing collagen deposition, while impaired keratinocyte differentiation hinders re-epithelialization. Moreover, diabetic wounds

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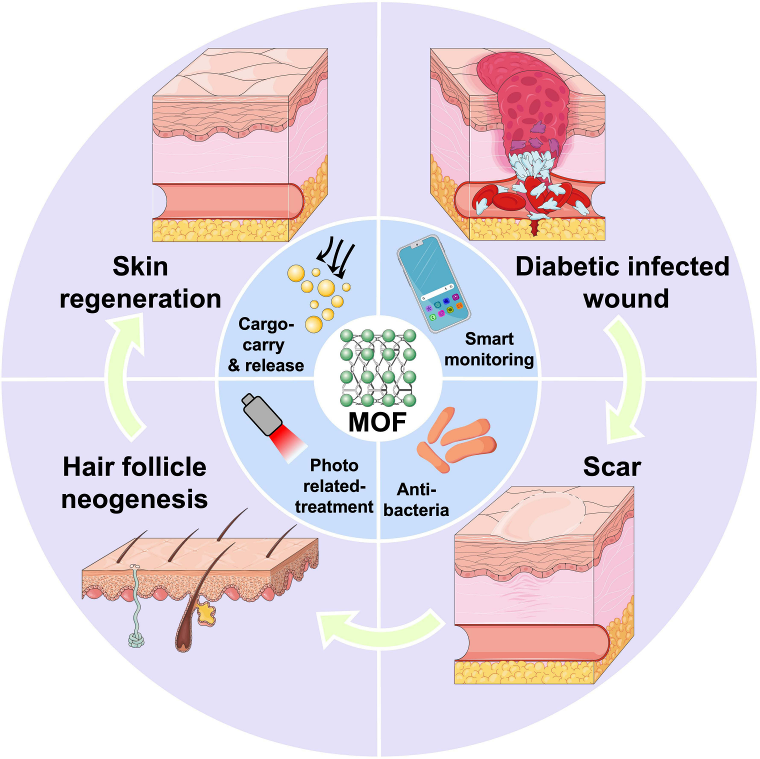
exhibit stem cell dysfunction and diminished angiogenic capacity, further limiting tissue repair potential.[7,8] Breaking this dual pathological loop from hyperglycemia and infection is critical for achieving skin regeneration.

Skin regeneration aims at structural reconstruction and functional recovery.[9] It requires not only wound closure and structural restoration but also the recovery of normal physiological functions, including barrier protection, sensory regulation, and appendage functionality. Ideal skin regeneration should prevent pathological scar formation while promoting the regeneration of appendages (eg, hair follicles, sweat glands) to maximally restore the skin's native state. Wound healing is typically accompanied by scar formation,[10] which fundamentally results from fibroblast overactivation and disordered collagen deposition such as an imbalanced type I/III collagen ratio. Pathological scars, including hypertrophic scars and keloids, represent typical manifestations of ECM metabolic dysregulation, closely associated with overactivation of the transforming growth factor-β (TGF-β) signaling pathway.[11] Current research focuses on modulating myofibroblast apoptosis, including targeting YAP/TAZ or localized delivery of anti-fibrotic silicone gel or 5-fluorouracil, to improve scar texture.[12] The core challenge of functional regeneration lies in restoring skin appendages like hair follicles, which depend on epithelial–mesenchymal interactions and stem cell niches.[13] Current approaches for hair follicle regeneration primarily involve exogenous activation of dermal papilla cells (DPC) or 3D-cultured organoids,[14] yet post-transplantation survival rates remain limited. Achieving rapid re-epithelialization while precisely regulating appendage morphogenesis remains a key challenge in advancing regenerative medicine toward "structural-functional" dual repair.

Metal-organic frameworks (MOFs) demonstrate significant potential in skin regeneration. MOFs are porous crystalline materials formed by the self-assembly of metal ions/clusters and organic ligands, offering advantages such as high specific surface area, tunable pore size, and surface functionalizability. Typically synthesized from metal salts and organic ligands, for instance, terephthalic acid and imidazolate, MOFs can be loaded with various cargoes and further combined with biomaterials like hydrogels[15] and nanofibers[16] to enhance biocompatibility and wound adaptability for clinical applications. Currently, MOFs have been widely used in drug delivery (eg, controlled release of anticancer drugs), gas storage (eg, hydrogen/carbon dioxide adsorption), and catalysis, but their potential in skin regeneration has only recently been explored.[17] Beyond these therapeutic properties, MOFs are particularly suitable for diabetic infected wounds. They can serve as antibacterial carriers to load antibiotics or antimicrobial metal ions for targeted pathogen eradication.[18] Through anti-inflammatory drugs or growth factor combination, MOFs can modulate the wound microenvironment to achieve both anti-inflammatory and pro-regenerative effects. Additionally, they can utilize wound microenvironment characteristics like low pH and high ROS to trigger smart and precise drug release (Scheme 1). However, there is currently no comprehensive review summarizing MOF applications in diabetic infected wounds and subsequent skin regeneration. Most reviews fixate on how fast wounds close yet overlook whether the quality of healed tissue.[19–21] Speed alone is mistaken for skin regeneration, while the reconstruction of architecture and function is ignored. Here, we scrutinize the entire MOF-driven trajectory—healing, scarring, appendage re-emergence—to reveal what these frameworks can truly achieve, and we integrate these facets to guide future MOF designs for continuous wound-to-regeneration strategies.

Therefore, this review examines the research progress of MOFs in diabetic infected wounds, pathological scars, and skin appendage regeneration, comprehensively evaluating their therapeutic potential throughout the entire process from wound healing to structural and functional skin regeneration, thereby providing a theoretical foundation for future MOF research in skin regeneration. Specifically, this review first summarizes the commonly used preparation methods and material selection criteria for MOFs, elucidating the applicable scenarios of different metal centers and the advantages/disadvantages of various preparation techniques. Subsequently, the review classifies MOF materials based on metal types and provides a review of their applications in treating diabetic infected wounds, modulating scar formation and promoting appendage regeneration. Through this comprehensive analysis, a theoretical framework for the development of next-generation MOF-based skin regenerative therapies is proposed while identifying current challenges and future research directions in this emerging field. In summary, this review adopts diabetic infected wounds as a paradigmatic case of refractory wound healing to elucidate the comprehensive regulatory potential of MOFs across the complete "wound healing-scar modulation-appendage regeneration" continuum in skin regeneration. By examining these interconnected processes, we advance cutting-edge understanding of MOF-based therapeutic strategies for skin regeneration while establishing a crucial theoretical framework to guide future research and development in this transformative field.



Scheme 1 Schematic illustration of treatment potential for MOF application in skin regeneration.

Materials and Fabrication Methods

Metal

Zinc

The choice of metal centers in MOFs fundamentally governs their physicochemical characteristics and biomedical performance (Table 1). Zinc (Zn)-based MOFs have emerged as particularly promising candidates for wound management due to their superior biocompatibility and multifunctional therapeutic effects. As the body's second most abundant transition metal after iron, Zn plays indispensable roles in enzymatic systems,[22] protein synthesis,[23] and tissue repair processes.[24] Its wound healing benefits are well documented, ranging from enhancing platelet functionality for hemostasis[25] to promoting angiogenesis[26] and exerting potent anti-inflammatory effects through Zn-finger protein upregulation and nuclear factor kappa-B (NF-κB) pathway inhibition,[27] which collectively reduce pro-inflammatory cytokine expression. These immunomodulatory properties extend to macrophage polarization regulation and B-cell population control.[28,29]

Representative Zn-MOFs like ZIF-8 combine structural stability with controlled Zn^{2+} release in wound microenvironments. The liberated Zn ions demonstrate broad-spectrum antimicrobial activity through dual mechanisms: membrane disruption via electrostatic interaction with microbial teichoic acids[49] and bacterial DNA damage through ROS generation.[30] This potent antibacterial action proves particularly effective against diabetic wound pathogens, including Staphylococcus aureus and Pseudomonas aeruginosa. The unique combination of antimicrobial, anti-inflammatory, and pro-healing properties positions zinc-based MOFs as ideal multifunctional materials for advanced wound dressings capable of simultaneously addressing infection control and tissue regeneration challenges in chronic wounds.

Copper

Copper (Cu)-based MOFs represent another class of materials with significant biomedical value, exemplified by characteristic structures such as HKUST-1.[31] Cu fundamentally participates in all stages of wound healing by regulating the activity of Cu-dependent growth factors, including platelet-derived growth factor (PDGF), vascular endothelial

Table 1 Metal Selection for MOF Fabrication

Metal Type	Advantages	Disadvantages	Ref.
Zinc (Zn)	- High biocompatibility, low toxicity - Broad-spectrum antibacterial activity (Zn^{2+} disrupts bacterial membranes) - Promotes epithelialization and collagen remodeling (modulates MMPs)	- Excessive Zn^{2+} release may inhibit cell migration - Low stability under acidic conditions	[24–27,30]
Copper (Cu)	- Potent antibacterial effects (ROS generation) - Pro-angiogenic (activates HIF-1α/VEGF) - Anti-biofilm properties	- High Cu^{2+} concentrations exhibit cytotoxicity - May induce oxidative stress damage	[31–34]
Iron (Fe)	- Enzyme-like activity (regulates ROS) - Anti-inflammatory (modulates macrophage polarization) - Low cost and readily available	- Valence changes in iron ions may exacerbate oxidative stress - Poor stability in physiological environments	[35–38]
Silver (Ag)	- Exceptional antibacterial activity (especially against drug-resistant strains) - Potential for photothermal synergistic therapy - Sustained release	- Low biocompatibility, requires dosage control - May cause local tissue silver deposition	[39–41]
Magnesium (Mg)	- Promotes appendage regeneration (hair follicles/sweat glands) - Improves microcirculation - Degradation products regulate pH	- Rapid degradation, short duration of action - Low mechanical strength	[42–44]
Zirconium (Zr)	- Ultrahigh stability (acid/water-resistant) - Excellent drug carrier capacity - Nearly no metal ion leakage	- Lacks intrinsic bioactivity - High synthesis cost	[45,46]
Calcium (Ca)	- Osteoconductivity (suitable for composite wounds) - Promotes osteogenic differentiation	- Limited research, insufficient data- Ineffective in soft tissue repair	[47,48]

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growth factor (VEGF), and angiopoietins, promoting collagen deposition and fibroblast MMPs expression.[32] Leveraging its distinctive redox properties, Cu generates ROS through Fenton-like reactions, demonstrating potent bactericidal activity against drug-resistant pathogens and biofilms. In diabetic wound therapy, Cu-based MOFs not only effectively eliminate pathogens but also mitigate chronic inflammation by modulating macrophage polarization.[33] Notably, Cu ions engage with multiple angiogenesis-related signaling pathways, such as the hypoxia-induced factor (HIF)-1α/VEGF pathway,[34] fostering neovascularization at wound sites to supply essential nutrients and oxygen for tissue regeneration. However, the cytotoxicity of Cu-based MOFs requires precise control, typically achieved by optimizing metal loading or surface modifications to balance therapeutic efficacy with biosafety.

Iron

Iron (Fe)-based MOFs exhibit distinctive advantages in wound repair due to the redox-active nature of iron ions (Fe^{3+}/Fe^{2+}). Their valence variability enables biomimetic enzymatic activities (eg, peroxidase and catalase-like functions),[35] allowing intelligent regulation of ROS in the wound microenvironment. This enzyme-mimicking characteristic equips Fe-MOFs with dual capabilities: scavenging excessive inflammation-associated ROS to mitigate oxidative stress damage while simultaneously catalyzing the generation of bactericidal-free radicals under hypoxic conditions. Furthermore, Fe-based MOFs can selectively clear senescent cells through ferroptosis pathways,[36] creating space for nascent tissue regeneration. Fe-MOFs discharge Fe^{2+} that engage endogenous H_2O_2 in a Fenton reaction, catalysing the formation of hydroxyl radicals and the ensuing peroxidation of membrane lipids – a central axis of ferroptosis[50] Because intracellular H_2O_2 is often limiting, Fe-MOFs are routinely co-delivered with H_2O_2-generating cargoes such as calcium peroxide to replenish the substrate pool, thereby sustaining the Fenton cycle and amplifying therapeutic output.[37] Emerging Fe-MOF architectures further subvert metal-ion homeostasis by accelerating iron liberation, promoting ferritin degradation or activating autophagic flux, and collectively intensifying the ferroptotic signal.[51] In diabetic wounds, these materials additionally optimize the inflammatory microenvironment by modulating macrophage phenotype switching,[38] thereby synergistically promoting wound healing through combined anti-inflammatory and pro-regenerative mechanisms. The multifaceted functionality of Fe-MOFs, spanning from oxidative stress modulation to cellular clearance and immunoregulation, positions them as versatile therapeutic platforms for comprehensive wound management, particularly in challenging pathological conditions like diabetic wounds.

Silver

Silver (Ag)-based MOFs occupy a unique position in the field of antimicrobial wound dressings. The remarkable antibacterial efficacy of Ag^+ ions stems from their multimodal mechanisms of action, including disruption of bacterial respiratory chains[52] and interference with DNA replication processes,[53] enabling potent pathogen eradication. In diabetic wound management, Ag-MOFs demonstrate particular value by not only effectively combating drug-resistant infections but also providing sustained antimicrobial activity through controlled ion release, thereby reducing dressing change frequency. Notably, their photothermal conversion capability allows for on-demand, precision antibacterial therapy when combined with near-infrared (NIR) radiation. However, the relatively lower biocompatibility of Ag necessitates strategic approaches such as carrier structure optimization or co-doping with other metals to mitigate potential toxicity while maintaining therapeutic effectiveness. This balance between potent antimicrobial action and biosafety considerations makes engineered Ag-MOFs promising candidates for advanced wound care, especially in treating complex, infected diabetic wounds where conventional antibiotics often prove inadequate. The continued development of Ag-based MOF systems focuses on enhancing their selective toxicity against pathogens while minimizing adverse effects on host tissue regeneration processes.

Magnesium

Magnesium (Mg)-based MOFs leverage the essential biological functions of Mg^{2+}, the fourth most abundant cation in humans,[42] which plays pivotal roles in cellular proliferation and signal transduction. In diabetic wound treatment, the controlled release of magnesium ions improves local microcirculation and disrupts the chronic inflammatory cycle by modulating inflammatory factor expression while interfering glucose metabolism and lipid profiles.[43] The gradual degradation profile of Mg-MOFs makes them particularly suitable for prolonged wound management, with their degradation products additionally serving to optimize wound pH, thereby creating a microenvironment conducive to tissue regeneration.[54] This unique combination of pro-regenerative signaling activation, anti-inflammatory modulation, and microenvironmental conditioning positions Mg-based MOFs as versatile therapeutic platforms for comprehensive wound care, especially in challenging diabetic cases where multiple pathological factors need simultaneous addressing. The inherent biocompatibility of magnesium further enhances its clinical translation potential for chronic wound applications requiring extended therapeutic duration.

Others

Beyond the above conventional metal-based MOFs, zirconium (Zr)-based MOFs have gained prominence in wound therapy primarily as drug carriers due to their exceptional chemical stability and low toxicity.[45] These MOFs demonstrate remarkable capacity for loading and controlled release of various growth factors and anti-inflammatory drugs, enabling precise therapeutic delivery. Calcium (Ca)-based MOFs, on the other hand, exhibit special value in repairing complex wounds involving bone exposure owing to their excellent osteoconductivity.[47] The complementary properties of different metal-based MOFs have driven researchers to develop bimetallic MOF systems (eg, Zn-Cu, Fe-Ag combinations), which leverage metal synergistic effects to integrate multiple functions, including antibacterial action, anti-inflammatory effects, pro-angiogenic activity, and tissue regeneration capabilities. This approach provides novel and comprehensive solutions for managing refractory wounds, addressing multifaceted pathological challenges through coordinated therapeutic mechanisms. The development of these multifunctional MOF systems represents a significant advancement in creating tailored treatments for complex wound healing scenarios.

Fabrication Method

Solvothermal Method

Different synthesis methods have been reported during MOF fabrication (Table 2). The most popular synthesis procedures are listed in Figure 1. The solvothermal method represents one of the most classical approaches for MOF synthesis, typically conducted in sealed autoclaves using organic solvents as media under elevated temperatures (80–200°C) and autogenous pressure. In this process, metal salts and organic ligands dissolve in solvent, followed by thermally promoted coordination self-assembly to form crystalline MOFs. This versatile method applies to most MOF systems (eg, ZIF-8), yielding products with high crystallinity and controllable porosity while allowing crystal morphology optimization through adjustments in solvent type (eg, DMF, methanol), temperature, and reaction duration. Common experimental procedures involve dissolving metal salts and organic linkers (eg, 2-methylimidazole) in a chosen solvent such as DMF, followed by sonication or stirring to ensure homogeneity before transferring the mixture to a Teflon-lined autoclave for heating.[55] Reaction times typically range from 6 to 48 hours, and post-reaction washing steps with ethanol or methanol are essential to remove unreacted ligands or solvents.[56] Particle size and morphology are highly sensitive to parameters such as reaction temperature, precursor concentration, and the presence of additives like acetic acid or sodium acetate. For instance, increasing acetic acid content can lead to the formation of well-defined rhombic dodecahedra, while sodium acetate tends to yield smaller spherical particles.[57] Moreover, higher synthesis temperatures typically favor smaller particle sizes due to faster nucleation, whereas longer reaction times promote crystal growth and increased uniformity.[55] Additives can also impact surface chemistry and indirectly influence bioactivity by altering ligand exposure or particle dispersibility.[58]

However, the solvothermal approach suffers from high energy consumption, prolonged reaction times (hours to days), and potential toxicity of organic solvents requiring post-synthetic removal. The environmental impact can be mitigated through green solvent alternatives like ionic liquids. Additionally, hydrothermal/solvothermal synthesis may lead to pore blockage in MOFs during washing procedures due to residual reaction media.[56]

Hydrothermal Method

The hydrothermal method shares similarities with solvothermal synthesis but employs water as the reaction medium, typically conducted at 100–250°C.[21] This approach offers lower costs and enhanced environmental compatibility, making it particularly suitable for water-stable MOFs. The polar nature of water facilitates the dissolution and coordination of metal ions with ligands, although hydrophobic ligands may require cosolvent addition. In practice, metal salts and organic linkers are mixed in deionized water, often with pH regulators or mineralizers such as nitric acid or sodium

Table 2 Synthesis Method of MOF

Synthesis Method	**Reaction Conditions**	**Reaction Time**	**Product Characteristics**	**Advantages**	**Disadvantages**	**Ref.**
Solvothermal	High temp/pressure (80–200°C)	Hours–days	High crystallinity, large pores	High crystal quality, controllable porosity	High energy consumption, toxic solvents, channel blockage	[55,56,59,60]
Hydrothermal	High temp/pressure (100–250°C)	Hours–days	High crystallinity, eco-friendly	Low cost, water as solvent	Poor water stability for some MOFs	[60,61]
Microwave	Microwave heating (2.45 GHz)	Minutes–hours	Nanocrystals, uniform size	Fast & energy-efficient, high-throughput screening	Specialized equipment, local overheating risk	[62–64]
Sonication	Room temp (20 kHz–1 MHz)	Minutes–hours	Nano-MOFs, low agglomeration	Ambient conditions, thermolabile ligand compatible	Potential defect introduction, power optimization required	[65,66]
Electrochemical	Ambient conditions (electrolysis)	Minutes–hours	Thin films/substrate integration	No metal salt residues, in situ deposition	Low yield, electrolyte limitations	[67,68]
Mechanochemical	Ball-milling/grinding (solid-state)	Minutes–hours	Low crystallinity, solvent-free	Green synthesis, insoluble ligand compatible	Poor crystallinity, post-treatment needed	[69–71]
Diffusion	Room temp/ambient pressure	Days–weeks	Large single crystals, high purity	Mild conditions, ideal for structure analysis	Extremely low yield, non-scalable	[72,73]
Template-Assisted	Template-dependent	Hours–days	Hierarchical pores, core-shell structures	Morphology control, functional design	Template removal challenging, high cost	[74,75]

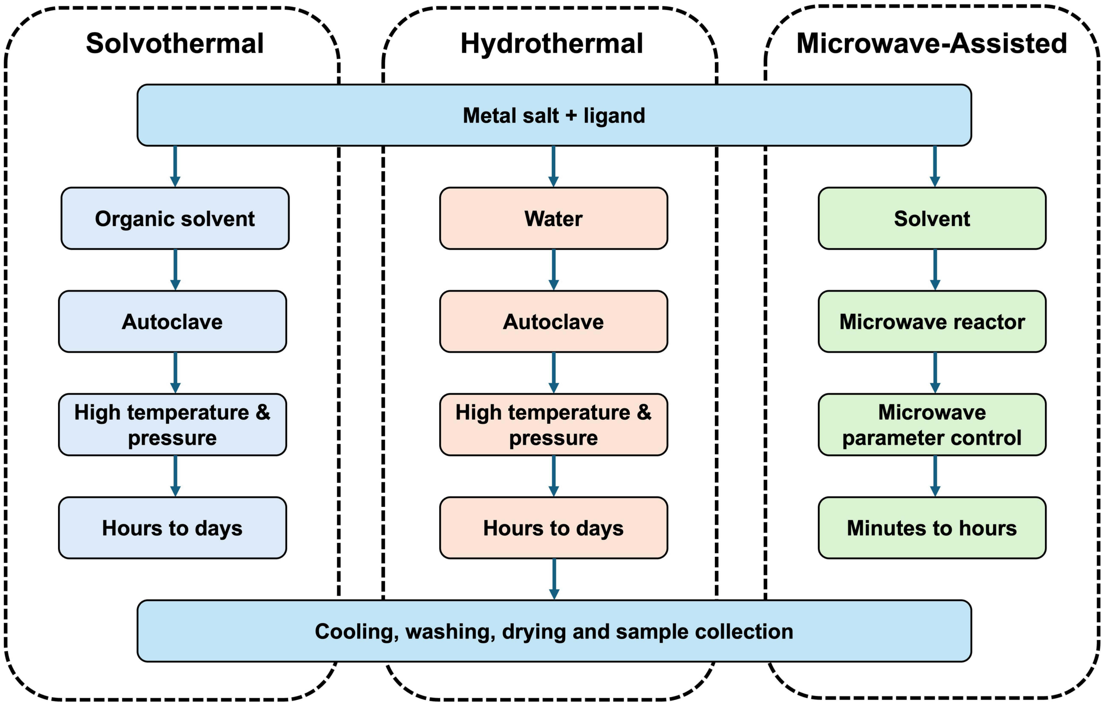

Figure 1 Three synthesis ways of MOF.

hydroxide to adjust the reaction environment.[76] The mixture is then transferred to a hydrothermal reactor, usually operated for 12–48 h depending on the desired crystal quality. Reaction temperature and pH are two key parameters influencing nucleation and crystal growth: lower pH may lead to incomplete coordination, while higher pH promotes deprotonation and accelerated assembly.[77] Additionally, morphology can be tuned by altering precursor concentrations and aging times: low concentration promotes larger, well-defined crystals, while high concentration yields nanocrystals with higher surface areas.

Key challenges include water's broad pH range, potentially compromising MOF stability, and the tendency of certain metal ions (eg, Al^{3+}, Cr^{3+}) to form hydroxide impurities. These limitations can be mitigated through pH adjustment or mineralizer additives to enhance crystallinity. While demonstrating significant potential for scale-up production, hydrothermal synthesis demands precise control over reaction parameters to prevent amorphous byproduct formation. The method's industrial applicability remains constrained by the water sensitivity of many MOF structures and the difficulty in completely eliminating competitive hydroxide formation during crystallization processes.

Microwave Irradiation Method

The microwave irradiation method utilizes microwave heating to achieve rapid and uniform molecular-level heating, significantly reducing reaction times to mere minutes or tens of minutes.[62] Through dielectric heating effects, microwaves selectively activate polar molecules, accelerating nucleation rates to yield small, monodisperse crystals (eg, <100 nm). Typical conditions involve reaction temperatures between 120°C and 200°C, with holding times of 5–30 minutes depending on the MOF system.[63] Power settings and ramp rates can be fine-tuned to avoid hot spots and prevent decomposition of sensitive ligands. The use of surfactants like polyvinylpyrrolidone (PVP) or PEG helps in morphology control and reduces particle aggregation.

This approach offers multiple advantages, including energy efficiency, precise process control, rapid heating, high product yield and purity, excellent reproducibility, and reduced energy consumption, making it particularly suitable for high-throughput screening. However, it requires specialized microwave reactors, and certain metal-ligand combinations (eg, Cu^{2+} with carboxylates) may undergo localized decomposition due to overheating. Additionally, microwave power and the dielectric constant of the solvent critically influence the crystal morphology.

However, improper power settings or incompatible solvents can lead to overheating and degraded framework integrity, especially for carboxylate-based linkers.[63] Furthermore, smaller particle sizes generally correlate with improved drug release kinetics and cellular internalization for biomedical applications.[78]

Sonication Method

The sonication method utilizes ultrasonic waves (20 kHz-1 MHz) to generate localized high-temperature and high-pressure conditions through cavitation effects, accelerating the diffusion and reaction between metal ions and organic ligands, enabling MOF synthesis at room temperature within tens of minutes.[65,66] Experimental procedures typically involve adding metal and ligand precursors to a solvent (eg, ethanol or water), followed by ultrasonication using a probe or bath system for 10–60 minutes. Ultrasound amplitude and pulse cycles can be optimized to avoid overheating or foam generation.[79] This approach eliminates the need for high-temperature and high-pressure equipment, making it particularly suitable for thermally sensitive ligands while readily yielding nano-sized MOF particles.

However, the sonication duration and power require precise optimization, as improper parameters may lead to crystal defects or particle aggregation. Additionally, the free radicals generated during ultrasonication may interfere with coordination processes. Particle size is primarily affected by sonication intensity and duration-higher energy input promotes smaller, more uniform particles but can also induce structural defects. Stabilizing agents like PVP may be introduced to suppress aggregation and enhance colloidal stability.[80]

While this method proves effective for rapid laboratory-scale preparation, its large-scale implementation faces challenges in achieving uniform energy distribution throughout the reaction system. The technique offers distinct advantages for nanoscale MOF synthesis under mild conditions but requires further development to address reproducibility issues in industrial-scale applications.

Electrochemical Method

The electrochemical method enables direct synthesis of MOF films or powders under ambient temperature and pressure conditions through electrolysis of solutions containing metal anodes and organic ligands.[67] In this process, anodic dissolution provides metal ions that undergo real-time coordination with ligands in solution, with reaction rates precisely controllable via current density adjustment. A typical setup includes a two-electrode system using metal foil (eg, Cu, Zn) as the anode and a Pt or graphite cathode immersed in a conductive solution containing the linker (eg, trimesic acid), with an applied current of 1–10 mA/cm².[58] Reaction durations range from 5 to 60 minutes depending on the desired film thickness or particle loading. This approach eliminates the need for metal salt precursors, minimizes impurities, and allows for in situ MOF deposition on conductive substrates (eg, electrodes, metal meshes), making it particularly suitable for integration with wound dressings. Crystal morphology and size are influenced by current density, and electrolyte composition-higher current promotes faster nucleation and smaller crystals while modulating the supporting electrolyte (eg, nitrate, acetate) alters coordination rates.

Notably, the method offers high synthesis efficiency and short reaction times. Through electrochemical synthesis, MOFs can also be directly deposited on specific substrates as functional coatings.[68] However, the technique demonstrates strong solvent and electrolyte dependence, typically requiring nitrate salts to maintain conductivity while also suffering from relatively low product yields. The electrochemical approach presents unique advantages for fabricating MOF-based medical devices but requires further optimization to improve production scalability and expand compatible electrolyte systems.

Mechanochemical Method

The mechanochemical synthesis method utilizes ball milling or grinding of solid-state mixtures containing metal salts and organic ligands, where mechanical force induces chemical reactions.[69] This solvent-free approach – or one requiring only minimal liquid additives – represents an environmentally friendly alternative with rapid reaction completion (typically within tens of minutes). A standard procedure involves mixing stoichiometric amounts of metal and ligand precursors in a zirconia or stainless steel ball mill jar, milling at 25–30 Hz for 10–60 minutes. Addition of a few drops of solvents such as ethanol (“liquid-assisted grinding”) can enhance reaction kinetics and crystallinity.[81]

Particularly valuable for synthesizing MOFs inaccessible through conventional methods (eg, systems with poorly soluble ligands), the technique nevertheless yields products with relatively low crystallinity that often require post-synthetic thermal treatment for enhancement.[70]

Particle size can be modulated by adjusting milling time, frequency, and ball-to-powder ratio, while the presence of modulators may help guide crystal shape or prevent agglomeration. Although bioactivity is less explored in this route, the lack of residual solvent and small particle sizes make it attractive for eco-friendly, skin-contact materials. Operational parameters, including milling frequency and ball-to-powder ratio, significantly influence the final porosity characteristics, while industrial-scale implementation must additionally address equipment wear issues.

Diffusion Method

The diffusion method facilitates gradual MOF single crystal formation at the interface through controlled mixing of metal salt and ligand solutions (eg, via layering or vapor diffusion) under mild conditions, which are room temperature and atmospheric pressure.[72] In liquid–liquid diffusion, one solution is gently layered above the other without mixing, allowing metal–ligand interaction to proceed over days or weeks. In vapor diffusion, a poor solvent diffuses into a MOF precursor solution to gradually lower solubility and initiate nucleation.[72]

While particularly suitable for growing large single crystals for structural characterization, this approach requires extended reaction times (days to weeks) and suffers from extremely low yields. Crystal dimensions and morphology can be tuned by changing the polarity and diffusion rate of solvents; slower diffusion promotes fewer nuclei and larger crystals. However, the lack of agitation may limit uniformity or scalability for biomedical formulations. Currently, diffusion synthesis serves primarily as a research tool for fundamental studies rather than practical applications.

Template-Assisted Method

In template-assisted synthesis, hard templates (eg, SiO_2 nanospheres) or soft templates (eg, surfactants) direct MOF growth to construct hollow, core-shell, or hierarchically porous architectures.[74] In a typical hard-template approach, sacrificial particles are first coated with MOF precursors, followed by crystallization and subsequent removal of the template via calcination or acid washing. Soft templates, such as Pluronic F127, self-assemble with MOF units to define micellar or lamellar structures.[59] These templates spatially confine MOF formation to control morphology and pore size distribution, but their subsequent removal (via acid etching, calcination, etc.) may compromise framework integrity.

Controlled parameters include template size, surfactant concentration, and the ratio of precursors to template. For example, larger templates result in larger internal voids, while higher surfactant concentration can induce more ordered mesostructures.[82] Although powerful for engineering functionalized MOFs (eg, drug delivery systems), the multi-step process and elevated costs limit widespread adoption. The technique's value lies in creating structurally sophisticated MOFs unobtainable through conventional methods, albeit with compromised practicality for scale-up production.

Large-Scale Production and Translation

Good Manufacturing Practice

Although MOFs exhibit tremendous potential in skin regeneration applications, their translation from laboratory-scale synthesis to clinical-grade production remains a complex and demanding task. Realizing this transition requires not only inherent biocompatibility and therapeutic activity of the material but also a fully integrated system spanning process optimization to regulatory compliance. Conventional synthesis routes such as solvothermal and hydrothermal methods can yield high-quality MOF crystals but often fail to meet the stringent Good manufacturing practice (GMP) criteria regarding environmental control, reagent traceability, purity, and batch-to-batch consistency. Emerging research has focused on greener and modular production strategies. Mechanochemical synthesis, characterized by minimal solvent use, low energy consumption, and high reproducibility, is particularly promising under GMP setting.[82] Precise tuning of ball-milling parameters enables controlled production of particle size and morphology, reducing by-product formation and simplifying downstream purification. Similarly, microwave-assisted synthesis in continuous-flow reactors offers rapid, energy-efficient, and predictable MOF fabrication, which can be further coupled with automation systems for scalable manufacturing.[83]

Downstream operations such as ultrafiltration, centrifugation, and supercritical drying must be standardized and integrated with inline quality control technologies (eg, X-ray diffraction, inductively coupled plasma mass spectrometry, transmission electron microscopy, etc.) to ensure sterility, structural integrity, and functional retention of MOFs.[84] Particularly in skin regeneration, sterilization methods such as gamma irradiation or autoclaving are essential, yet they must not compromise the porous architecture or drug-loading capacity of MOFs. Zirconium-based MOFs, for instance, have demonstrated excellent thermal and chemical stability, making them viable candidates for sterilizable medical frameworks.[85]

Cost Consideration

From an economic standpoint, the feasibility of MOF translation remains largely constrained by the high costs of precursors, such as multivalent metal salts and custom-designed organic linkers, and the complexity of multi-step synthesis protocols. To overcome these limitations, researchers have explored the use of low-cost, earth-abundant metal sources (eg, Fe, Mg) and renewable organic ligands derived from biomass or polyphenols.[86] Simultaneously, synthetic routes are being re-engineered for higher yield and lower energy demand to minimize overall process input. Cost optimization is not limited to raw materials; it also depends on the ability to recycle unreacted ligands and solvents during MOF synthesis. Recovery systems that integrate yield enhancement with solvent reuse are gaining traction, especially in continuous production setups. Importantly, MOF production economics lie at the intersection of yield, structural control, and purification difficulty. Breaking this trade-off requires a holistic, end-to-end optimization of design, synthesis, purification, and packaging into an integrated manufacturing pipeline.[87]

Biosafety and Regulatory Hurdle

Perhaps the most formidable challenge in MOF clinical translation lies in regulatory clearance, particularly from agencies like the FDA. MOFs, as nanostructured drug delivery vehicles with novel compositions, must undergo rigorous evaluation in toxicology, pharmacokinetics (ADME), long-term biocompatibility, and batch reproducibility.[88]

One central issue is the in vivo biodegradation pathway and clearance mechanism of MOFs, which vary greatly depending on the metal node, ligand chemistry, particle size, and surface properties. In acidic or enzyme-rich environments-such as inflamed skin wounds-MOFs may undergo progressive degradation, releasing therapeutic metal ions. For example, ZIF-8 degrades in acidic conditions to release Zn^{2+}, which is excreted via the urinary tract with low systemic toxicity.[89–91] Fe-based MOFs release Fe^{2+}/Fe^{3+}, which can be sequestered by ferritin and excreted via bile or feces through regulated iron homeostasis.[92,93] In contrast, Cu-based MOFs pose oxidative stress risks when copper ions accumulate, while Ag-based MOFs risk argyria due to slow clearance of Ag.[+94,95] Zr-based MOFs, while chemically robust and minimally degradable, raise concerns over long-term tissue accumulation due to prolonged biological half-lives.[96] In contrast, Mg-based MOFs degrade into bioavailable Mg^{2+}, which is quickly excreted renally and shows excellent systemic biocompatibility.[97]

In skin regeneration, MOFs are usually administered topically via dressings or hydrogel matrices. Local accumulation in skin tissues is desirable but enhanced permeability – especially in injured or inflamed skin – raises the possibility of systemic absorption. Once in circulation, MOFs or their degradation products can accumulate in the liver, spleen, or kidneys, which are part of the reticuloendothelial system (RES).[98] Although short-term exposure is often well tolerated, long-term retention poses immunogenic or toxicological risks, especially in immunocompromised patients. Clearance mechanisms depend on size and solubility: particles <10 nm may be filtered by the glomerulus, while larger particles are taken up by phagocytes and eliminated via bile. Regulatory bodies such as the FDA require thorough biodistribution studies, long-term toxicity evaluations, and metabolism/excretion analysis before clinical approval.

Successful clinical translation of MOF products also requires well-defined therapeutic indications and delivery strategies. For skin-related conditions such as diabetic wounds, chronic ulcers, hypertrophic scars, or follicle regeneration, the efficacy, safety, and dosing strategy of MOF-based dressings must be rigorously validated. Batch consistency, degradability, drug release kinetics, and long-term stability are all necessary quality control endpoints. Since MOFs may not fully align with existing nanomedicine regulatory frameworks, proactive engagement with regulatory agencies is needed to develop or amend dedicated evaluation guidelines for MOF-based products.[99]

Despite the promising therapeutic potential of MOFs in skin regeneration, their clinical translation faces significant biosafety and regulatory hurdles, as outlined above. These challenges are not unique to MOFs but are shared—to varying degrees—by other established nanocarriers such as liposomes, polymeric nanoparticles, and dendrimers, all of which have navigated the FDA approval process with distinct advantages and limitations.[100] For instance, liposomes (eg, Doxil®) and PLGA-based nanoparticles (eg, Lupron Depot®) have achieved clinical success by leveraging well-characterized biodegradation pathways and scalable production methods, yet they struggle with low drug-loading capacity and limited stimulus-responsive release. Dendrimers, despite their precise molecular architecture, face toxicity concerns due to cationic surface charges and lacks large-scale clinical adoption.[101] In contrast, MOFs offer unparalleled structural tunability and high payload capacity but must address uncertainties in long-term metal ion biodistribution and industrial-scale reproducibility.[102] To objectively evaluate MOFs' competitiveness in skin applications, a systematic comparison with these alternative platforms is essential, focusing on key parameters such as drug-loading efficiency, release kinetics, biocompatibility, and regulatory readiness (Table 3). Such a comparison will not only highlight MOFs' unique value proposition but also identify critical gaps that require further research to meet translational standards.

MOFs Application in Skin Regeneration

Diabetic Infected Wounds

Chronic refractory wounds, particularly diabetic wounds and infected wounds, pose significant clinical challenges.[109] When infection complicates diabetic wounds, the vicious cycle of multiple pathological mechanisms substantially increases therapeutic difficulty. The hyperglycemic microenvironment induces vascular and neural impairments, leading to local ischemia, hypoxia, and compromised immune defenses that foster pathogen proliferation.[110] Treatment-resistant bacteria (eg, MRSA, Pseudomonas aeruginosa) readily form biofilms, creating physical barriers and metabolic resistance to antibiotics.[111] Concurrently, excessive oxidative stress and sustained release of pro-inflammatory cytokines in chronic inflammation suppress fibroblast activation and angiogenesis, trapping wounds in the inflammatory phase.[109] Moreover, diminished cellular repair capacity in diabetic patients impedes re-epithelialization and ECM remodeling, entrapping wounds in an "infection-inflammation-nonhealing" loop. This triad of multidrug resistance, persistent inflammation, and regenerative dysfunction renders conventional debridement and antibiotic therapies largely ineffective. Thus, comprehensive management of diabetic infected wounds necessitates a multifaceted approach encompassing meticulous wound microenvironment care, optimized glycemic control, rigorous infection control, debridement of devitalized tissue, and techniques promoting wound closure.[112]

In recent years, numerous reports on MOF applications for such complex wounds have been published, with their therapeutic advantages summarized in Table 4. Based on antibacterial mechanisms, MOF-based therapies can be categorized into four primary classes (Table 5). Nevertheless, the metallic components remain central to MOF functionality. Strategic modification of different metal centers enables tailored therapeutic approaches for infected diabetic wound management, as will be detailed in subsequent metal-specific discussions.

Zn-MOF

Zn, as the most prevalent metal for MOF fabrication, has been extensively reported in numerous studies, with Zn-based ZIF-8 representing the most common form.[122] One study developed a ZIF-8-based cascade catalytic antibacterial system co-loaded with glucose oxidase (GOx) and peroxidase-like bovine hemoglobin (BHb).[123] In this system, GOx consumes glucose to starve bacteria while generating hydrogen peroxide (H_2O_2), which is subsequently converted by BHb into hydroxyl radicals for bactericidal action. This "starve-and-kill" strategy effectively targets multidrug-resistant bacteria (Figure 2). The concomitant production of gluconic acid lowers environmental pH, enhancing peroxidase activity while further inhibiting bacterial growth. Notably, this nanoreactor demonstrates biodegradability and fecal excretion, ensuring biosafety.[123] In another Zn-based ZIF-8 design, quercetin (QCT)-loaded nanoparticles were incorporated into a self-crosslinking carboxymethyl chitosan (CMC)/tannic acid (TA) hydrogel through dynamic ionic and hydrogen bonds.[124] This system enables localized QCT delivery to diabetic wounds, correcting aberrant mitochondrial function and endoplasmic reticulum stress. The synergistic effects of Zn^{2+} (angiogenesis promotion), TA (ROS scavenging), and QCT collectively ameliorate oxidative stress and inflammation, significantly improving diabetic wound healing.[124]

Building on GOx-catalyzed H_2O_2 generation, precise H_2O_2 regulation becomes crucial, particularly given the characteristic pH fluctuations in infected wounds.[125] A study engineered injectable nanoreactor hydrogels by

Table 3 Comparison of MOF with Other Nanocarriers

Comparison Dimension	MOF	Liposome[103,104]	Polymeric Nanoparticle[105–107]	Dendrimer[101,108]
Structure & Properties	- Hybrid inorganic-organic framework, high surface area - Tunable size, diverse topologies	- Phospholipid bilayer structure - Typically 50–200 nm, low mechanical strength	- Polymer matrix - Size depends on matrix	- Highly branched 3D structure - Monodisperse, dense surface groups
Drug Loading Capacity	- High loading - Dual hydrophilic/hydrophobic loading	- Moderate - Hydrophilic in core, hydrophobic in bilayer	- Low-moderate - Physical entrapment or conjugation	- Low - Surface adsorption/conjugation
Release Control	- Responsive (eg pH) - Photo/thermal triggers (eg NIR)	- Passive diffusion	- Polymer degradation-dependent	- Surface group-mediated - Premature leakage
Biocompatibility	- Metal-dependent - Requires surface modification	- Excellent - Cationic types may hemolyze	- Mostly safe degradation	- High-generation cationic types cause membrane damage
Multifunctionality	- Intrinsic antimicrobial - Photothermal activity - Catalysis - Gas carriers (NO)	- Requires targeting ligands - Limited multifunctionality	- Targetable - Complex synthesis for multiple functions	- Easy surface modification- Low payload
Stability	- Variable aqueous stability - Silica coating improves stability	- Oxidation/fusion risks - Lyophilization required	- Physically stable - Long-term storage may aggregate	- Poor solution stability - Requires lyophilization
Scalability	- Hydro/solvothermal synthesis - Few industrial products	- Established methods - FDA-approved (Doxil®)	- Emulsion-solvent evaporation - Commercial PLGA products (Lupron Depot®)	- Iterative synthesis - No clinical-scale production
Clinical Status	- Preclinical - Limited long-term toxicity data	- Marketed	- Approved products	- Few clinical candidates (VivaGel®)

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Table 4 Advantages of MOF for Skin Application

Advantage	Explanation	Ref.
High Porosity and Large Specific Surface Area	The porous structure enables efficient loading of drugs, growth factors, or gas molecules (eg, nitric oxide), facilitating controlled and sustained release.	[113–115]
Tunable Pore Size and Functionality	Selection of metal ions and organic linkers allows customization of MOF pore size and surface chemistry to accommodate therapeutic molecules of varying sizes or tissue-targeting requirements.	[115]
Encapsulation and Protection of Active Agents	The porous framework shields drugs from enzymatic degradation or burst release, enhancing the stability of biomacromolecules (eg, VEGF, antibiotics).	[116]
Stimuli-Responsive Release	Triggered release in response to pH, enzymes, light, or magnetic fields (eg, acidic infection sites triggering antibiotic release) improves precision therapy.	[117]
Biocompatibility and Biodegradability	Certain MOFs (eg, Mg/Zr-based) are biodegradable, preventing systemic accumulation while exhibiting negligible toxicity to vital organs.	[118]
Multifunctional Integration	Simultaneous incorporation of antibacterial (Ag^+), pro-angiogenic (Cu^{2+}), and imaging (fluorescence/MRI) functions enables theranostic applications.	[119]
Antibacterial Activity	Metal ions (Ag, Zn) or loaded antibacterial agents (eg, NO) exert bactericidal effects via membrane disruption or reactive oxygen species generation.	[120]
Mechanical Reinforcement and Thermal Stability	Polymer composites enhance mechanical strength to withstand dressing changes, while maintaining structural stability during high-temperature sterilization.	[121]
Facilitated Gas Exchange and Moist Wound Environment	The highly porous structure promotes oxygen permeability and exudate absorption, while hydrogel integration maintains an optimal moist wound microenvironment.	[113]

Table 5 MOF Classification Based on Antibacterial Activity

Classification	Antibacterial Components	Antibacterial Mechanisms	Advantages	Disadvantages
Metal-centered antimicrobial agents	Ag^+, Zn^{2+}, Cu^{2+}, Fe^{2+} metal ions	- Bacterial membrane disruption - Enzyme/protein function interference - Reactive oxygen species (ROS) generation	Broad-spectrum antibacterial activity Sustained release	Potential cytotoxicity at high metal ion concentrations
Antimicrobial effects of organic ligands in MOFs	Carboxylic acids, porphyrins, imidazoles, phenols	- Direct pathogen killing - Photodynamic therapy (PDT) - Photothermal therapy (PTT)	Rapid onset High biocompatibility	Some ligands have narrow antibacterial spectrum
Antimicrobial-loaded MOFs	Encapsulated antibiotics/ nanoparticles (eg, Ag NPs)	- Sustained drug release for membrane disruption - Chemodynamic therapy (CDT) - Bacterial metabolism interference	Synergistic enhancement of efficacy Reduced drug resistance	Limited drug loading capacityPotential burst release
MOF composites for antibacterial treatment	MOF composites with fibers, hydrogels, patches	- Synergistic multiple mechanisms (PTT/PDT/CDT) - Physical barrier + chemical killing	High antibacterial efficiency Reduced recurrence rate	Complex preparation processHigher cost

encapsulating arginine (Arg) in porous Zn-MOF with electrostatically bound GOx (Arg@Zn-MOF-GOx nanoparticles, AZG-NPs), followed by physical crosslinking with chitosan/F127.[126] The system operates through three coordinated mechanisms: (1) GOx-mediated glucose depletion and acidic microenvironment creation, (2) pH-triggered Zn-MOF disintegration, releasing Arg to catalytically convert H_2O_2 into nitric oxide (NO), preventing H_2O_2 accumulation while promoting vasodilation, and (3) inflammation modulation through NO-mediated pathways.[126] This exemplifies how pH-responsive MOF decomposition can be strategically harnessed for wound therapy. Expanding beyond therapeutics, researchers have leveraged wound pH variations for diagnostic applications. A porphyrin-based MOF nanosystem was constructed through Zn-coordinated tetra(4-carboxyphenyl)porphyrin, forming rod-shaped nanostructures with pH-dependent fluorescence (intensity increasing with alkalinity).[127] The porous architecture permits rapid OH^- diffusion, enabling real-time wound pH monitoring (Figure 3). This diagnostic capability, coupled with photodynamic inactivation under spatial-temporal light stimulation, enables the nanorods to generate microbicidal ROS while sparing healthy tissues, achieving imaging-guided precision antimicrobial therapy.[127]

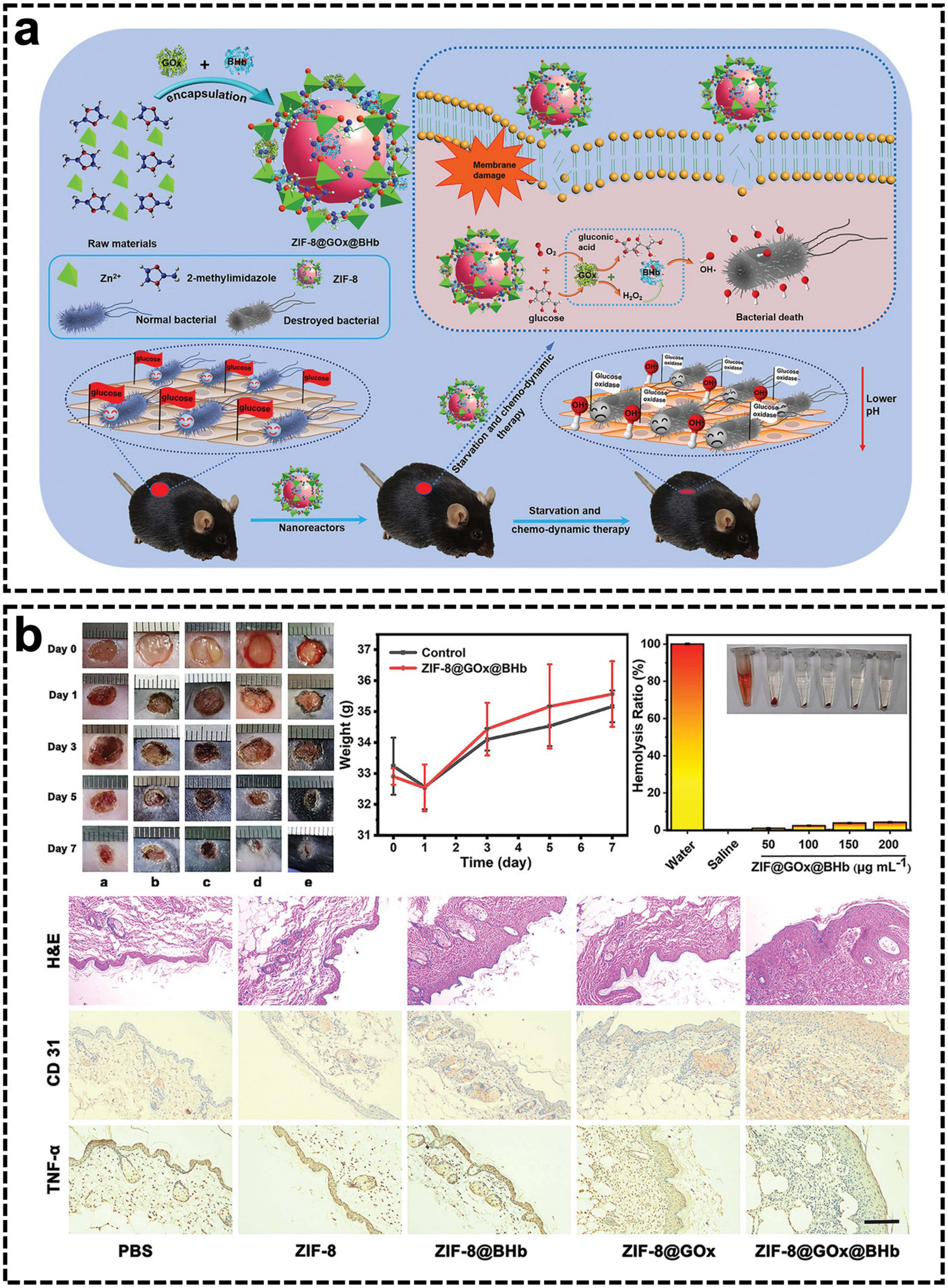

Figure 2 (**a**) Scheme of the preparation process of ZIF-8@GOx@BHb and its applications in treatment of wound infection in diabetic mice based on its cascaded catalytic activity; (**b**) In vivo treatment outcome based on starving and killing strategy (Reproduced with permission[123] Copyright © 2021, Wiley-VCH).

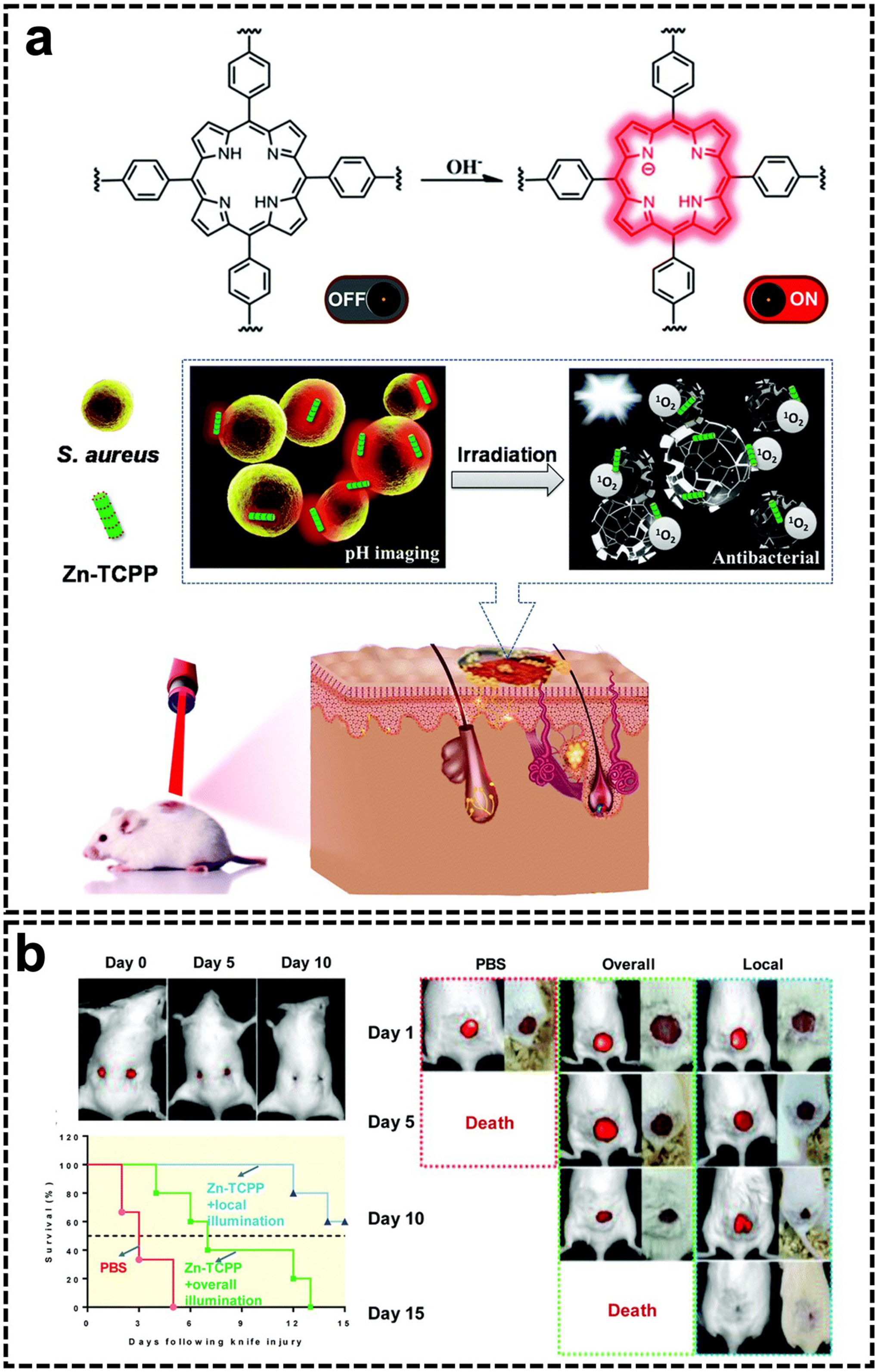

Figure 3 (**a**) Sensing and fluorescence changes of porphyrin-based MOF nanorods used in pH imaging and the precise suppression of bacterial infection in wounds; **(b)** Fluorescence images of the wound beds (Reproduced with permission[127] Copyright © 2021, The Royal Society of Chemistry).

Cu-MOF

Cu-based MOFs have also found extensive application in the treatment of diabetic infected wounds. Building upon design concepts similar to the aforementioned zinc-based MOFs,[126] researchers developed GOx-loaded Cu-MOF (Cu-MOF/GOx) and integrated it with a thermosensitive chitosan-arginine (CS-Arg) hydrogel to construct a multifunctional Cu-MOF/GOx-Gel hydrogel system.[128] In this system, GOx consumes glucose at the wound site to generate H_2O_2 and gluconic acid, initiating an efficient antibacterial cascade reaction that effectively prevents infection during the early stages of wound healing. The hydrogel gradually releases L-arginine (L-Arg), which is catalytically converted to NO by the locally generated H_2O_2, thereby promoting angiogenesis and collagen deposition to accelerate subsequent wound healing.[128]

Current research has evolved in two additional innovative directions beyond these conventional designs. The first approach involves modifying the paddlewheel structure of Cu-dimers in HKUST-1 to control the surface structure of Cu clusters while maintaining the overall crystallinity of the MOF through controlled calcination that gradually removes carboxyl groups from the Cu-dimers.[129] This process enables precise tuning of copper's asymmetric bond-order strain, local atomic structure, and electronic configuration. The resulting nanomaterial exhibits more exposed active sites and higher catalytic activity while retaining its ideal octahedral morphology after calcination at 250°C for 1 hour. Compared to the initial water-sensitive MOF, the modified version demonstrates significantly improved moisture stability and enhanced catalytic capacity, making it more suitable for infected wound applications. Similar structural optimization approaches have been reported for cobalt-based MOFs to compare the antibacterial effects of cubic versus dodecahedral morphologies (Figure 4a).[130] The second innovative direction focuses on developing more controllable diagnostic-therapeutic systems for wound monitoring. Researchers prepared Cu-MOF loaded with carbon dots (CDs) and GOx, which was then dispersed in a polyvinyl butyral (PVB) electrospinning solution and deposited onto wound surfaces using a handheld electrospinning device to form GOx/CDs@MOF nanofibers (NFs).[131] In the diabetic wound microenvironment, the GOx in GOx/CDs@MOF NFs continuously catalyzes physiological glucose to produce gluconic acid and H_2O_2. The generated gluconic acid lowers the system's pH and effectively enhances the peroxidase-like activity of Cu-MOF, converting H_2O_2 into •OH for bacterial killing. Furthermore, the GOx/CDs@MOF nanofibers inherit the pH-responsive fluorescent properties of CDs, enabling real-time wound monitoring through smartphone-captured fluorescence signals that are converted to RGB color values (Figure 4b).[131] In vivo experiments demonstrate that these multifunctional nanofiber dressings can accurately measure wound pH while significantly promoting wound healing. This MOF-based multifunctional nanofiber system provides a novel strategy for clinical diagnosis and treatment of diabetic infected wounds.

Other Monometallic MOF

Beyond Zn and Cu-based MOFs, various other monometallic MOFs have been explored for diabetic-infected wound applications. Mg-based MOFs represent a common alternative, though their standalone use often results in insufficient antibacterial efficacy.[132] One innovative approach combines antimicrobial peptide jelleine-1 with a magnesium ion/gallic acid MOF to create a multifunctional acellular matrix hydrogel.[133] This system demonstrates antioxidant, anti-inflammatory, and pro-angiogenic effects in diabetic wounds. The hydrogel effectively releases gallic acid in the acidic wound microenvironment, scavenges excess free radicals in vitro, and reduces inflammation levels in vivo by modulating M2 macrophage polarization.[133] Innovative dressing designs represent another strategy to enhance MOF therapeutic performance. Fe-based MOFs, as conventional metal materials, have been fabricated into microneedle arrays.[134] Unlike magnesium systems, these Fe-MOFs achieve satisfactory antibacterial effects without requiring additional antimicrobial agents.[135] A study encapsulated GOx within Fe-doped ZIF structures, constructing hierarchically porous MOFs through carefully controlled tannic acid etching processes.[134] The microneedle platform enables uniform deep tissue delivery, where the encapsulated GOx consumes excess glucose in infected diabetic wounds to generate gluconic acid and H_2O_2. The latter is catalytically converted by Fe^{2+} into antibacterial •OH radicals, providing antimicrobial effects without inducing drug resistance.[134] Zr-based MOFs have also been incorporated into microneedle systems. Researchers encapsulated dimethyloxalylglycine (DMOG), a prolyl hydroxylase competitive inhibitor that promotes angiogenesis in chronic wounds,[136] within Zr-MOF nanoparticles.[137] These nanoparticles were co-loaded with the antibiotic meropenem (MEM) into dissolvable microneedle patches fabricated from hyaluronic acid (HA). Upon skin penetration, the

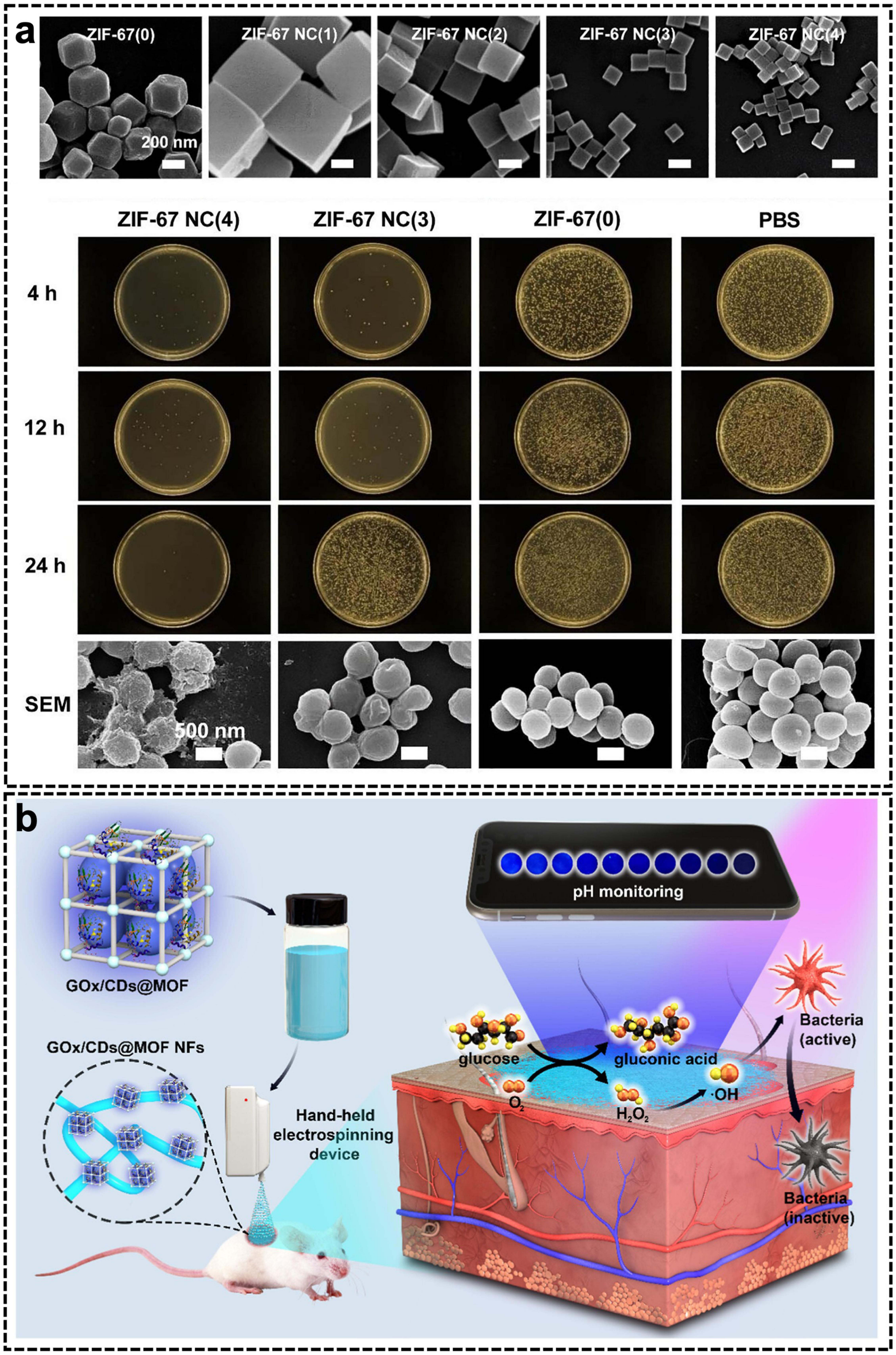

Figure 4 (a) Characterizations of various ZIF-67 and their antibacterial activity (Reproduced with permission;[130] Copyright © 2022, Elsevier); **(b)** Schematic illustration of GOx/CDs@MOF NF dressing for visual monitoring and antibacterial treatment of diabetic-infected wounds (Reproduced with permission;[131] Copyright © 2023, American Chemical Society).

microneedle tips rapidly dissolve, efficiently delivering both antimicrobial agents and DMOG-loaded MOFs into wound tissue.[137] Under laser irradiation, the system converts O_2 into singlet oxygen ($^1O_2$), synergizing with MEM to achieve potent chemo-photodynamic antibacterial effects while reducing antibiotic doses by tenfold. Furthermore, the gradual degradation of MOFs enables sustained DMOG release, promoting epithelialization and neovascularization to accelerate chronic wound healing.[137] These studies demonstrate how alternative metal centers in MOFs – including Mg, Fe, and Zr – can be engineered through either cargo combination or advanced delivery platforms to address the multifaceted challenges of diabetic wound healing. The emerging designs highlight three key development trends: (1) synergistic combination therapies overcoming single-agent limitations, (2) precision delivery systems enhancing treatment depth and uniformity, and (3) responsive material systems adapting to wound microenvironmental cues. Continued innovation in metal selection and composite design will further expand MOF versatility for personalized wound care solutions.

The integration of light irradiation for photodynamic therapy (PDT) has become a prevalent treatment approach across various metal-based MOF systems.[138] For more clinically convenient applications, visible light-activated systems have been developed. Using tetrabutyl titanate and 2-aminoterephthalic acid (NH_2-BDC) as precursors, researchers synthesized visible-light-responsive titanium (Ti)-MOF via the hydrothermal method.[139] This Ti-MOF was then loaded with metformin (Met) and encapsulated within a dynamically crosslinked hydrogel composed of polyvinyl alcohol (PVA), sodium alginate (SA), and borax (Met/MOF(Ti)@gel). The phenylboronic ester bonds endow the hydrogel with excellent adhesiveness, self-healing properties, and shape adaptability, enabling optimal coverage of irregular wound geometries to maximize therapeutic efficacy. This dual-responsive dressing to both acidic pH and H_2O_2 rapidly releases Ti-MOF and Met at the wound site. The liberated Ti-MOF becomes activated under visible light to efficiently catalyze H_2O_2 decomposition into antibacterial ·OH, while Met helps regulate both local and systemic glucose levels.[139]

Bimetallic MOF

Bimetallic MOFs demonstrate distinct advantages over monometallic MOFs, primarily in terms of synergistic effects, structural tunability, and functional diversity.[140] By incorporating two distinct metal nodes, bimetallic MOFs leverage electronic interactions between metals like charge transfer or valence complementarity to optimize the catalytic performance of active sites, thereby exhibiting enhanced activity and selectivity in applications such as redox reactions, gas adsorption, or organic transformations.[141,142] Moreover, the synergistic interplay of bimetallic systems can improve material stability. For instance, one metal may provide structural support, while the other facilitates catalysis, thereby delaying the deactivation of active sites.[143] Structurally, bimetallic MOFs enable more flexible ligand coordination modes, allowing the formation of topologies unattainable with monometallic systems, which in turn modulates pore size and specific surface area to enhance adsorption capacity for target molecules such as CO_2 or H_2.[144] Functionally, integrating two metals combines their distinct properties, enabling multifunctional designs, such as materials that simultaneously possess catalytic and sensing capabilities.[145] Consequently, bimetallic MOFs exhibit significantly broader application potential than monometallic systems, particularly in fields like biomedicine.

Among these, Zn-based MOFs remain the most prevalent. One study developed a Cu nanozyme supported by ultrasmall carbon dots (Cu/C-dots) with high antioxidative activity.[146] The researchers then utilized Cu/C-dots as ligands and Zn^{2+} as the core metal to construct an integrated nanozyme-MOF.[146] The Cu/C-dots exhibited excellent oxidase-like activity, protecting biological systems from ROS damage while suppressing the expression of TNF-α and IL-1β. Zn^{2+} also demonstrated strong antibacterial activity. This integration strategy prevents nanozyme aggregation, enhances biocompatibility, slows the degradation of ZIFs, and enables on-demand release of Cu/C-dots and Zn^{2+} for controlled nanozyme delivery. The system was further combined with ZIF-8 to form a ZIF-Cu/C-dots nanocomposite.[146] Alternatively, another study co-embedded GOx and quasi-amorphous Fe_2O_3 into Zn-MOF nanoparticles to achieve cascade enzymatic activity.[147] These nanoparticles consume glucose at wound sites, generating H_2O_2 and gluconic acid via GOx catalysis. Subsequent nanoparticle degradation releases Zn^{2+}, which synergizes with the exposed quasi-amorphous Fe_2O_3 to catalyze H_2O_2 into ·OH, enabling potent antibacterial therapy enhanced by the low-pH micro-environment from gluconic acid and the typical pH range (≈4.5–6.5) during bacterial infection. Concurrently, during the relatively higher pH, the nanoparticles can scavenge ROS and alleviate hypoxia by catalyzing H_2O_2 to produce O_2. The resulting oxygen supply promotes mature collagen formation and fibroblast deposition.[147] Notably, damaged pancreatic islets exhibited recovery, including improved glucose tolerance and enhanced insulin secretion. This effect may arise from Zn^{2+} supplementation via the multifunctional hydrogel, which suppresses the expression of zinc transporter 8 (ZnT8, an autoantigen), thereby inhibiting immune activation of the islets.

More sophisticated designs have also been explored in Zn-based bimetallic MOFs, representing cutting-edge advancements. A hybrid strategy combining solvent treatment and electrostatic adsorption was employed to construct a maltodextrin-loaded MOF-on-MOF (ZIF-67 core, ZIF-8 shell) "all-in-one" therapeutic platform (Figure 5).[148] First, Co^{2+} was assembled with imidazole ligands to form the ZIF-67 core; subsequently, Zn^{2+} was coordinated with the imidazole ligands on ZIF-67 to generate a ZIF-8 shell, yielding a core-shell ZIF-8@ZIF-67 structure. When bacteria invade wounds, maltodextrin acts as a bacterial attractant, where bacteria-secreted acidic metabolites trigger the degradation of ZIF-8 and ZIF-67, releasing Zn/Co ions to eradicate most bacteria. Simultaneously, the released Zn/Co ions restore phagocytic and xenophagic functions in M1 macrophages, eliminating residual bacteria and exhibiting superior antibacterial efficacy. Subsequently, valence transitions between Co^{2+} and Co^{3+} scavenge both extracellular and intracellular ROS, driving the polarization of M1 macrophages toward the M2 phenotype. The cytokines secreted by M2 macrophages, synergizing with Zn/Co ions, upregulate neurovascular regeneration, accelerating wound healing in diabetic infection models.[148] Concurrently, Zn-based bimetallic MOFs have been investigated for wound monitoring. A multifunctional Janus membrane was developed by incorporating Zn-MOFs, Eu-MOFs, and phenol red into nanofibers for diabetic wound management. This Janus membrane features directional water transport to rapidly remove excess exudate in diabetic patients (Figure 6).[149] Zn-MOFs establish an antibacterial environment during membrane fabrication to prevent wound infections, while phenol red (pH indicator) and Eu-MOFs (H_2O_2-responsive fluorescent material) are integrated into the nanofiber membrane to monitor wound status. A smartphone with RGB algorithms enables real-time wound monitoring via this multifunctional dressing.[149]

In iron-based bimetallic MOFs, Prussian blue (PB) particles were prepared hydrothermally using potassium ferricyanide as the raw material and polyvinylpyrrolidone (PVP) as the template control agent.[150] The in situ uniform growth of gold nanoclusters on PB particles presents significant challenges.[150] To address this, for the preparation of PB-Au, sodium citrate and tannic acid were employed as dual reducing agents and template regulators, respectively, to control gold deposition on PB. Tannic acid served as a linker, connecting gold particles to PB through coordination interactions between catechol groups and metal atoms. Subsequently, the obtained PB-Au spheres were immobilized on a hydrogel. The resulting composite exhibits antibacterial capability, peroxidase-like activity, catalytic stability, and photostability. Significant therapeutic effects were achieved at low photothermal temperatures below 60°C, demonstrating enhanced photothermal capability and ROS catalytic activity.[150] Due to the presence of iron, the MOF shows high relevance to ferroptosis, and leveraging this pathway may enable improved treatment of diabetic infected wounds.[151] Under an acidic biofilm environment, platinum-loaded iron-based MOF nanoparticles (Pt@FeMOF NPs) generate reactive oxygen species through synergistic Fenton reactions, thereby eliminating drug-resistant bacteria and their biofilms.[152] Furthermore, based on transcriptomic results and ferroptosis marker evaluation, Pt@FeMOF NPs were found to induce bacterial ferroptosis via lipid peroxidation, GSH depletion, iron overload, and arginine metabolism disruption. Additionally, Pt@FeMOF NPs may restore angiogenesis by inhibiting oxidative stress-mediated endothelial cell senescence in the microenvironment, thereby promoting vascular repair. Finally, Pt@FeMOF NPs were loaded into GelMA cryogel to further enhance the hemostatic performance and exudate the absorption capacity.[152] This ferroptosis-like antibacterial strategy may provide novel insights for treating drug-resistant bacterial infections and combating biofilm-associated infections.

The combination of Mn and Cu leverages Mn's capacity to decompose H_2O_2, thereby addressing the issue of excessive H_2O_2 generation previously observed in Cu-GOx coupled systems.[153] The Cu-MOF@MnO_2 nanocomposite was functionalized with GOx through physical adsorption to establish an efficient cascade reaction system. Subsequently, quaternized chitosan (QCS) was employed to encapsulate the nanozyme, preventing premature degradation of GOx.[153] The GOx loaded on the nanozyme catalyzes glucose decomposition, generating H_2O_2 and gluconic acid. The Cu-MOF then facilitates a Fenton-like reaction, promoting H_2O_2 decomposition to yield highly antibacterial •OH, achieving antimicrobial effects through chemodynamic therapy (CDT). Furthermore, MnO_2 decomposes H_2O_2 to produce oxygen, which further accelerates wound healing.[154] Alternatively, antimicrobial agents can be incorporated to mitigate issues associated with H_2O_2-based antibacterial strategies. A porphyrin-based bimetallic MOF featuring Mn-N4 active sites was synthesized via a coordination network between Mn-metalloporphyrin and Zr6 clusters, mimicking catalase (CAT)-like nanozyme activity.[155] By further integrating the MOF-nanozyme with the natural antimicrobial agent chlorogenic acid

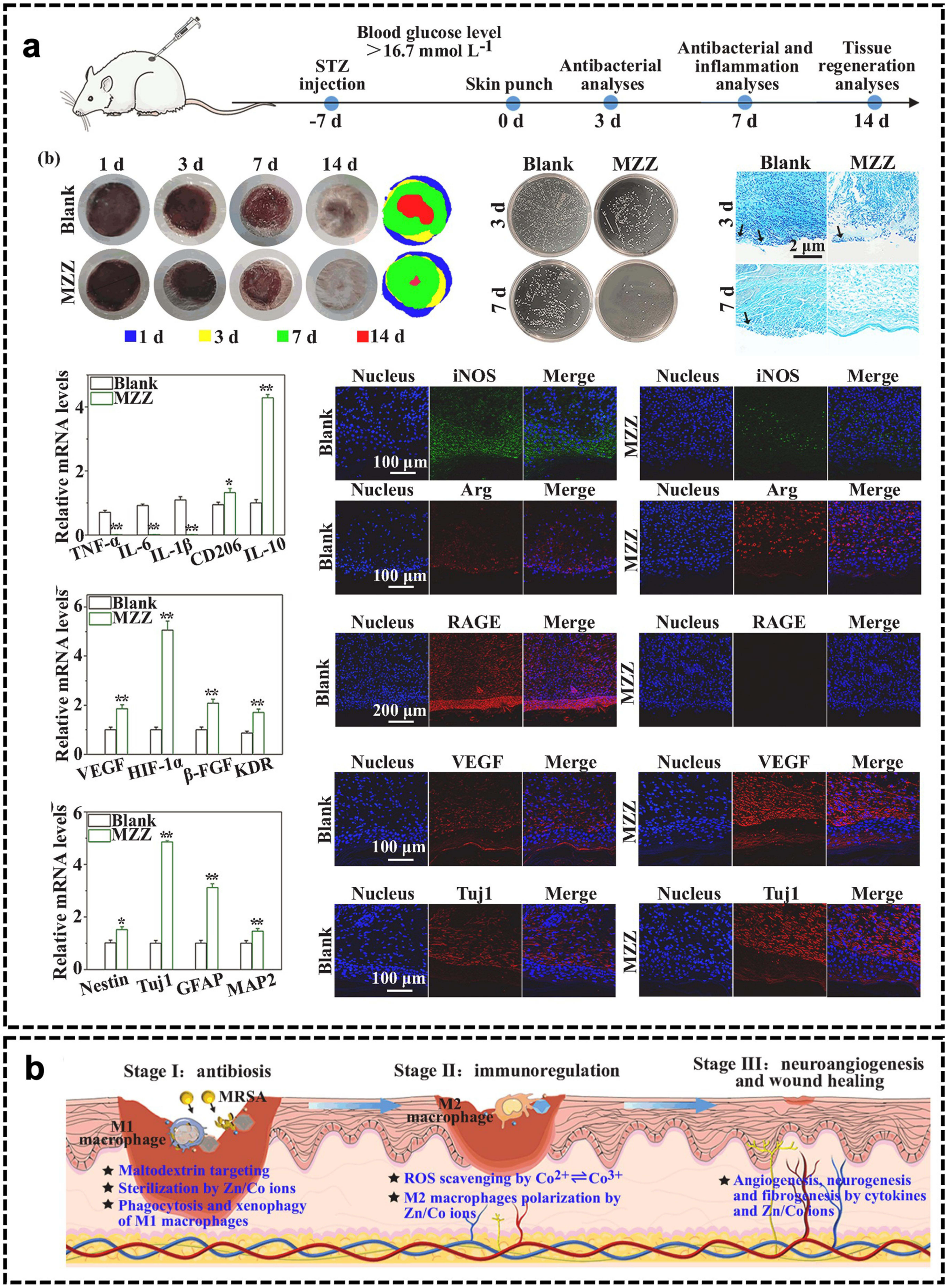

Figure 5 (a) In vivo application of MOF-on-MOF platform; **(b)** MOF-on-MOF reduced bacterial infection, relieved inflammation and enhanced neuroangiogenesis for diabetic infected wound repair (Blue arrows denote progression to subsequent therapeutic stages) (Reproduced with permission;[148] Copyright © 2025, Elsevier).

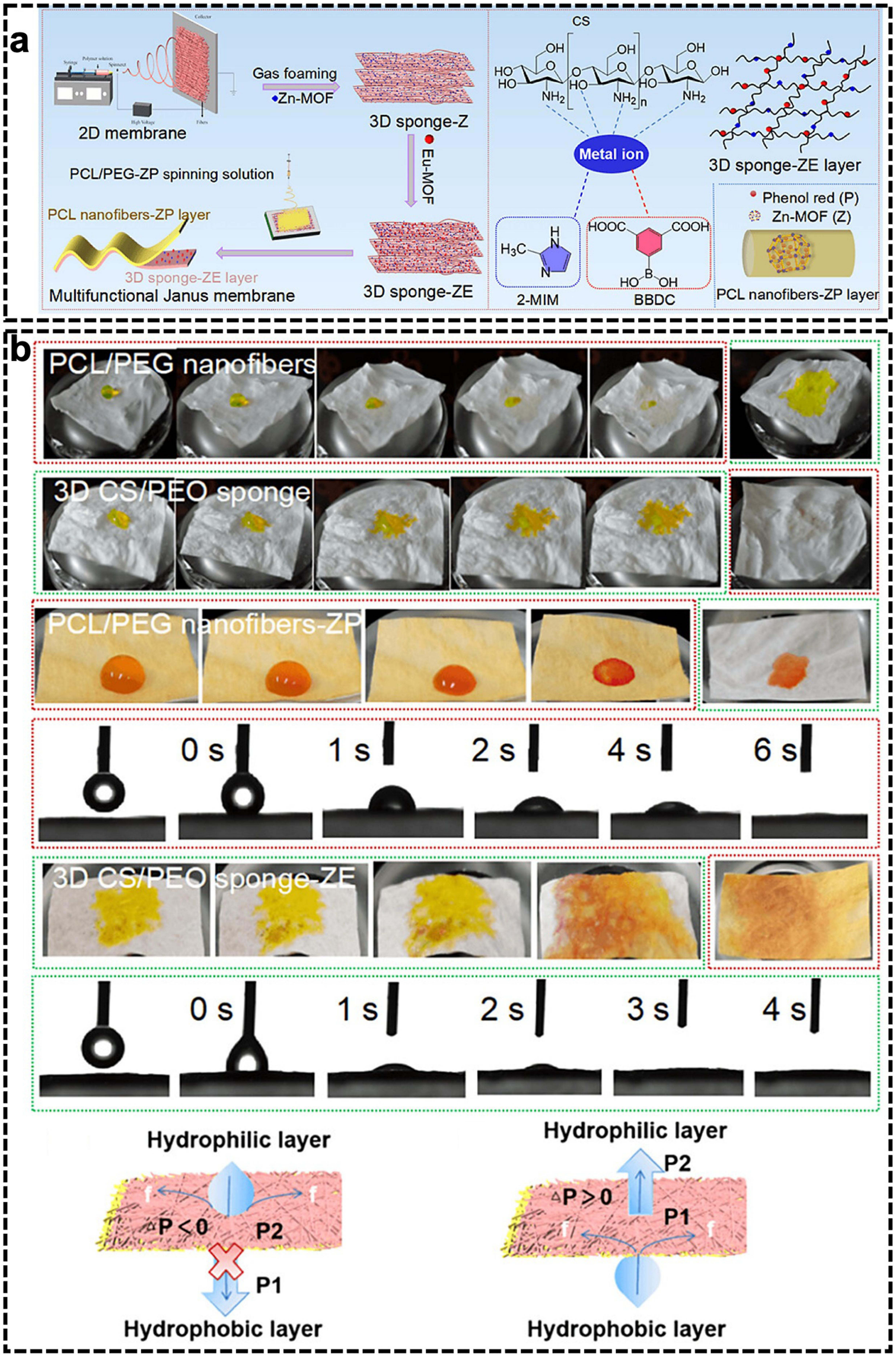

Figure 6 (a) Preparation of the multifunctional Janus membrane; **(b)** Directional water transport capacity of multifunctional Janus membrane (Reproduced with permission;[149] Copyright © 2024, American Chemical Society).

(CGA), a biocompatible genipin (GP)-crosslinked chitosan-based hydrogel was successfully developed as a foundational scaffold. GP-mediated crosslinking endowed the hydrogel with injectable, adhesive, and self-healing properties. During the catalytic process of the CAT-like nanozyme, accumulated H_2O_2 in diabetic wounds is scavenged to generate oxygen, alleviating oxidative stress and hypoxia.[156] As a natural antimicrobial agent, CGA provides a mild yet effective strategy to inhibit bacterial proliferation and prevent antibiotic resistance.[155]

In summary, diabetic infected wounds present complex clinical challenges due to persistent hyperglycemia, microbial resistance, chronic inflammation, and impaired tissue repair. MOFs have emerged as versatile platforms to address these issues through tailored antibacterial, anti-inflammatory, and pro-regenerative strategies. Zn-MOFs, such as ZIF-8, dominate therapeutic designs, enabling glucose-deprivation ("starve-and-kill") tactics,[123] pH-responsive drug release,[126] and real-time diagnostic monitoring via fluorescence.[127] Cu-MOFs enhance catalytic cascades (eg, NO generation) and integrate with smart dressings for infection control and angiogenesis promotion.[130] Innovations in bimetallic MOFs (eg, Zn/Cu, Fe/Mn) further amplify synergistic effects, combining ROS scavenging, ferroptosis induction, and macrophage polarization to resolve inflammation and biofilm resistance.[146,147] Advanced delivery systems—microneedles,[137] hydrogels,[156] and Janus membranes[149]—ensure precise spatiotemporal control over therapeutic actions while enabling non-invasive wound monitoring. Light-activated MOFs (eg, Ti-based)[139] and nanozyme hybrids (eg, MnO_2-Cu)[153] exemplify multifunctional designs that adapt to dynamic wound microenvironments. Collectively, MOF-based therapies transcend conventional antibiotics by simultaneously targeting infection, oxidative stress, and tissue regeneration, offering a paradigm shift in managing diabetic wounds. Future directions emphasize personalized combinatorial approaches, leveraging metal-ligand chemistry and responsive material engineering to break the "infection-inflammation-nonhealing" cycle.

Pathological Scar

Conventional treatment of pathological scars typically involves a combination of corticosteroid injections, silicone therapy, and pressure therapy.[157] However, most of these treatments fail due to inefficient scar suppression, recurrent scarring, and lack of patient compliance. MOFs demonstrate promising potential in scar therapy, primarily attributed to their precisely tunable drug delivery capacity and multifunctional synergistic effects. The high porosity and modifiable surfaces of MOFs enable the loading of anti-fibrotic drugs and subsequent localized sustained release, thereby targeting key pathways in scar formation. Simultaneously, metal ions released from Zn- or Cu-based MOFs can modulate the wound microenvironment by attenuating excessive inflammatory responses and oxidative stress, effectively inhibiting abnormal activation of myofibroblasts and collagen deposition. Furthermore, the photothermal or photodynamic properties of MOFs allow for on-demand therapy when combined with external stimuli, further optimizing the scar repair process. These distinctive characteristics position MOFs as a novel class of intelligent materials capable of overcoming the limitations of conventional scar treatments.

Unlike open wounds, hypertrophic scars (HS) present an intact epidermal barrier, making transdermal delivery of MOFs a significant therapeutic challenge. Two major obstacles severely limit treatment efficacy: low transdermal penetration rates and overexpression of intracellular GSH. Innovative solutions have emerged to address these limitations, including the utilization of low Young's modulus extracellular vesicles (EVs) for stratum corneum penetration. The RGD-modified cucumber-derived EVs coupled with Cu-MOFs were designed for PDT-mediated HS treatment. These EVs exhibit exceptional deformability due to their low Young's modulus, enabling them to overcome the dense stratum corneum barrier and significantly enhance transdermal delivery efficiency. Notably, the RGD targeting peptide specifically binds to $\alpha 1\beta 1$ integrins on HS fibroblast membranes, resulting in high accumulation efficiency of MOF at HS sites. Under near-infrared laser irradiation, this system generates abundant ROS, inducing apoptosis in hyperproliferative fibroblasts. Furthermore, the Cu-MOFs interact with local GSH, leading to GSH depletion and substantially enhanced PDT efficacy.[158] However, additional challenges persist, including low transdermal delivery rates of photosensitizers in scar tissue and PDT-induced protective autophagy, which significantly diminish therapeutic outcomes. To overcome these barriers, researchers have developed microneedle patches (MNPs) as a convenient transdermal delivery solution.[12] A photosensitizer with photocatalytic properties was designed and synthesized using Cu-MOFs, which were then co-loaded with the autophagy inhibitor chloroquine (CQ) into high-mechanical-strength MNPs for transdermal delivery. These functionalized MNPs effectively deliver both the photosensitizer and CQ deep into hypertrophic scar tissue. Under high-intensity visible light irradiation, autophagy inhibition increases ROS levels. This multifaceted approach successfully overcomes obstacles in PDT and significantly enhances anti-scarring effects. In vitro studies demonstrate that the combined treatment downregulates type I collagen expression and TGF-β1 levels, reduces the LC3II/I ratio (an autophagy marker) while upregulating P62 expression.[159]

Recent years have been witnessed expanding applications of microneedle delivery systems in scar treatment beyond Cu-MOF formulations, with researchers developing various innovative delivery strategies. A recent discovery revealed that hypertrophic scar fibroblast (HSF) membranes possess homologous targeting properties, leading to the development of an active targeted drug delivery system (Figure 7). This system involves encapsulating quercetin (QUE) within a carbonate-diester-crosslinked cyclodextrin metal-organic framework (CDF), coating it with HSF membranes (QUE@HSF/CDF), and subsequently incorporating it into dissolvable MNP. This biomimetic nanodrug delivery platform demonstrates enhanced therapeutic efficacy against hypertrophic scars by simultaneously regulating both Wnt/β-catenin and JAK2/STAT3 signaling pathways, effectively reducing expression of type I and III collagen in scar tissue.[160] Further innovations emerged from observations that myofibroblasts derived from hypertrophic scars exhibit a high-iron state, showing particular susceptibility to ferroptosis induction. Researchers developed a pH-responsive self-assembled nanoplatform by encapsulating silver nanoclusters (AgNCs) and the herbal compound trigonelline (TRG) within ZIF-8 for synergistic ferroptosis-based scar therapy. The resulting composite demonstrates excellent biocompatibility while undergoing pH-dependent degradation specifically within myofibroblasts. The ZIF-8 framework enhances lipid ROS generation and depletes intracellular GSH, while AgNCs further consume GSH and TRG inhibits glutathione peroxidase (GPX4) activity, collectively inducing potent ferroptotic effects. When loaded into gelatin methacryloyl (GelMA)-based microneedle patches, this MOF nanocomposite exhibits remarkable anti-scarring efficacy in rabbit ear models, significantly reducing scar elevation index, collagen density, and α-SMA expression.[161]

These advances highlight the evolution of MOF-based scar therapies toward more sophisticated targeting mechanisms, including MNP, homologous HSF membrane-mediated delivery, and ferroptosis induction while integrating natural

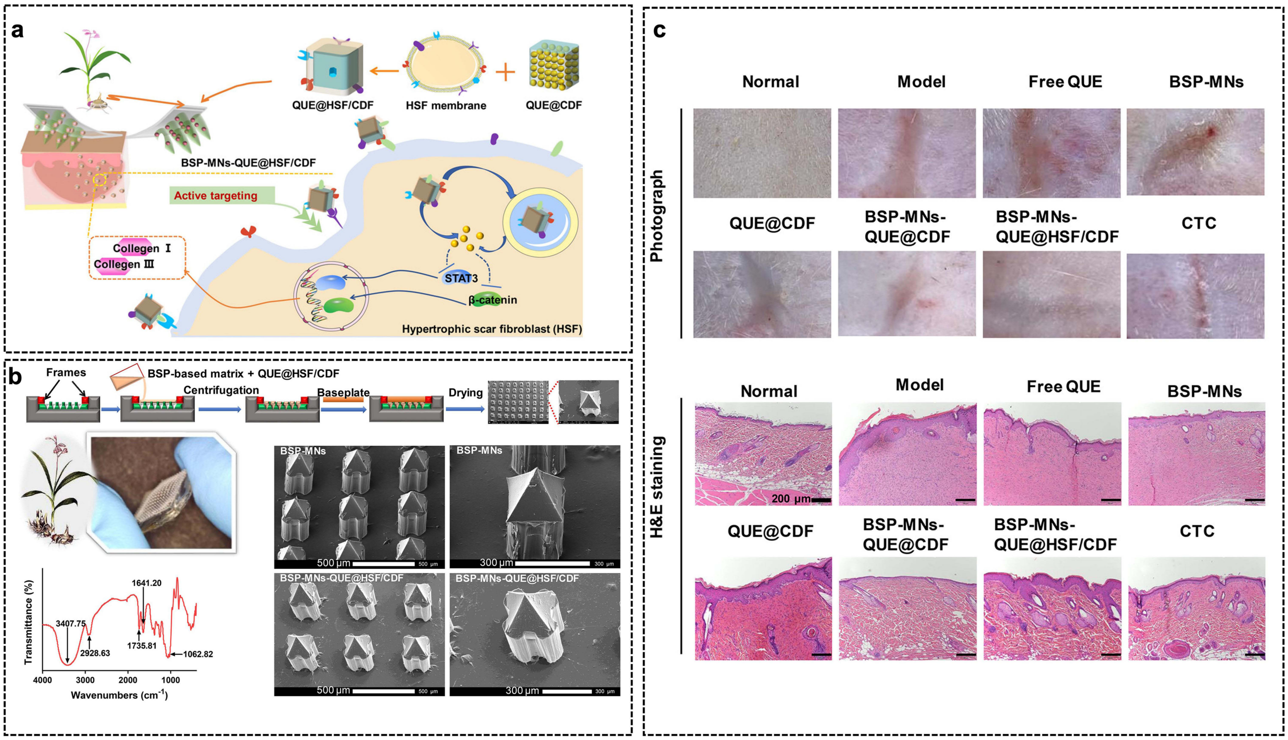

Figure 7 (**a**) Schematic illustration of fabrication and administration of BSP-MNs-QUE@HSF/CDF; (**b**) Characteristics of the fabricated microneedles; (**c**) Rats' HS tissues analysis after being treated with the tested preparations (Reproduced with permission;[160] Copyright © 2021, American Chemical Society).

compounds with nanotechnology for enhanced therapeutic outcomes. The successful translation of these systems from bench to animal models underscores their potential to address clinical challenges in scar management, particularly for cases resistant to conventional treatments. Future research should focus on optimizing release kinetics and expanding the therapeutic window for clinical application. Currently, research progress has primarily focused on hypertrophic scars, while more severe pathological scarring, such as keloids, remains unexplored to the best of our knowledge. This represents a significant gap in the field of MOF-based scar therapy, as keloids differ fundamentally from hypertrophic scars in their biological behavior and clinical management challenges.

Hair Regeneration

MNP represents not only a drug delivery approach applicable to scar treatment but also enables deep transdermal delivery for promoting hair regeneration. A novel Zn glycyrrhizinate formulation was developed by adsorbing glycyrrhizic acid (GA) into ZIF-8, followed by the fabrication of a bicontinuous microneedle patch for simultaneous transdermal delivery of GA@ZIF-8 and monitoring of Zn^{2+} in local tissues. The dissolvable microneedles serving as drug delivery units were composed of hyaluronic acid, while the swelling hydrogel microneedles functioning as diagnostic units were fabricated through dual crosslinking of N-acryloyl glycinamide and α-methacrylic acid, hybridized with Eu^{3+} and terpyridine (TPy). The GA@ZIF-8-loaded microneedles completely dissolved within 2 minutes, ameliorating cyclophosphamide-induced hair follicle degeneration in mice by reducing $CD8^{+}NKG2D^{+}$ T cell infiltration, inhibiting JAK receptor activation, and decreasing IL-15 and IFN-γ levels. Furthermore, as sensing components, the microneedles rapidly absorbed water and swelled upon skin penetration, emitting red fluorescence under 365 nm wavelength. Zn^{2+} in tissue fluid competed with Eu^{3+} in the TPy-Eu^{3+} complex and coordinated with Tpy, thereby inducing fluorescence changes. Notably, the system detected Zn^{2+} concentrations without interference from metal ions such as Na^{+}, K^{+}, Mg^{2+}, and Ca^{2+}, demonstrating its potential as a real-time chemical sensor for Zn^{2+} (Figure 8).[162] As one of the most commonly used MOF metals, Zn's applications extend beyond this scope. Curcumin and Zn ions were incorporated into a MOF, which was then encapsulated with γ-polyglutamic acid (γ-PGA) to create soluble Zn-MOF microneedle patches for promoting hair growth under various conditions. The Zn-MOF protected DPCs from apoptosis induced by Zn deficiency and oxidative stress. Moreover, it upregulated genes associated with DPC proliferation and Wnt/β-catenin signaling activation (CCND1, AMER3, LEF1, DKK1) while downregulating genes related to apoptosis (Caspase-3, Caspase-9) and androgen metabolism (HSD17B2, SRD5A1). Experimental results demonstrated accelerated wound healing and enhanced hair growth in trauma models, exhibiting broad-spectrum therapeutic effects against the complex mechanisms of scalp alopecia, including zinc deficiency, ROS infiltration, and poor cell growth, with confirmatory evidence.[163]

Potassium (K)-based crosslinked cyclodextrin-MOF (CD-MOFs) have garnered attention in hair regeneration applications. The biologically safe natural product cedrol demonstrates synergistic effects when combined with minoxidil, thereby enhancing medication safety by significantly reducing the clinical dosage of minoxidil. Researchers designed CD-MOFs as hair follicle delivery vehicles, where γ-cyclodextrin in the carrier was covalently crosslinked with diphenyl carbonate to prevent rapid degradation in aqueous environments. This improved nano-carrier achieved a drug loading capacity of 25% and enhanced drug delivery to hair follicles through a ratchet effect while increasing drug uptake by human DPC via endocytic pathways primarily mediated by lattice proteins, energy-dependent active transport, and lipid raft-dependent mechanisms. The system significantly improved cell viability, proliferation, and migration capacity, thereby markedly enhancing the therapeutic effect against androgenetic alopecia. In this combination, cedrol primarily inhibits 5α-reductase and activates the Shh/Gli pathway, while minoxidil upregulates VEGF, downregulates TGF-β, and activates the ERK/AKT pathway.[164] This drug combination offers a novel therapeutic strategy for androgenetic alopecia, with the newly developed crosslinked CD-MOF proving to be a promising hair follicle delivery vehicle. To address moisture sensitivity challenges, researchers developed CD-MOFs as targeted hair follicle delivery systems by modifying the MOFs with stearic acid (SA) to form a protective hydrophobic layer on the framework surface while conferring additional hair growth-promoting effects. The newly discovered biologically safe natural product cardamonin (CAR) was encapsulated within SA-MOFs (CAR@SA-MOF) to enhance its therapeutic efficacy against androgenetic alopecia. The surface-engineered nanoparticles of SA-modified CD-MOFs prevented rapid hydration and disintegration in water, thereby improving drug release and follicular deposition.[165] The SA modification also promoted proliferation of human dermal papilla cells, regulated keratinocyte growth factor, and activated key signaling pathways.

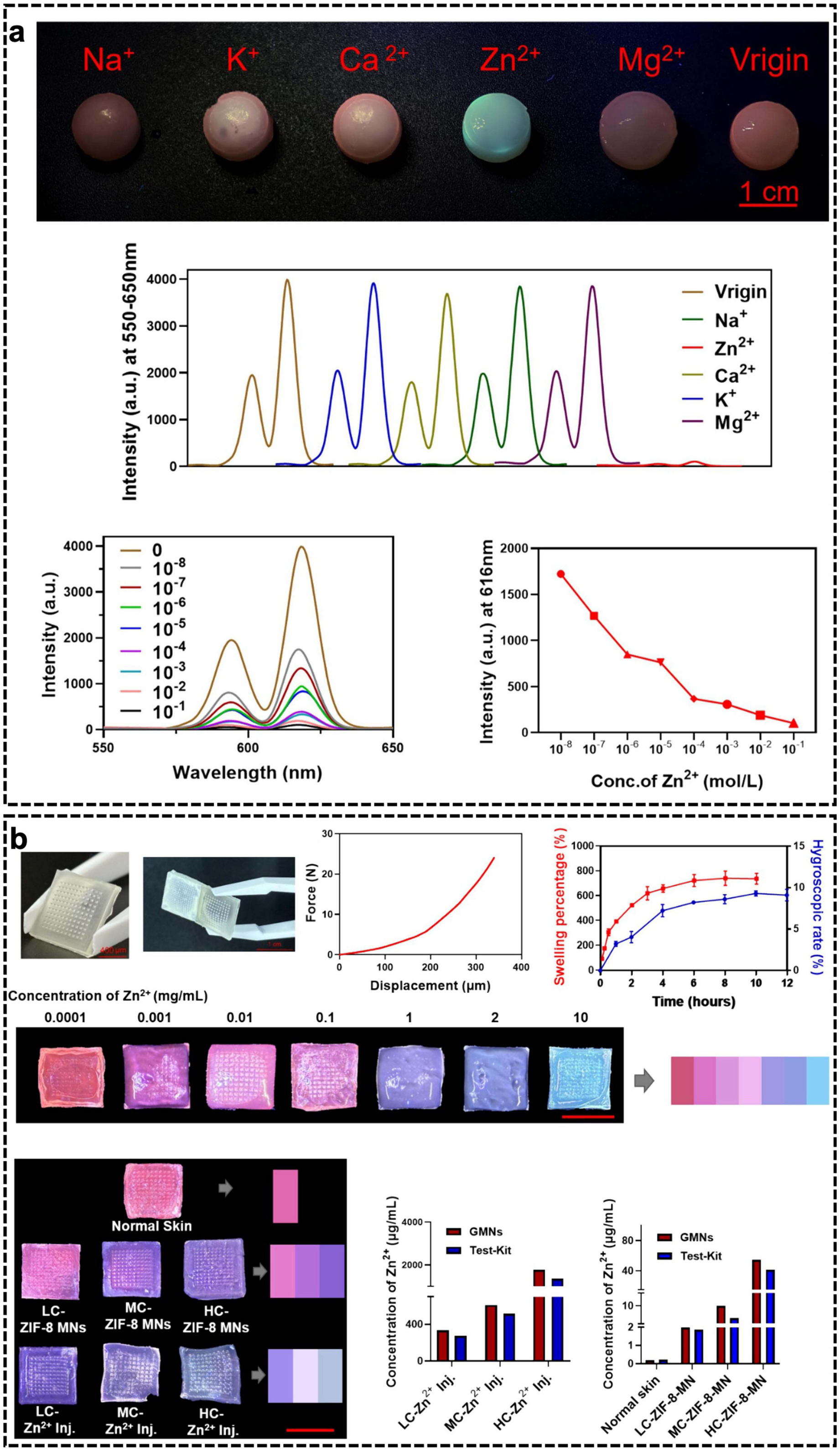

Figure 8 (**a**) Sensitivity of P(NAGA-co-MAAc)/Eu/TPy in response to Zn^{2+}; (**b**) Characterization of the sensor unit (GMNs) of the dual-continuous microneedle patch (Reproduced with permission;[162] Copyright © 2024, Elsevier).

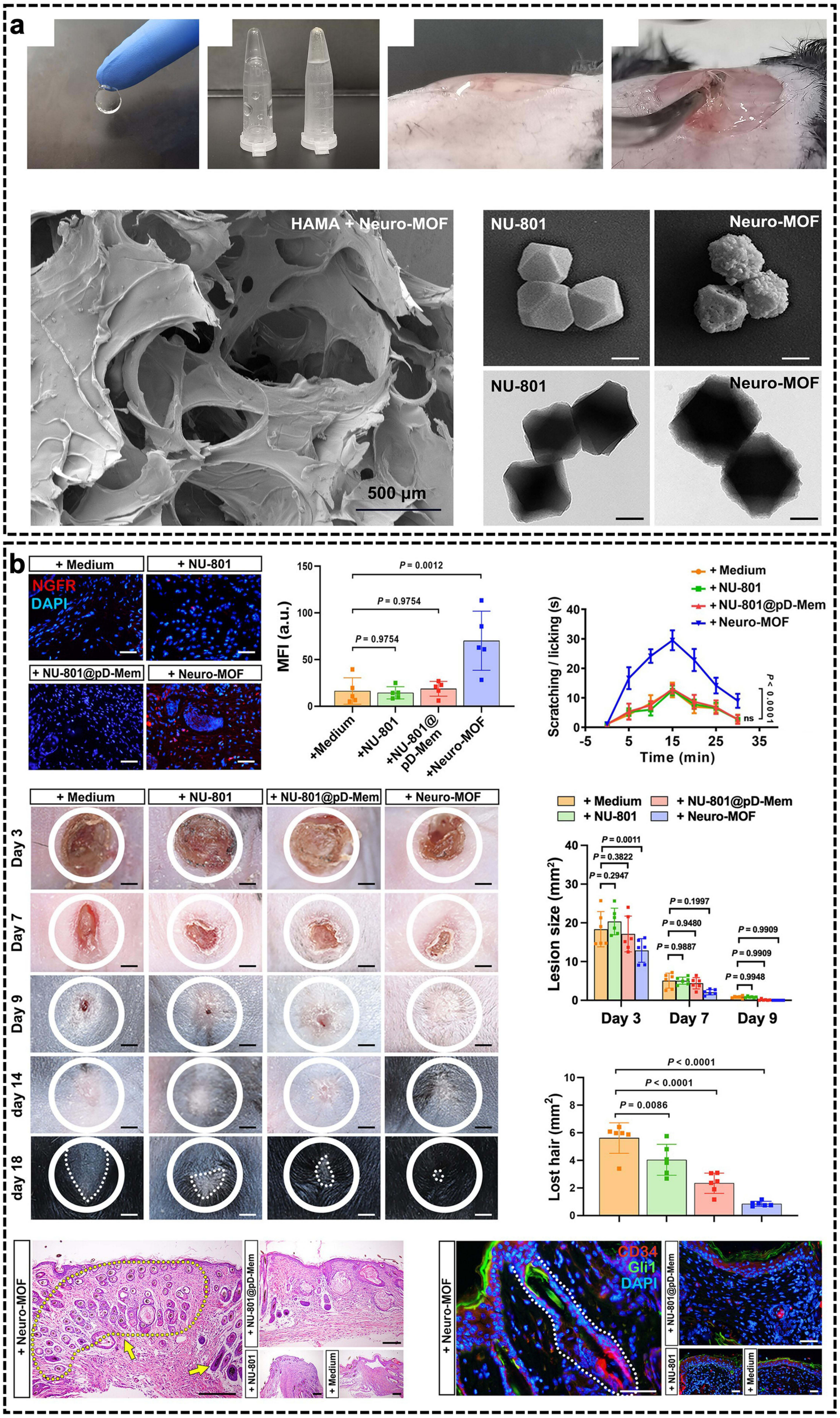

Figure 9 (**a**) Characterization of neuro-MOF; (**b**) Therapeutic effect of neuro-MOF on wound for hair regeneration (White dotted lines on gross specimens demarcate hairless regions; Yellow dotted lines and arrows in H&E-stained sections denote cutaneous appendages; White dotted lines in immunofluorescence micrographs delineate hair follicles) (Reproduced with permission;[166] Copyright © 2023, American Chemical Society).

Table 6 Summary of MOF Application in Skin Regeneration

Application Field	Metal Type	Author	Year	Therapeutic Mechanism and Featured Design	Ref.
Diabetic infected wounds	Zn	Li	2021	- Cascade catalysis consumes glucose to produce reactive oxygen - Acidic environment enhances antibacterial activity - Biodegradable	[123]
Diabetic infected wounds	Zn	Zhang	2021	- pH-responsive fluorescence activation - Precise photodynamic sterilization - Real-time infection monitoring	[127]
Diabetic infected wounds	Zn	Gong	2024	- Corrects mitochondrial dysfunction - Promotes angiogenesis - Synergistic antibacterial effect	[124]
Diabetic infected wounds	Zn	Xiang	2024	- Gluconic acid modulates microenvironment - NO gas therapy - Zinc ion synergistic antibacterial	[126]
Diabetic infected wounds	Fe	Yang	2022	- Hierarchical porous structure enhances catalysis - Hydroxyl radical sterilization - Avoids drug resistance	[134]
Diabetic infected wounds	Mg	Liu	2025	- Antioxidant stress - Regulates macrophage polarization - Antimicrobial peptide synergy	[133]
Diabetic infected wounds	Cu	Chen	2023	- Calcination regulates active sites - Enhances water stability - Highly efficient catalysis	[129]
Diabetic infected wounds	Cu	Zhang	2023	- Cascade produces reactive oxygen - Smartphone fluorescence monitoring - Rapid sterilization	[131]
Diabetic infected wounds	Cu	Chen	2025	- Thermosensitive hydrogel controlled release - NO promotes vascularization - Promotes cell migration	[128]
Diabetic infected wounds	Ce	Chen	2023	- Dynamically scavenges free radicals - Visual glucose detection - Alleviates oxidative stress	[167]
Diabetic infected wounds	Au	Zhao	2022	- Photothermal synergistic catalysis - Destroys membrane structure for sterilization - Near-infrared responsive	[168]
Diabetic infected wounds	Zr	Zeng	2023	- Antibiotic co-delivery - Photodynamic sterilization - Promotes vascular growth factor release	[137]
Diabetic infected wounds	Ti	Tian	2025	- Visible-light catalyzes reactive oxygen production - Blood glucose regulation - Self-healing hydrogel	[139]
Diabetic infected wounds	Co	Chen	2022	- Cobalt ion promotes angiogenesis - Enhances HIF-1α expression - Antibacterial activity	[130]
Diabetic infected wounds	Mn/Zr (Bimetallic)	Wei	2024	- Biomimetic catalysis produces oxygen - Relieves hypoxia - Natural antibacterial agent synergy	[155]
Diabetic infected wounds	Cu/Mn (Bimetallic)	Huang	2025	- Cascade reaction produces oxygen - Fenton catalytic sterilization - Improves microenvironment	[153]
Diabetic infected wounds	Pt/Fe (Bimetallic)	Li	2025	- Induces bacterial ferroptosis - Hemostatic gel carrier - Promotes vascular repair	[152]
Diabetic infected wounds	Fe/Au (Bimetallic)	Ren	2025	- Low-temperature photothermal therapy - ROS catalytic sterilization - Prussian blue carrier	[150]

(Continued)

Table 6 (Continued).

Application Field	Metal Type	Author	Year	Therapeutic Mechanism and Featured Design	Ref.
Diabetic infected wounds	Zn/Co (Bimetallic)	Xue	2025	- Responsive release of metal ions - Regulates macrophage polarization - Promotes neurovascular regeneration	[148]
Diabetic infected wounds	Cu/Zn (Bimetallic)	Dai	2024	- Single-atom nanozyme antioxidation - Zinc ion antibacterial - Controlled release carrier	[146]
Diabetic infected wounds	Zn/Eu (Bimetallic)	Liu	2024	- Bidirectional fluid management - Real-time pH/H_2O_2 monitoring - Antibacterial environment	[149]
Diabetic infected wounds	Fe/Zn (Bimetallic)	Deng	2022	- Dynamically switches sterilization/healing modes - Modulates immune microenvironment - Improves islet function	[147]
Pathological scar	K	Wu	2021	- HSF membrane homologous targeting delivery - Regulates Wnt/β-catenin and JAK2/STAT3 pathways - Reduces Type I/III collagen expression - Bletilla striata polysaccharide microneedles enhance stability	[160]
Pathological scar	Cu	Chen	2023	- Transdermal photosensitizer delivery - Combined with autophagy inhibitor chloroquine - Visible-light catalyzed ROS production - Downregulates TGF-β1 and collagen expression	[159]
Pathological scar	Cu	Kong	2024	- RGD-modified EV enhances transdermal permeability - Targets α1β1 integrin - Near-infrared photodynamic induced apoptosis - GSH depletion enhances efficacy	[158]
Pathological scar	Ag	Zhao	2023	- pH-responsive ZIF-8 carrier - Synergistic ferroptosis therapy - Depletes GSH and inhibits GPX4 - Gelatin microneedle delivery system	[161]
Hair regeneration	Zn	Yang	2023	- γ-PGA microneedle delivers ZnMOF - Protects dermal papilla cells from apoptosis - Activates Wnt/β-catenin pathway - Downregulates androgen metabolism-related genes	[163]
Hair regeneration	Zn	Ruan	2024	- Acid-responsive GA@ZIF-8 release - Dual-function microneedles (delivery + Zn^{2+} monitoring) - Reduces CD8+NKG2D+ T cell infiltration - Real-time fluorescence detection of Zn^{2+} concentration	[162]
Hair regeneration	Zr	Zhao	2023	- Neuro-bionic microreactor design - Wrapped with neuroblastoma cell membrane - Releases nerve growth factor - Promotes hair follicle microenvironment regeneration	[166]
Hair regeneration	Ka	He	2024	- CD-MOF hair follicle-targeted delivery - Cedrol synergizes with minoxidil - Inhibits 5α-reductase - Activates Shh/Gli and ERK/AKT pathways	[164]
Hair regeneration	Ka	He	2025	- Stearic acid modification enhances stability - Cardamonin drug loading system - Promotes dermal papilla cell proliferation - Regulates keratinocyte growth factor	[165]

A novel MOF-based therapeutic approach has emerged through neural therapy-mediated hair regeneration, leading to the development of a MOF-inspired neural biomimetic microreactor (termed Neuro-MOF) (Figure 9). This system was constructed based on the immunoevasive outer membrane of neuroblastoma cells and neuro-associated intracellular proteins. Specifically, neuroblastoma cell membranes were coated onto the MOF surface while intracellular proteins were encapsulated within its framework. The microreactor was subsequently loaded into crosslinkable hyaluronic acid methacrylate (HAMA), with NIR triggering the release of its protein payload. The released proteins primarily consisted of nerve growth factor along with activators of Wnt and Shh pathways, which collectively compensate for the post-burn skin microenvironment to initiate peripheral nerve regeneration and facilitate new hair follicle microenvironment formation. Furthermore, the neuroblastoma cell membrane displayed on the Neuro-MOF microreactor surface effectively reduced immunogenicity and suppressed local inflammation. In murine models of deep skin burns and mechanical injuries, the Neuro-MOF microreactor demonstrated remarkable functional skin regeneration outcomes, particularly in sensory recovery and de novo hair follicle formation.[166]

In summary, the development of MOF-based MNPs represents a significant advancement in transdermal drug delivery for scar treatment and hair regeneration. By encapsulating bioactive compounds such as Zn glycyrrhizinate, curcumin, and cedrol within MOF structures (eg, ZIF-8, Zn-MOF, and CD-MOFs), researchers have engineered innovative systems that enhance therapeutic efficacy while enabling real-time monitoring of biomarkers like Zn^{2+}. These MNPs combine dissolvable and swelling microneedles for simultaneous drug delivery and diagnostic sensing, demonstrating rapid release kinetics and targeted action. Key therapeutic mechanisms include the suppression of inflammatory pathways (eg, JAK/STAT, IL-15/IFN-γ), activation of hair growth-related signaling (eg, Wnt/β-catenin, Shh/Gli), and protection against oxidative stress and apoptosis. Further refinements, such as hydrophobic modifications (eg, stearic acid-coated CD-MOFs) and neural biomimetic microreactors (Neuro-MOFs), have improved stability, follicular targeting, and immunoevasion, broadening their applications in androgenetic alopecia and wound-induced hair loss. Notably, these systems synergize with natural compounds to reduce side effects while enhancing regenerative outcomes. Collectively, MOF-based MNPs exemplify a versatile platform integrating drug delivery, biosensing, and microenvironment modulation, offering promising solutions for complex dermatological and trichological challenges.

Conclusion and Perspectives

MOFs demonstrate unique multifunctional therapeutic potential in comprehensive management of refractory wounds, with advantages stemming from their intrinsic material properties, drug-loading capacity, and synergistic integration with biomaterials (Table 6). For diabetic infected wounds, MOFs directly eradicate pathogens through release of antimicrobial metal ions (eg, Ag^+, Zn^+) or antibiotic loading, while their stimulus-responsive characteristics (eg, pH/enzyme-triggered release) enable precise drug delivery to overcome biofilm barriers. In pathological scar inhibition, MOFs serve dual roles as efficient regulators of wound redox homeostasis, reducing excessive myofibroblast activation and thereby improving collagen alignment. For skin appendage regeneration, the nanoporous structure of MOFs facilitates loading of follicular activation factors (eg, Wnt agonists) and promotes DPC proliferation through microenvironment modulation. These functions are achieved through three principal modalities: (1) MOFs as therapeutic agents per se, (2) MOFs as drug delivery platforms, and (3) MOF composites with hydrogel/electrospun matrices to construct multifunctional dressings. This integrated "healing-promotion – structural regeneration – functional reconstruction" strategy enables MOFs to not only accelerate wound closure but also drive true skin regeneration across both structural dermal remodeling and functional appendage regeneration dimensions, offering revolutionary solutions for complex wounds.

Despite their long research history and emerging potential as wound therapeutics, MOFs face several critical challenges hindering clinical translation.[113,114] These limitations span material safety, stability, synergistic therapeutic efficacy, and practical implementation, necessitating interdisciplinary collaboration for systematic optimization. Specifically, six core issues currently constrain MOF applications in wound therapy: 1) Biocompatibility and toxicity concerns must be comprehensively addressed before clinical adoption. Clinical adoption of MOFs is impeded by potential toxicity, primarily from organic ligands and solvents used in synthesis. Excessive release of metal ions (eg, Ag^+, Cu^+) may damage healthy tissues. Development of low-toxicity ligands optimized sustained-release systems and standardized toxicity assessment protocols is imperative. 2) Material stability and structural control remain major obstacles in wound environments. MOFs are prone to degradation in moist wound environments. Strategies such as hydrophobic modification, core-shell design, or high-stability metal nodes can markedly improve stability. Simultaneously, precise modulation of pore size and morphology is critical for cell interactions, requiring a balance between drug-loading capacity and biocompatibility. 3) Synergistic effects with polymers critically influence composite performance and durability. The interfacial bonding strength between MOFs and polymers directly governs the composite performance. Weak interactions may cause MOF leakage, while excessive covalent crosslinking could compromise porosity. Natural polymer modifications enhance biocompatibility and strengthen interfacial adhesion via hydrogen bonding, though crosslinking density must be optimized to preserve MOF porosity. 4) Catalytic and phototherapeutic efficiency under physiological conditions represents a key technical bottleneck. MOF-based nanozymes often suffer from activity decay under physiological conditions due to pH/ionic strength-induced deactivation of catalytic centers. Incorporating bimetallic sites or carbon supports can improve stability. Phototherapeutic MOFs are limited by tissue penetration depth; NIR-responsive MOFs and upconversion nanoparticle hybrids represent promising solutions. 5) Barriers to clinical translation stem from insufficient in vivo data and regulatory gaps. The lack of large-scale animal studies and long-term follow-up data remains a major hurdle. Systematic evaluation of MOF metabolic pathways and degradation byproducts is essential for clinical approval. Additionally, research gaps persist for other scar types (eg, atrophic, keloid). 6) Functional integration and standardization are essential prerequisites for industrial scalability. Future innovation should prioritize green synthesis, multifunctional design, and intelligent systems, such as ECM-mimicking MOF scaffolds integrating growth factor-controlled release and electroactivity, to enable full-cycle wound management from infection control to functional restoration. Finally, standardized production protocols and large-scale safety assessments are prerequisites for industrialization, advancing MOFs toward broader medical applications.

Data Sharing Statement

The data presented in the study are all included in the paper.

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Disclosure

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.

References

1. Lazzarini PA, Raspovic KM, Meloni M, van Netten JJ. A new declaration for feet's sake: halving the global diabetic foot disease burden from 2% to 1% with next generation care. *Diabetes/Metab Res Rev*. 2024;40(3):e3747. doi:10.1002/dmrr.3747
2. Hennessy C, Abram S, Loizou C, Brown R, Sharp B, Kendal A. Mortality, re-amputation, and postoperative complication rates following 28,000 below-knee amputations in diabetic patients in England: a national population study, 2002–2022. *Orthopaed Proc*. 2025;107-B(SUPP_1):18. doi:10.1302/1358-992X.2025.1.018
3. Meshkin DH, Zolper EG, Chang K, et al. Long-term mortality after nontraumatic major lower extremity amputation: a systematic review and meta-analysis. *J Foot Ankle Surg*. 2021;60(3):567–576. doi:10.1053/j.jfas.2020.06.027
4. Lee D, Yang K, Xie J. Innovative microfluidic technologies in precision research and therapy development in diabetic neuropathy: a narrative review. *Adv Technol Neurosci*. 2024;1(1):123–137.
5. Uberoi A, McCready-Vangi A, Grice EA. The wound microbiota: microbial mechanisms of impaired wound healing and infection. *Nat Rev Microbiol*. 2024;22(8):507–521. doi:10.1038/s41579-024-01035-z
6. Younesi FS, Miller AE, Barker TH, Rossi FM, Hinz B. Fibroblast and myofibroblast activation in normal tissue repair and fibrosis. *Nat Rev Mol Cell Biol*. 2024;25:1–22. doi:10.1038/s41580-023-00651-6
7. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. *Science*. 2017;356(6342):1026–1030. doi:10.1126/science.aam7928
8. Martin P, Pardo-Pastor C, Jenkins RG, Rosenblatt J. Imperfect wound healing sets the stage for chronic diseases. *Science*. 2024;386(6726):eadp2974. doi:10.1126/science.adp2974
9. Ramirez GA, Viel TA. Potential of natural senolytic compounds in eliminating senescent cells and alleviating age-related skin deterioration: a narrative review. *Aging Adv*. 2024;1(2):143–153. doi:10.4103/AGINGADV.AGINGADV-D-24-00014
10. Li M, Zhou J, Ning Y, Xiong Y. Chemical materials involved in neural tissue engineering scaffold techniques: a narrative review. *Adv Technol Neurosci*. 2024;1(2):244–260.

11. Zhang T, Zhong X-C, Feng Z-X, et al. An active shrinkage and antioxidative hydrogel with biomimetic mechanics functions modulates inflammation and fibrosis to promote skin regeneration. *Bioact Mater*. 2025;45:322–344. doi:10.1016/j.bioactmat.2024.11.028
12. Zhuang Z-M, Wang Y, Feng Z-X, et al. Targeting diverse wounds and scars: recent innovative bio-design of microneedle patch for comprehensive management. *Small*. 2024;20(18):2306565. doi:10.1002/smll.202306565
13. Canella M, Nalick S, Gharbi A, et al. Telocyte networks are an essential stem cell niche component in hair follicle regeneration. *bioRxiv*. 2023;2023:2025–03.
14. Bejaoui M, Oliva AK, Ke MS, Ferdousi F, Isoda H. 3D spheroid human dermal papilla cell as an effective model for the screening of hair growth promoting compounds: examples of minoxidil and 3, 4, 5-tri-O-caffeoylquinic acid (TCQA). *Cells*. 2022;11(13):2093. doi:10.3390/cells11132093
15. Miao Q, Jiang L, Yang J, et al. MOF/hydrogel composite-based adsorbents for water treatment: a review. *J Water Process Eng*. 2022;50:103348. doi:10.1016/j.jwpe.2022.103348
16. Ariyamparambil VJ, Kandasubramanian B. A mini-review on the recent advancement of electrospun MOF-derived nanofibers for energy storage. *Chem Eng J Adv*. 2022;11:100355. doi:10.1016/j.ceja.2022.100355
17. Pinto RV, Wang S, Tavares SR, et al. Tuning cellular biological functions through the controlled release of NO from a porous Ti-MOF. *Angew Chem Int Ed*. 2020;59(13):5135–5143. doi:10.1002/anie.201913135
18. Hasan MN, Bera A, Maji TK, Pal SK. Sensitization of nontoxic MOF for their potential drug delivery application against microbial infection. *Inorganica Chim Acta*. 2021;523:120381. doi:10.1016/j.ica.2021.120381
19. Xing F, Ma H, Yu P, et al. Multifunctional metal–organic frameworks for wound healing and skin regeneration. *Mater Des*. 2023;233:112252.
20. Zhao X, Chen Z, Zhang S, et al. Application of metal-organic frameworks in infectious wound healing. *J Nanobiotechnol*. 2024;22(1):387. doi:10.1186/s12951-024-02637-8
21. Bigham A, Islami N, Khosravi A, Zarepour A, Iravani S, Zarrabi A. MOFs and MOF-based composites as next-generation materials for wound healing and dressings. *Small*. 2024;20(30):2311903. doi:10.1002/smll.202311903
22. Maret W. Zinc biochemistry: from a single zinc enzyme to a key element of life. *Adv Nutr*. 2013;4(1):82–91. doi:10.3945/an.112.003038
23. Kaur H, Garg N. Zinc toxicity in plants: a review. *Planta*. 2021;253(6):129. doi:10.1007/s00425-021-03642-z
24. Pan X, Ou M, Lu Y, Nie Q, Dai X, Liu O. Immunomodulatory zinc-based materials for tissue regeneration. *Biomater Adv*. 2023;152:213503. doi:10.1016/j.bioadv.2023.213503
25. Ahmed NS, Lopes-Pires M, Pugh N. Zinc: an endogenous and exogenous regulator of platelet function during hemostasis and thrombosis. *Platelets*. 2021;32(7):880–887. doi:10.1080/09537104.2020.1840540
26. Sreenivasamurthy SA, Akhter FF, Akhter A, Su Y, Zhu D. Cellular mechanisms of biodegradable zinc and magnesium materials on promoting angiogenesis. *Biomater Adv*. 2022;139:213023. doi:10.1016/j.bioadv.2022.213023
27. Rakhra G, Rakhra G. Zinc finger proteins: insights into the transcriptional and post transcriptional regulation of immune response. *Molecular Biology Reports*. 2021;48:5735–5743. doi:10.1007/s11033-021-06556-x
28. Dierichs L, Kloubert V, Rink L. Cellular zinc homeostasis modulates polarization of THP-1-derived macrophages. *Eur J Nutr*. 2018;57:2161–2169. doi:10.1007/s00394-017-1491-2
29. Fraker PJ, King LE. Reprogramming of the immune system during zinc deficiency. *Annu Rev Nutr*. 2004;24(1):277–298. doi:10.1146/annurev.nutr.24.012003.132454
30. Krishnamoorthy R, Athinarayanan J, Periyasamy VS, et al. Antibacterial mechanisms of zinc oxide nanoparticle against bacterial food pathogens resistant to beta-lactam antibiotics. *Molecules*. 2022;27(8):2489. doi:10.3390/molecules27082489
31. Zhao T, Nie S, Luo M, Xiao P, Zou M, Chen Y. Research progress in structural regulation and applications of HKUST-1 and HKUST-1 based materials. *J Alloys Compd*. 2024;974:172897.
32. Zhang Y, Mo Y, Zhang Y, Yuan J, Zhang Q. MMP-3-mediated cleavage of OPN is involved in copper oxide nanoparticle-induced activation of fibroblasts. *Particle Fibre Toxicol*. 2023;20(1):22. doi:10.1186/s12989-023-00532-y
33. Lu Y, Fan X, Pan Q, He B, Pu Y. A mitochondria-targeted anticancer copper dithiocarbamate amplifies immunogenic cuproptosis and macrophage polarization. *J Mat Chem B*. 2024;12(8):2006–2014. doi:10.1039/D3TB02886K
34. Rigiracciolo DC, Scarpelli A, Lappano R, et al. Copper activates HIF-1α/GPER/VEGF signalling in cancer cells. *Oncotarget*. 2015;6(33):34158. doi:10.18632/oncotarget.5779
35. Xu D, Wu L, Yao H, Zhao L. Catalase-like nanozymes: classification, catalytic mechanisms, and their applications. *Small*. 2022;18(37):2203400. doi:10.1002/smll.202203400
36. Crescenzi E, Leonardi A, Pacifico F. Iron metabolism in cancer and senescence: a cellular perspective. *Biology*. 2023;12(7):989. doi:10.3390/biology12070989
37. Cai M, Fu T, Zhu R, et al. An iron-based metal-organic framework nanoplatform for enhanced ferroptosis and oridonin delivery as a comprehensive antitumor strategy. *Acta Pharmaceutica Sinica B*. 2024;14(9):4073–4086. doi:10.1016/j.apsb.2024.05.015
38. Ding H, Zhang Y, Mao Y, et al. Modulation of macrophage polarization by iron-based nanoparticles. *Medical Review*. 2023;3(2):105–122. doi:10.1515/mr-2023-0002
39. Song H, Wang N, Shi X, et al. Photocatalytic active silver organic framework: ag (I)-MOF and its hybrids with silver cyanamide. *Appl Organomet Chem*. 2020;34(12):e5972. doi:10.1002/aoc.5972
40. Dadashi Firouzjaei M, Shamsabadi AA, Rahimpour A, Akbari Afkhami F, Elliott M. Functionality review and life cycle assessment of a silver-based MOF for advanced material and sustainability applications. *Graphene 2D Mater*. 2024;1–18.
41. Zhang W, Ye G, Liao D, et al. Recent advances of silver-based coordination polymers on antibacterial applications. *Molecules*. 2022;27(21):7166. doi:10.3390/molecules27217166
42. Čepelak I, Dodig S, Čulić O. Magnesium–more than a common cation. *Rad Hrvatske akademije znanosti i umjetnosti Medicinske znanosti*. 2013;(517= 39):47–68.
43. Razzaghi R, Pidar F, Momen-Heravi M, Bahmani F, Akbari H, Asemi Z. Magnesium supplementation and the effects on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *Biol Trace Elem Res*. 2018;181:207–215. doi:10.1007/s12011-017-1056-5

44. Riaz U, Shabib I, Haider W. The current trends of Mg alloys in biomedical applications—A review. *J Biomed Mater Re sPart B*. 2019;107(6):1970–1996. doi:10.1002/jbm.b.34290
45. Lázaro IA, Forgan RS. Application of zirconium MOFs in drug delivery and biomedicine. *Coord Chem Rev*. 2019;380:230–259. doi:10.1016/j.ccr.2018.09.009
46. Bannunah AM. Biomedical applications of zirconia-based nanomaterials: challenges and future perspectives. *Molecules*. 2023;28(14):5428. doi:10.3390/molecules28145428
47. Hou Y, Luo C-Z, Xie D-H, et al. Convenient synthesis of zwitterionic calcium (II)-carboxylate metal organic frameworks with efficient activities for the treatment of osteoporosis. *Int J Pharm*. 2021;608:121083.
48. Subramaniam T, Fauzi MB, Lokanathan Y, Law JX. The role of calcium in wound healing. *Int J Mol Sci*. 2021;22(12):6486. doi:10.3390/ijms22126486
49. Mandal S, Hazra C, Joshi N, Sen R, Das S, Das K. Evaluating antimicrobial activity: biogenic vs. Chemically functionalized zinc oxide nanoparticles. *Mater Lett*. 2025;392:138548. doi:10.1016/j.matlet.2025.138548
50. Deng Y, Huang S, Jiang G, et al. Current status and prospects of MOFs loaded with H 2 O 2-related substances for ferroptosis therapy. *RSC Med Chem*. 2024;15(9):2996–3016. doi:10.1039/D4MD00261J
51. Du J, Zhou M, Chen Q, et al. Disrupting intracellular iron homeostasis by engineered metal-organic framework for nanocatalytic tumor therapy in synergy with autophagy amplification-promoted ferroptosis. *Adv Funct Mater*. 2023;33(24):2215244. doi:10.1002/adfm.202215244
52. Xu Z, Zhang C, Wang X, Liu D. Release strategies of silver ions from materials for bacterial killing. *ACS Appl Bio Mater*. 2021;4(5):3985–3999. doi:10.1021/acsabm.0c01485
53. Tao Y, Aparicio T, Li M, Leong KW, Zha S, Gautier J. Inhibition of DNA replication initiation by silver nanoclusters. *Nucleic Acids Res*. 2021;49(9):5074–5083. doi:10.1093/nar/gkab271
54. Lian C, Liu J, Wei W, et al. Mg-gallate metal-organic framework-based sprayable hydrogel for continuously regulating oxidative stress microenvironment and promoting neurovascular network reconstruction in diabetic wounds. *Bioact Mater*. 2024;38:181–194.
55. Zheng SQ, Lim SS, Foo CY, et al. Solvothermal synthesis of nanostructured nickel-based metal–organic frameworks (Ni-MOFs) with enhanced electrochemical performance for symmetric supercapacitors. *J Mater Sci*. 2023;58(29):11894–11913.
56. Kamal K, Bustam MA, Ismail M, Grekov D, Mohd Shariff A, Pré P. Optimization of washing processes in solvothermal synthesis of nickel-based MOF-74. *Materials*. 2020;13(12):2741. doi:10.3390/ma13122741
57. Łuczak J, Kroczewska M, Baluk M, Sowik J, Mazierski P, Zaleska-Medynska A. Morphology control through the synthesis of metal-organic frameworks. *Adv Colloid Interface Sci*. 2023;314:102864. doi:10.1016/j.cis.2023.102864
58. Li YS, Bux H, Feldhoff A, Li GL, Yang WS, Caro J. Controllable synthesis of metal–organic frameworks: from MOF nanorods to oriented MOF membranes. *Adv Mater*. 2010;22(30):3322–3326. doi:10.1002/adma.201000857
59. Bagherzadeh E, Zebarjad SM, Hosseini HRM, Khodaei A. Interplay between morphology and band gap energy in Fe-MIL-88A prepared via a high temperature surfactant-assisted solvothermal method. *Mater Chem Phys*. 2022;277:125536. doi:10.1016/j.matchemphys.2021.125536
60. Mahreni M, Ristianingsih Y. A review on Metal-Organic Framework (MOF): synthesis and solid catalyst applications. *Proceedings of the Proceeding of LPPM UPN "Veteran" Yogyakarta Conference Series 2020–Engineering and Science Series*; 2020.
61. Derbe T, Sani T, Amare E, Girma T. Mini review on synthesis, characterization, and application of zeolite@ MOF composite. *Adv Mater Sci Eng*. 2023;2023(1):8760967. doi:10.1155/2023/8760967
62. Wu X, Bao Z, Yuan B, et al. Microwave synthesis and characterization of MOF-74 (M= Ni, Mg) for gas separation. *Microporous Mesoporous Mater*. 2013;180:114–122. doi:10.1016/j.micromeso.2013.06.023
63. Patro B, Vijaylakshmi S, Sharma P. Rapid microwave-assisted solvothermal synthesis of Cu2ZnSnS4 (CZTS) nanocrystals for low-cost thin film photovoltaic: investigation of synthesis parameters and morphology control. *J Mater Sci*. 2018;29(4):3370–3380.
64. Thomas-Hillman I, Laybourn A, Dodds C, Kingman SW. Realising the environmental benefits of metal–organic frameworks: recent advances in microwave synthesis. *J Mater Chem A*. 2018;6(25):11564–11581. doi:10.1039/C8TA02919A
65. Du B, Yan F, Lin X, et al. A bottom-up sonication-assisted synthesis of Zn-BTC MOF nanosheets and the ppb-level acetone detection of their derived ZnO nanosheets. *Sens Actuators B*. 2023;375:132854. doi:10.1016/j.snb.2022.132854
66. Asghar A, Iqbal N, Noor T. Ultrasonication treatment enhances MOF surface area and gas uptake capacity. *Polyhedron*. 2020;181:114463. doi:10.1016/j.poly.2020.114463
67. Varsha M, Nageswaran G. Direct electrochemical synthesis of metal organic frameworks. *J Electrochem Soc*. 2020;167(15):155527. doi:10.1149/1945-7111/abc6c6
68. Li W-J, Tu M, Cao R, Fischer RA. Metal–organic framework thin films: electrochemical fabrication techniques and corresponding applications & perspectives. *J Mater Chem A*. 2016;4(32):12356–12369. doi:10.1039/C6TA02118B
69. Beamish-Cook J, Shankland K, Murray CA, Vaqueiro P. Insights into the mechanochemical synthesis of MOF-74. *Cryst Growth Des*. 2021;21(5):3047–3055. doi:10.1021/acs.cgd.1c00213
70. Jin C, Shi S, Liao S, et al. Post-synthetic ligand exchange by mechanochemistry: toward green, efficient, and large-scale preparation of functional metal–organic frameworks. *Chem Mater*. 2023;35(11):4489–4497. doi:10.1021/acs.chemmater.3c00652
71. Tanaka S. Mechanochemical synthesis of MOFs. *Metal-Organic Frameworks Biomed Appl*. 2020;197–222.
72. Pezhhanfar S, Farajzadeh MA, Hosseini-Yazdi SA, Mogaddam MRA. Synthesis of MOF-70 based on diffusion method; microgram amount application as a highly efficient sorbent in dispersive micro solid phase extraction prior to dispersive liquid–liquid microextraction for the preconcentration and extraction of pesticides from fruit juices. *J Iran Chem Soc*. 2022;19(6):2407–2419.
73. Zhou Y, Zhang X-F, Yao J, Wang H. Contra-diffusion synthesis of metal-organic framework separation membranes: a review. *Sep Purif Technol*. 2022;300:121837. doi:10.1016/j.seppur.2022.121837
74. Salari H, Sadeghinia M. MOF-templated synthesis of nano Ag2O/ZnO/CuO heterostructure for photocatalysis. *J Photochem Photobiol*. 2019;376:279–287. doi:10.1016/j.jphotochem.2019.03.010
75. Swain N, Saravanakumar B, Kundu M, Schmidt-Mende L, Ramadoss A. Recent trends in template assisted 3D porous materials for electrochemical supercapacitors. *J Mater Chem A*. 2021;9(45):25286–25324. doi:10.1039/D1TA06122D
76. Luković Golić D, Branković Z, Daneu N, Bernik S, Branković G. Solvothermal syntheses of nano-and micro-sized ZnO powders with a controllable morphology. *J Sol Gel Sci Techn*. 2012;63(1):116–125. doi:10.1007/s10971-012-2773-z

77. Kovács Z, Molnár C, Gyulavári T, et al. Solvothermal synthesis of ZnO spheres: tuning the structure and morphology from nano-to micro-meter range and its impact on their photocatalytic activity. *Catal Today*. 2022;397:16–27. doi:10.1016/j.cattod.2022.03.004
78. Morales EMC, Méndez-Rojas MA, Torres-Martínez LM, et al. Ultrafast synthesis of HKUST-1 nanoparticles by solvothermal method: properties and possible applications. *Polyhedron*. 2021;210:115517. doi:10.1016/j.poly.2021.115517
79. Xu B, Guo H, Wang S, Li Y, Zhang H, Liu C. Solvothermal synthesis of luminescent Eu (BTC)(H 2 O) DMF hierarchical architectures. *CrystEngComm*. 2012;14(8):2914–2919. doi:10.1039/c2ce06572j
80. Rónavári A, Bélteky P, Boka E, et al. Polyvinyl-pyrrolidone-coated silver nanoparticles—the colloidal, chemical, and biological consequences of steric stabilization under biorelevant conditions. *Int J Mol Sci*. 2021;22(16):8673. doi:10.3390/ijms22168673
81. Nandiyanto ABD. Nano metal-organic framework particles (ie MIL-100 (Fe), HKUST-1 (Cu), Cu-TPA, and MOF-5 (Zn)) using a solvothermal process. *Indonesian J Sci Technol*. 2019;4(2):220–228. doi:10.17509/ijost.v4i2.18178
82. Wang Z, Han Y, Xu Y, Guo Z, Han M, Yang W. Controlled Regulation of N-Involved TiO2 Nanoflowers in Size and Morphology via Solvothermal Synthesis for Enhanced Photocatalytic Performance. *Adv Sustainable Syst*. 2024;8(10):2400186. doi:10.1002/adsu.202400186
83. He B, Sadiq MM, Batten MP, et al. Continuous flow synthesis of a zr magnetic framework composite for post-combustion CO2 capture. *Chemistry*. 2019;25(57):13184–13188. doi:10.1002/chem.201902560
84. Wauteraerts N, Tu M, Chanut N, Rodríguez-Hermida S, Gandara-Loe J, Ameloot R. Vapor-assisted synthesis of the MOF-74 metal–organic framework family from zinc, cobalt, and magnesium oxides. *Dalton Trans*. 2023;52(47):17873–17880. doi:10.1039/D3DT01785K
85. Khan SN, Zhao M, Fennell PS, Anthony EJ. Construction of highly mesoporous metal-organic frameworks via green metallic solvents assisted route for chemical CO2 fixation. *Small*. 2025;21(21):2502624. doi:10.1002/smll.202502624
86. Tao Y, Du J, Cheng Y, Lu J, Min D, Wang H. Advances in application of cellulose—MOF composites in aquatic environmental treatment: remediation and regeneration. *Int J Mol Sci*. 2023;24(9):7744. doi:10.3390/ijms24097744
87. Chedid G, Yassin A. Recent trends in covalent and metal organic frameworks for biomedical applications. *Nanomaterials*. 2018;8(11):916. doi:10.3390/nano8110916
88. Keskin S, Kızılel S. Biomedical applications of metal organic frameworks. *Ind Eng Chem Res*. 2011;50(4):1799–1812. doi:10.1021/ie101312k
89. Li M, Zhang Z, Yu Y, et al. Recent advances in Zn-MOFs and their derivatives for cancer therapeutic applications. *Mater Adv*. 2023;4(21):5050–5093. doi:10.1039/D3MA00545C
90. Moharramnejad M, Ehsani A, Salmani S, et al. Zinc-based metal-organic frameworks: synthesis and recent progress in biomedical application. *J Inorg Organomet Polym Mater*. 2022;32(9):3339–3354. doi:10.1007/s10904-022-02385-y
91. Bahrani S, Hashemi SA, Mousavi SM, Azhdari R. Zinc-based metal–organic frameworks as nontoxic and biodegradable platforms for biomedical applications: review study. *Drug Metab Rev*. 2019;51(3):356–377. doi:10.1080/03602532.2019.1632887
92. Liu X, Liang T, Zhang R, et al. Iron-based metal–organic frameworks in drug delivery and biomedicine. *ACS Appl Mater Interfaces*. 2021;13(8):9643–9655. doi:10.1021/acsami.0c21486
93. Zhu R, Cai M, Fu T, et al. Fe-based metal organic frameworks (Fe-MOFs) for bio-related applications. *Pharmaceutics*. 2023;15(6):1599. doi:10.3390/pharmaceutics15061599
94. Lu X, Ye J, Zhang D, et al. Silver carboxylate metal–organic frameworks with highly antibacterial activity and biocompatibility. *J Inorg Biochem*. 2014;138:114–121. doi:10.1016/j.jinorgbio.2014.05.005
95. Mota L, Dinis-Oliveira RJ. Clinical and forensic aspects of the different subtypes of argyria. *J Clin Med*. 2021;10(10):2086. doi:10.3390/jcm10102086
96. Chattopadhyay K, Mandal M, Maiti DK. A review on zirconium-based metal–organic frameworks: synthetic approaches and biomedical applications. *Mater Adv*. 2024;5(1):51–67. doi:10.1039/D3MA00735A
97. Houillier P, Lievre L, Hureaux M, Prot-Bertoye C. Mechanisms of paracellular transport of magnesium in intestinal and renal epithelia. *Ann N Y Acad Sci*. 2023;1521(1):14–31. doi:10.1111/nyas.14953
98. Guo J, Yu Y, Zhu W, et al. Modular assembly of red blood cell superstructures from metal–organic framework nanoparticle-based building blocks. *Adv Funct Mater*. 2021;31(10):2005935. doi:10.1002/adfm.202005935
99. Pretze M, Reffert L, Diehl S, et al. GMP-compliant production of [68Ga] Ga-NeoB for positron emission tomography imaging of patients with gastrointestinal stromal tumor. *EJNMMI Radiopharm Chem*. 2021;6(1):22. doi:10.1186/s41181-021-00137-w
100. Di Filippo LD, de Paula MC, Duarte JL, de Paula GA, Frigieri I, Chorilli M. Nanocarrier functionalization strategies for targeted drug delivery in skin cancer therapy: current progress and upcoming challenges. *Expert Opin Drug Deliv*. 2023;20(6):831–849. doi:10.1080/17425247.2023.2221026
101. Kannan R, Nance E, Kannan S, Tomalia DA. Emerging concepts in dendrimer-based nanomedicine: from design principles to clinical applications. *J Internal Med*. 2014;276(6):579–617. doi:10.1111/joim.12280
102. Moni SS, Moshi JM, Matou-Nasri S, et al. Advances in materials science for precision melanoma therapy: nanotechnology-enhanced drug delivery systems. *Pharmaceutics*. 2025;17(3):296. doi:10.3390/pharmaceutics17030296
103. Large DE, Abdelmessih RG, Fink EA, Auguste DT. Liposome composition in drug delivery design, synthesis, characterization, and clinical application. *Adv Drug Delivery Rev*. 2021;176:113851. doi:10.1016/j.addr.2021.113851
104. Patil YP, Jadhav S. Novel methods for liposome preparation. *Chem Phys Lipids*. 2014;177:8–18. doi:10.1016/j.chemphyslip.2013.10.011
105. Tehrani SF, Bharadwaj P, Chain JL, Roullin VG. Purification processes of polymeric nanoparticles: how to improve their clinical translation? *J Control Release*. 2023;360:591–612. doi:10.1016/j.jconrel.2023.06.038
106. Palazzolo S, Bayda S, Hadla M, et al. The clinical translation of organic nanomaterials for cancer therapy: a focus on polymeric nanoparticles, micelles, liposomes and exosomes. *Curr Med Chem*. 2018;25(34):4224–4268. doi:10.2174/0929867324666170830113755
107. Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. *Chem Soc Rev*. 2012;41(7):2971–3010. doi:10.1039/c2cs15344k
108. Hsu HJ, Bugno J, Lee S, Hong S. Dendrimer-based nanocarriers: a versatile platform for drug delivery. *Wiley Interdiscip Rev*. 2017;9(1):e1409.
109. Zhuang Z-M, Wang Y, Chen L, et al. Triple-molded, reinforced arrowhead microneedle patch of dual human-derived matrix for integrated management of diabetic wounds. *Biomaterials*. 2026;324:123520. doi:10.1016/j.biomaterials.2025.123520
110. Zhao Y, Zhao Y, Xu B, Liu H, Chang Q. Microenvironmental dynamics of diabetic wounds and insights for hydrogel-based therapeutics. *J Tissue Eng*. 2024;15:20417314241253290. doi:10.1177/20417314241253290

111. Arshad MS, Zahra AT, Zafar S, et al. Antibiofilm effects of macrolide loaded microneedle patches: prospects in healing infected wounds. *Pharm Res*. 2021;38(1):165–177. doi:10.1007/s11095-021-02995-0
112. Bahadoran Z, Mirmiran P, Hosseinpanah F, Kashfi K, Ghasemi A. Nitric oxide-based treatments improve wound healing associated with diabetes mellitus. *Med Gas Res*. 2025;15(1):23–35. doi:10.4103/mgr.MEDGASRES-D-24-00020
113. Deng L-E, Qiu Y, Zeng Y, et al. Current and promising applications of MOF composites in the healing of diabetes wounds. *RSC Med Chem*. 2024;15(8):2601–2621. doi:10.1039/D4MD00232F
114. Xiong Y, Feng Q, Lu L, et al. Metal–organic frameworks and their composites for chronic wound healing: from bench to bedside. *Adv Mater*. 2024;36(2):2302587. doi:10.1002/adma.202302587
115. Du R, Wu Y, Yang Y, et al. Porosity engineering of MOF-based materials for electrochemical energy storage. *Adv Energy Mater*. 2021;11(20):2100154. doi:10.1002/aenm.202100154
116. Li G, Zhao S, Zhang Y, Tang Z. Metal–organic frameworks encapsulating active nanoparticles as emerging composites for catalysis: recent progress and perspectives. *Adv Mater*. 2018;30(51):1800702. doi:10.1002/adma.201800702
117. Cai W, Wang J, Chu C, Chen W, Wu C, Liu G. Metal–organic framework-based stimuli-responsive systems for drug delivery. *Adv Sci*. 2019;6(1):1801526. doi:10.1002/advs.201801526
118. Singh N, Qutub S, Khashab NM. Biocompatibility and biodegradability of metal organic frameworks for biomedical applications. *J Mat Chem B*. 2021;9(30):5925–5934. doi:10.1039/D1TB01044A
119. Kirchon A, Feng L, Drake HF, Joseph EA, Zhou H-C. From fundamentals to applications: a toolbox for robust and multifunctional MOF materials. *Chem Soc Rev*. 2018;47(23):8611–8638. doi:10.1039/C8CS00688A
120. Liu Y, Zhou L, Dong Y, et al. Recent developments on MOF-based platforms for antibacterial therapy. *RSC Med Chem*. 2021;12(6):915–928. doi:10.1039/D0MD00416B
121. Yang X, Bonnett BL, Spiering GA, et al. Understanding the mechanical reinforcement of metal–organic framework–polymer composites: the effect of aspect ratio. *ACS Appl Mater Interfaces*. 2021;13(44):51894–51905. doi:10.1021/acsami.1c05430
122. Dai H, Yuan X, Jiang L, et al. Recent advances on ZIF-8 composites for adsorption and photocatalytic wastewater pollutant removal: fabrication, applications and perspective. *Coord Chem Rev*. 2021;441:213985. doi:10.1016/j.ccr.2021.213985
123. Li D, Chen T, Zhang Y, Xu Y, Niu H. Synergistical starvation and chemo-dynamic therapy for combating multidrug-resistant bacteria and accelerating diabetic wound healing. *Adv Healthcare Mater*. 2021;10(18):2100716. doi:10.1002/adhm.202100716
124. Gong J, Wang H, Xie C, Dai Y, Wang Y, Guo W. A multifunctional injectable hydrogel for boosted diabetic wound healing assisted by Quercetin-ZIF system. *Chem Eng J*. 2024;495:153425. doi:10.1016/j.cej.2024.153425
125. Bennison L, Miller C, Summers R, Minnis A, Sussman G, McGuiness W. The pH of wounds during healing and infection: a descriptive literature review. *Wound Pract Res*. 2017;25(2):63–69.
126. Xiang G, Wang B, Zhang W, et al. A Zn-MOF-GOx-based cascade nanoreactor promotes diabetic infected wound healing by NO release and microenvironment regulation. *Acta Biomater*. 2024;182:245–259. doi:10.1016/j.actbio.2024.05.015
127. Zhang L, Ouyang M, Zhang Y, et al. The fluorescence imaging and precise suppression of bacterial infections in chronic wounds by porphyrin-based metal–organic framework nanorods. *J Mat Chem B*. 2021;9(38):8048–8055. doi:10.1039/D1TB01649K
128. Chen S, Chen J, Wang X, et al. Glucose-activated self-cascade antibacterial and pro-angiogenesis nanozyme-functionalized chitosan-arginine thermosensitive hydrogel for chronic diabetic wounds healing. *Carbohydr Polym*. 2025;348:122894. doi:10.1016/j.carbpol.2024.122894
129. Chen L, Lin C, Shi X, Zhang L, Sun D. Quasi-HKUST-1 nanostructures with enhanced catalytic activity and water stability for bacteria-infected diabetic wound therapy. *ACS Appl Nano Mater*. 2023;6(5):3835–3847. doi:10.1021/acsanm.2c05523
130. Chen J, Bao X, Meng T, Sun J, Yang X. Zeolitic imidazolate framework-67 accelerates infected diabetic chronic wound healing. *Chem Eng J*. 2022;430:133091. doi:10.1016/j.cej.2021.133091
131. Zhang S, Wang L, Xu T, Zhang X. Luminescent MOF-based nanofibers with visual monitoring and antibacterial properties for diabetic wound healing. *ACS Appl Mater Interfaces*. 2023;15(7):9110–9119. doi:10.1021/acsami.2c21786
132. Ashique S, Kumar S, Hussain A, et al. A narrative review on the role of magnesium in immune regulation, inflammation, infectious diseases, and cancer. *J Health Popul Nutr*. 2023;42(1):74. doi:10.1186/s41043-023-00423-0
133. Liu L, Ding Z, Huang Y, Zou J. Magnesium ion/gallic acid MOF-laden multifunctional acellular matrix hydrogels for diabetic wound healing. *ACS Appl Bio Mater*. 2025;8:3811–23.
134. Yang -X-X, Chen Y-L, Feng P-F, et al. Hierarchically porous MOF-based microneedles for glucose-responsive infected diabetic wound treatment. *Mater Chem Front*. 2022;6(6):680–688. doi:10.1039/D1QM01512E
135. Zheng X, Duan Y, Pang J, Feng X, Gao L, Li J. Antibacterial effects of nano-decoction iron polysulfide in epididymitis and the systematic evaluation of its toxicity on the reproductive health of male mice. *Ecotoxicol Environ Saf*. 2022;231:113184. doi:10.1016/j.ecoenv.2022.113184
136. Zhu T, Park HC, Son KM, Yang H-C. Effects of dimethyloxalylglycine on wound healing of palatal mucosa in a rat model. *BMC Oral Health*. 2015;15(1):60. doi:10.1186/s12903-015-0047-1
137. Zeng Y, Wang C, Lei K, et al. Multifunctional MOF-based microneedle patch with synergistic chemo-photodynamic antibacterial effect and sustained release of growth factor for chronic wound healing. *Adv Healthcare Mater*. 2023;12:2300250. doi:10.1002/adhm.202300250
138. Lismont M, Dreesen L, Wuttke S. Metal-organic framework nanoparticles in photodynamic therapy: current status and perspectives. *Adv Funct Mater*. 2017;27(14):1606314. doi:10.1002/adfm.201606314
139. Tian M, Fan C, Ge R, Liu G, Su L, Dong H. Visible light-activated Ti-MOF loaded metformin-hydrogel composite dressing for accelerated chronic diabetic wound healing. *Chem Eng J*. 2025;506:160179. doi:10.1016/j.cej.2025.160179
140. Mouhamed AA, Nadim AH, Mahmoud AM, Mostafa NM, Eltanany BM. Bimetallic MOF-based electrochemical sensor for determination of paracetamol in spiked human plasma. *BMC Chemist*. 2024;18(1):148. doi:10.1186/s13065-024-01247-7
141. Kannan P, Maduraiveeran G. Bimetallic nanomaterials-based electrochemical biosensor platforms for clinical applications. *Micromachines*. 2021;13(1):76.
142. Xiang K, Wu H, Liu Y, et al. MOF-derived bimetallic nanozyme to catalyze ROS scavenging for protection of myocardial injury. *Theranostics*. 2023;13(8):2721. doi:10.7150/thno.83543
143. Chen L, Wang H-F, Li C, Xu Q. Bimetallic metal–organic frameworks and their derivatives. *Chem Sci*. 2020;11(21):5369–5403.

144. Luo J, Luo X, Gan Y, et al. Advantages of bimetallic organic frameworks in the adsorption, catalysis and detection for water contaminants. *Nanomaterials*. 2023;13(15):2194.
145. Mohammed Ameen SS, Omer KM. Recent advances of bimetallic-metal organic frameworks: preparation, properties, and fluorescence-based biochemical sensing applications. *ACS Appl Mater Interfaces*. 2024;16(25):31895–31921. doi:10.1021/acsami.4c06931
146. Dai S, Jiang L, Liu L, et al. MOF-encapsulated copper-doped carbon dots nanozymes with excellent biological activity promote diabetes wound healing. *Regenerative Biomaterials*. 2024;11:rbae119. doi:10.1093/rb/rbae119
147. Deng M, Zhang M, Huang R, et al. Diabetes immunity-modulated multifunctional hydrogel with cascade enzyme catalytic activity for bacterial wound treatment. *Biomaterials*. 2022;289:121790. doi:10.1016/j.biomaterials.2022.121790
148. Xue Y, Zhang L, Chen J, Ma D, Zhang Y, Han Y. An “all-in-one” therapeutic platform for programmed antibiosis, immunoregulation and neuroangiogenesis to accelerate diabetic wound healing. *Biomaterials*. 2025;321:123293. doi:10.1016/j.biomaterials.2025.123293
149. Liu R, Xi P, Yang N, Cheng B. Multifunctional Janus membrane for diabetic wound healing and intelligent monitoring. *ACS Appl Mater Interfaces*. 2024;16(32):41927–41938. doi:10.1021/acsami.4c09353
150. Ren X, Hu Y, Sang Z, Li Y, Mei X, Chen Z. Preparation of Au-modified metal organic framework nanozyme with tunable catalytic activity used for diabetic wound healing. *J Colloid Interface Sci*. 2025;687:643–658. doi:10.1016/j.jcis.2025.02.104
151. Dai W, Shu R, Yang F, et al. Engineered bio-heterojunction confers extra-and intracellular bacterial ferroptosis and hunger-triggered cell protection for diabetic wound repair. *Adv Mater*. 2024;36(9):2305277. doi:10.1002/adma.202305277
152. Li F, Du Y, Zheng Y, et al. Microenvironment-responsive MOF nanozymes armored cryogels promoted wound healing via rapid hemostasis, infection elimination and angiogenesis. *J Control Release*. 2025;384:113838. doi:10.1016/j.jconrel.2025.113838
153. Huang Y, Chen D, Wong T, Li B, Shi Y. Multivariate MOF nanozyme utilizes glucose-activated self-cascade strategy for enhanced antibacterial efficacy and accelerated diabetic wounds healing. *APL Mater*. 2025;13(5). doi:10.1063/5.0267620
154. Jiang N, Liu X, Sui B, Wang J, Liu X, Zhang Z. Using hybrid MnO2-Au nanoflowers to accelerate ROS scavenging and wound healing in diabetes. *Pharmaceutics*. 2024;16(10):1244. doi:10.3390/pharmaceutics16101244
155. Wei YJ, Chen H, Zhou ZW, et al. Kill two birds with one stone: dual-metal MOF-nanozyme-decorated hydrogels with ROS-scavenging, oxygen-generating, and antibacterial abilities for accelerating infected diabetic wound healing. *Small*. 2024;20(48):2403679. doi:10.1002/smll.202403679
156. Chen Y, Yuan B, Yang Z, et al. Catalase-like nanozyme-hybrid hydrogels utilizing endogenous ROS as an oxygen source to synergically regulate oxidative stress and hypoxia for enhanced diabetic wound healing. *Biomacromolecules*. 2025;26(3):1672–1685. doi:10.1021/acs.biomac.4c01481
157. Franzini M, Valdenassi L, Tirelli U, et al. Post-surgical wounds treated with ozone: a preliminary case series. *Med Gas Res*. 2024;14(4):225–227. doi:10.4103/mgr.MEDGASRES-D-23-00017
158. Kong T, Zhang K, Wang Y, et al. Cucumber-derived extracellular vesicle-functionalized metal-organic frameworks for enhanced photodynamic therapy of hypertrophic scars. *Adv Funct Mater*. 2024;34(29):2400379. doi:10.1002/adfm.202400379
159. Chen D, Zhang Y, Long W, et al. Visible light-driven photodynamic therapy for hypertrophic scars with MOF armored microneedles patch. *Front Chem*. 2023;11:1128255. doi:10.3389/fchem.2023.1128255
160. Wu T, Hou X, Li J, et al. Microneedle-mediated biomimetic cyclodextrin metal organic frameworks for active targeting and treatment of hypertrophic scars. *Acs Nano*. 2021;15(12):20087–20104. doi:10.1021/acsnano.1c07829
161. Zhao B, Guo W, Zhou X, et al. Ferroptosis-mediated synergistic therapy of hypertrophic scarring based on metal–organic framework microneedle patch. *Adv Funct Mater*. 2023;33:2300575. doi:10.1002/adfm.202300575
162. Ruan H, Zhong Y, Ding H, et al. Dual-continuous microneedle patch integrating transdermal delivery of pH-sensitive licorzinc MOFs and Zn2+ hydrogel sensors for treating alopecia areata. *Chem Eng J*. 2024;499:155961. doi:10.1016/j.cej.2024.155961
163. Yang Y, Wang P, Gong Y, et al. Curcumin-zinc framework encapsulated microneedle patch for promoting hair growth. *Theranostics*. 2023;13(11):3675. doi:10.7150/thno.84118
164. He Z, Zhang Y, Liu Z, et al. Synergistic treatment of androgenetic alopecia with follicular co-delivery of minoxidil and cedrol in metal–organic frameworks stabilized by covalently cross-linked cyclodextrins. *Int J Pharm*. 2024;654:123948. doi:10.1016/j.ijpharm.2024.123948
165. He Z, Liu Z, Zhang Y, Guo T, Feng N. Modulating metal-organic frameworks by surface engineering of stearic acid modification for follicular drug delivery and enhanced hair growth promotion. *J Nanobiotechnol*. 2025;23(1):118. doi:10.1186/s12951-025-03234-z
166. Zhao Q, Wang J, Qu S, et al. Neuro-inspired biomimetic microreactor for sensory recovery and hair follicle neogenesis under skin burns. *ACS nano*. 2023;17(22):23115–23131. doi:10.1021/acsnano.3c09107
167. Chen Z, Song S, Zeng H, Ge Z, Liu B, Fan Z. 3D printing MOF nanozyme hydrogel with dual enzymatic activities and visualized glucose monitoring for diabetic wound healing. *Chem Eng J*. 2023;471:144649. doi:10.1016/j.cej.2023.144649
168. Zhao X, Chang L, Hu Y, et al. Preparation of photocatalytic and antibacterial MOF nanozyme used for infected diabetic wound healing. *ACS Appl Mater Interfaces*. 2022;14(16):18194–18208. doi:10.1021/acsami.2c03001