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Harnessing the power of copper-based metal–organic framework (HKUST-1) nanostructures for advanced wound healing

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This review explores the potential of copper-based metal–organic frameworks (MOFs), particularly HKUST-1 (Hong Kong University of Science and Technology-1), as an innovative solution for advanced wound healing. Wound healing is a multifaceted process involving antimicrobial defense, inflammation control, and tissue regeneration, areas where copper ions play a vital role. HKUST-1, a porous, crystalline MOF with copper as its core component, offers unique structural properties that enhance its utility in biomedical applications. This review delves into the biocompatibility of HKUST-1, its ability to release copper ions in a controlled manner, and its antimicrobial and pro-regenerative effects on wound healing. We further analyze the potential benefits of incorporating HKUST-1 into wound care products, such as dressings, gels, and drug delivery systems, while also addressing challenges like stability under physiological conditions, potential toxicity, and scalability issues. Finally, this review discusses the prospects for translating HKUST-1-based nanostructures into clinical practice, aiming for improved patient outcomes and faster wound healing.

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1. Introduction

1.1. Background on wound healing

Wound healing is a complex and essential biological process that restores skin integrity and function following an injury. It is composed of four distinct yet interconnected stages, each of which plays a crucial role in ensuring the wound is properly healed.[1–3] Hemostasis as the initial phase occurs immediately after injury and is essential for preventing blood loss. The body responds by initiating clot formation through the aggregation of platelets, which helps to seal the wound and create a barrier against external pathogens.[4] In the second stage, immune cells, primarily neutrophils and macrophages, are recruited to the wound site. These cells clear the wound of dead tissue, debris, and bacteria, preventing infection. The inflammatory response also signals the subsequent healing phases, laying the foundation for tissue repair.[5] During proliferation, new tissue begins to form as cells, including fibroblasts and keratinocytes, divide and migrate to the wound site. This stage is marked by two key processes: angiogenesis, where new blood vessels form to supply oxygen and nutrients to the growing tissue, and collagen deposition, which creates a new extracellular matrix (ECM) that supports the structure of the developing tissue.[6,7] The final stage of wound healing involves the maturation and strengthening of the newly formed tissue. Over time, collagen fibers are reorganized, cross-linked, and aligned along tension lines to provide tensile strength. This remodeling process can continue for months or even years, gradually restoring the skin's full integrity (Fig. 1).[8,9]

While these stages occur sequentially in normal wound healing, various factors can disrupt the process, leading to chronic, non-healing wounds.[10] Chronic wounds, such as diabetic ulcers, venous leg ulcers, or pressure sores, are characterized by prolonged inflammation, impaired blood flow, and delayed proliferation.[11–13] Such wounds can persist for months or even years, significantly affecting the patient's quality of life and placing a heavy burden on healthcare systems due to the extended need for care and the increased risk of complications like infection.

Traditional wound care treatments, such as the use of dressings, topical antibiotics, and debridement, often provide only limited success in promoting healing, particularly in the case of chronic wounds.[13,14] This limitation has spurred interest in developing advanced therapeutic materials, including bioactive materials, growth factors, and drug-delivery systems, which can actively support and accelerate the healing process.[15–18] These advanced treatments hold promise for addressing the challenges of chronic wound management by promoting faster healing, reducing inflammation, and restoring tissue function more effectively.

1.2. Overview of metal–organic frameworks (MOFs)

In recent years, nanostructures have gained significant attraction due to their biomedical and pharmacological uses.[19–22]

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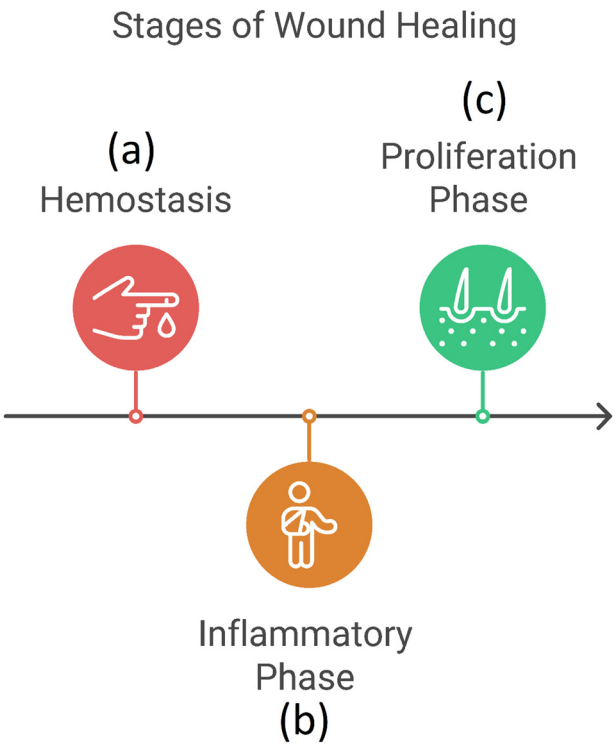

Fig. 1 Stages of wound healing: hemostasis, inflammatory phase, and proliferation phase. Hemostasis phase (a): the initial response to injury, where blood vessels constrict and platelets form a fibrin clot to stop bleeding. Inflammatory phase (b): immune cells (*e.g.*, neutrophils and macrophages) clear debris and prevent infection, marked by redness, swelling, and heat. Proliferative phase (c): tissue rebuilding occurs, involving angiogenesis (new blood vessel formation), collagen deposition, and granulation tissue development to close the wound.

Metal–organic frameworks (MOFs) were identified as an innovative and rapidly growing class of materials characterized by their unique structure, consisting of metal ions coordinated with organic ligands to create highly porous networks.[23–26] This combination of metal centers and organic linkers provided MOFs with remarkable structural versatility, enabling the design of materials tailored for a wide range of applications.[27] Their customizable nature stemmed from the nearly limitless combinations of metals and organic ligands, making MOFs highly adaptable for specific functions.[23–25,28–37] For diabetic wound healing, MOFs like HKUST-1 (Cu-based) and ZIF-8 (Zn-based) were engineered to release therapeutic metal ions (*e.g.*, Cu^{2+}, Zn^{2+}, and Co^{2+}) that promote angiogenesis, collagen deposition, and antimicrobial activity.[38,39]

MOFs are distinguished by several key properties that make them particularly attractive for biomedical applications.[23,24,31,33,34] Firstly, their high surface area was noted as an exceptional feature due to their porous nature, making them ideal for applications requiring the adsorption, storage, or controlled release of molecules. In diabetic wound care, this porosity enabled MOFs to encapsulate drugs (*e.g.*, dimethylacetylglycine and curcumin) or gases (*e.g.*, nitric oxide) for sustained release, addressing challenges like bacterial infection and oxidative stress.[38,39] In drug delivery, this property enabled MOFs to encapsulate substantial amounts of drugs or bioactive compounds, facilitating their release over time. Secondly, the tunability of MOFs was highlighted as a significant advantage.[23,24,31,33,34] By selecting specific metal ions and organic linkers, MOFs could be designed with precise structural and functional properties, allowing for the controlled release of therapeutic agents. For instance, glucose-responsive MOFs (*e.g.*, GOx@Fe-ZIF-TA) released antibacterial agents in hyperglycemic environments, while pH-sensitive systems (*e.g.*, PCN-224@hydrogel) enabled on-demand drug delivery in infected wounds.[38,39] MOFs could be engineered to release drugs in response to specific stimuli, such as changes in pH, temperature, or the presence of certain biomolecules, which was crucial for achieving sustained and targeted drug release in biomedical applications.[23,31] Lastly, the modifiable functionality of MOFs can be emphasized. The functionality could be further enhanced through chemical modification of both the metal centers and the organic linkers, enabling the incorporation of additional properties such as antimicrobial activity or improved biocompatibility.[24,25,33,34] For example, Ce@LTA NPs mimicked superoxide dismutase (SOD) and catalase (CAT) to scavenge reactive oxygen species (ROS), while porphyrin-based MOFs (*e.g.*, PCN-224) combined photodynamic therapy (PDT) with the hypoxia relief strategy to enhance tissue regeneration.[38,39] The introduction of metal ions like copper or silver could impart antimicrobial effects, beneficial in wound healing applications, while the selection of biocompatible linkers ensured that MOFs did not elicit adverse immune responses, making them safer for clinical use.[40–43]

In recent years, MOFs garnered significant attention in the field of biomedicine, particularly in tissue engineering and drug delivery.[44–46] Their integration into advanced transdermal drug delivery systems (TDDS), such as hydrogels, microneedle patches, and electrospun fibers, demonstrated synergistic therapeutic effects. For example, MOF-loaded hydrogels (*e.g.*, F-GZ@G) exhibited cascade enzymatic activity for glucose depletion and H_2O_2 generation, while microneedle arrays (*e.g.*, MN-MOF-GO-Ag) enabled deep tissue penetration for localized metal ion and drug delivery.[38,39] Their ability to serve as carriers for therapeutic agents, as well as scaffolds that support tissue regeneration, positioned them as promising materials for promoting wound healing.[47–49] MOFs could be loaded with bioactive compounds, such as growth factors, antimicrobial agents, or anti-inflammatory drugs, and could deliver these agents directly to the wound site, thereby enhancing the healing process.[39,50–52] Notably, photothermal MOF composites (*e.g.*, CuPDA NPs) achieved >95% bacterial eradication under near-infrared (NIR) light, while dual-layer hydrogels with cyanobacteria and MOFs (*e.g.*, HA-DA/Fe^{3+}/PCN@BP) provided real-time infection monitoring and oxygen generation.[38,39] Furthermore, their porous structure served as a scaffold for tissue regeneration, providing a supportive matrix that facilitated cell growth and the formation of new tissue.[48,53] For example, electrospun MOF fibers (*e.g.*, DMOG@ZIF-67) promoted angiogenesis and collagen remodeling *via* sustained HIF-1α stabilization, addressing diabetic wound chronicity.[38,39]

Additional insights from recent advances in MOF research have expanded the therapeutic horizons beyond conventional drug delivery. For example, a novel MOF platform developed for

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sonodynamic therapy demonstrates that external stimuli like ultrasound can trigger on-demand drug release. This approach offers a promising strategy that could be adapted for wound healing applications, where controlled, stimulus-responsive release of therapeutic agents may further optimize the healing process.[54] Similarly, studies on Zn-MOFs and Cu-based MOFs in cancer therapies reveal robust dual-drug loading capabilities and synergistic treatment effects. These design principles, emphasizing the simultaneous delivery of multiple agents, can enable the development of wound care systems where the co-delivery of antibiotics, growth factors, and anti-inflammatory compounds is essential. The incorporation of such strategies can lead to enhanced antimicrobial action and accelerated tissue regeneration.[55] Moreover, recent reviews in the field of biomedical MOF materials for antimicrobial therapy and MOF composites for osteoporosis have underscored the importance of tailoring drug release profiles to specific physiological conditions. This concept is directly applicable to wound healing, where dynamic and responsive drug release, adjusting to changes in pH, temperature, or enzymatic activity at the wound site, can significantly improve therapeutic outcomes. In particular, the controlled release of bioactive metal ions, as demonstrated in Cu-based MOF studies, reinforces the dual role of these frameworks in both preventing infections and promoting tissue repair.[55–59]

Given their unique properties and versatility, MOFs represent a promising frontier in the development of advanced wound care technologies, where their ability to deliver therapeutics and promote tissue regeneration could address the challenges of chronic and complex wounds. However, challenges such as long-term biocompatibility, scalable fabrication, and clinical translation remain critical areas for future research.

1.2.1. MOFs: features, characterization and fabrication methods. MOFs exhibit exceptional porosity, with surface areas often exceeding 6000 $m^2\ g^{-1}$. This enables vast internal spaces for molecular adsorption, making them ideal for gas storage and catalysis.[60] By varying metal nodes (*e.g.*, Zn, Cu, and Fe) and organic linkers (*e.g.*, carboxylates and imidazolates), MOFs can be tailored for specific functions. For instance, MOF-5 (Zn-based) and HKUST-1 (Cu-based) show structural versatility.[61] Advanced MOFs like UiO-66 (Zr-based) demonstrate remarkable stability at high temperatures and in harsh chemical environments.[62] Post-synthetic modifications allow pore functionalization with groups like amines or sulfonates, enhancing selectivity in applications such as CO_2 capture.[63]

Understanding MOF properties requires robust analytical methods. X-ray diffraction (XRD) confirms crystallinity, while scanning/transmission electron microscopy (SEM/TEM) visualizes morphology. Brunauer–Emmett–Teller (BET) analysis quantifies surface area, and gas physisorption measures pore size distribution. Fourier-transform infrared (FTIR) spectroscopy and X-ray photoelectron spectroscopy (XPS) identify functional groups and bonding. Thermogravimetric analysis (TGA) assesses decomposition temperatures. High-pressure volumetric systems evaluate gas storage capacity (*e.g.*, H_2 and CH_4).[64–67]

MOF synthesis balances crystallinity, scalability, and functionality. Solvothermal/hydrothermal synthesis is the most common method, involving heated mixtures of metal salts and ligands in solvents (*e.g.*, DMF). It yields high-quality crystals but requires long reaction times. Microwave-assisted synthesis accelerates crystallization (minutes *vs.* days) with uniform particle sizes. Electrochemical synthesis enables the formation of thin-film MOFs under mild conditions, useful for sensors. Mechanochemical synthesis include solvent-free grinding of precursors, promoting green chemistry. Post-Synthetic Modification (PSM) also introduces functional groups post-synthesis (*e.g.*, adding amines to enhance CO_2 affinity).[68,69]

Recent advances focus on MOF composites (*e.g.*, MOF-polymer membranes) and computational design using machine learning to predict novel structures. Challenges remain in scaling production and enhancing stability under operational conditions, yet MOFs continue to redefine possibilities in nanotechnology and sustainability.

1.2.2. MOFs in drug delivery and wound healing. The porosity of MOFs allows for high drug-loading capacities, while their surfaces can be functionalized to achieve stimuli-responsive release mechanisms, such as pH-, temperature-, or light-triggered drug delivery.[70–72] For instance, the acidic microenvironment of chronic wounds can trigger the degradation of pH-sensitive MOFs like ZIF-8 (zeolitic imidazolate framework-8), enabling targeted release of therapeutic agents.[73–76] In wound healing, MOFs have been engineered to deliver antimicrobial, anti-inflammatory, and pro-angiogenic agents.[41,49,52] Chronic wounds, such as diabetic ulcers, often involve bacterial colonization and dysregulated inflammation. MOFs like MIL-100(Fe) and ZIF-8 have demonstrated efficacy in encapsulating antibiotics (*e.g.*, ciprofloxacin) and growth factors (*e.g.*, VEGF), ensuring sustained release to mitigate infection and promote tissue regeneration.[77] For example, Chen *et al.* (2020)[78] developed a MOF–hydrogel composite loaded with deferoxamine, which enhanced angiogenesis and accelerated diabetic wound closure in murine models by stabilizing hypoxia-inducible factors. Additionally, intrinsic antimicrobial properties of certain MOFs, such as Zn-based frameworks, arise from the gradual release of metal ions (*e.g.*, Zn^{2+}), which disrupt bacterial membranes.[79,80] The clinical translation of MOFs necessitates rigorous evaluation of their biocompatibility.[81,82] Studies highlight that MOFs constructed from endogenous metals (*e.g.*, Fe^{3+} and Zn^{2+}) and biodegradable ligands (*e.g.*, carboxylates) degrade into non-toxic byproducts under physiological conditions. For instance, *in vivo* assessments of Fe-MOFs revealed minimal systemic toxicity and complete renal clearance of degradation products.[83] However, long-term accumulation and dose-dependent cytotoxicity require further investigation, particularly for MOFs with non-biodegradable components. MOFs represent a versatile platform for advanced wound care, offering tailored drug delivery and inherent therapeutic properties. While preclinical studies are encouraging, interdisciplinary efforts are needed to address scalability, toxicity, and regulatory hurdles, paving the way for clinical adoption.

1.3. Copper as a therapeutic agent

Copper, a transition metal and essential trace element, plays a pivotal role in numerous biological processes, including wound healing.[84–87] As a key component in various enzymatic

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reactions, copper contributed to critical functions such as angiogenesis, inflammation control, and microbial defense. These properties rendered copper an attractive therapeutic agent for promoting wound healing, especially when incorporated into advanced materials like metal–organic frameworks (MOFs).[88–94] By integrating copper into wound care products, the metal's inherent therapeutic effects could be harnessed to enhance the healing process. Copper's role in wound healing is multifaceted, involving several key mechanisms. One of copper's most significant therapeutic functions is its strong antimicrobial activity.[95–97] Copper ions were known to disrupt bacterial cell membranes, destabilizing their structure and function. Moreover, copper catalyzed the production of reactive oxygen species (ROS), which further contributed to microbial death by causing oxidative damage to essential cellular components such as DNA, proteins, and lipids.[95,98–101] This antimicrobial effect was particularly valuable in wound care, as bacterial infections were a common complication that could significantly delay the healing process.[102–104] By reducing the microbial load at the wound site, copper helped to prevent infections and created a more favorable environment for tissue repair.

Copper also played a vital role in stimulating angiogenesis, the process of forming new blood vessels.[91,105,106] This was crucial for wound healing because newly formed blood vessels supplied oxygen and essential nutrients to the regenerating tissue.[107] Copper ions promoted angiogenesis by upregulating the expression of angiogenic factors such as vascular endothelial growth factor (VEGF), which was essential for the proliferation and migration of endothelial cells.[108–111] By facilitating the growth of new blood vessels, copper accelerated the delivery of oxygen and nutrients to the wound site, speeding up tissue repair and regeneration.[112–114] Another important function of copper in wound healing was its involvement in collagen synthesis.[86,112,115] Copper acted as a cofactor for several enzymes, including lysyl oxidase, which was responsible for cross-linking collagen fibers.[86] This cross-linking was critical for the structural integrity and strength of newly formed tissue. Without adequate collagen formation, the wound could not properly close, and the tissue remained fragile.[10] By supporting collagen production and maturation, copper enhanced the wound's structural foundation and helped ensure long-term healing and tissue stability.[116,117]

Incorporating copper into MOFs, such as HKUST-1, allowed for a synergistic combination of copper's biological benefits with the structural advantages of MOFs.[89–92,94,118–123] HKUST-1, a copper-based MOF, offered a porous architecture that facilitated the controlled, gradual release of copper ions over time. This sustained release ensured continuous antimicrobial action and pro-healing effects, making HKUST-1 an ideal candidate for advanced wound care applications. By delivering copper ions in a controlled manner, HKUST-1 not only helped to maintain an infection-free environment but also promoted angiogenesis and collagen synthesis, thereby accelerating wound closure and tissue regeneration[118,124–126] (Fig. 2).

The combination of copper's therapeutic properties with the versatility and tunability of MOFs positioned materials like HKUST-1 at the forefront of innovative wound care solutions. This approach holds promise for the development of advanced wound dressings and treatment strategies that could address the challenges of chronic and complex wounds, where traditional therapies often fall short.

1.4. Advantages and drawbacks of HKUST-1 in wound healing

HKUST-1, a copper-based MOF, releases bioactive Cu^{2+} ions, which exhibit strong antibacterial effects against pathogens like

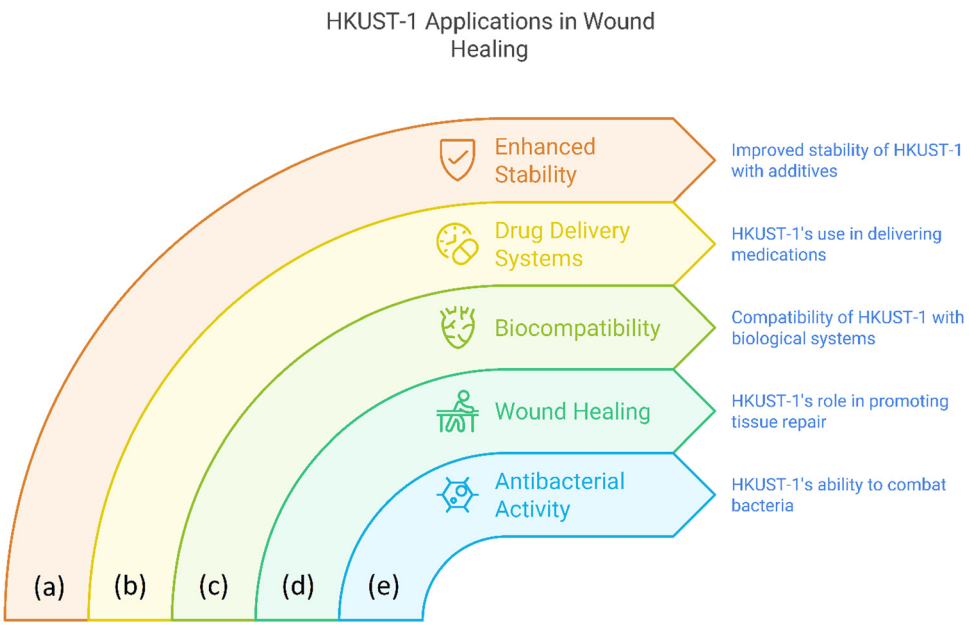

Fig. 2 Multifunctional applications of HKUST-1 in wound healing: (a) enhanced stability *via* additive incorporation, (b) controlled drug delivery for therapeutic release, (c) biocompatibility with host tissues, (d) acceleration of tissue regeneration, and (e) broad-spectrum antibacterial activity to prevent infections.

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S. aureus and *E. coli*. This property is particularly beneficial for preventing infections in chronic wounds, such as diabetic ulcers.[38,118,127] Cu^{2+} ions released by HKUST-1 stimulate angiogenesis by upregulating vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), which are critical for tissue regeneration and wound healing.[123] HKUST-1 can be modified (*e.g.*, with biotin or polymers) to achieve sustained release of Cu^{2+}, reducing the risk of ion toxicity while maintaining therapeutic efficacy.[123] When stabilized, HKUST-1 demonstrates good biocompatibility, making it suitable for biomedical applications. For example, biotin-stabilized HKUST-1 scaffolds promote mesenchymal stem cell (MSC) adhesion and endothelial differentiation, enhancing wound healing.[123] HKUST-1 can be integrated into advanced wound dressings, such as hydrogels and electrospun fibers, to provide combined antibacterial, anti-inflammatory, and tissue-regenerative effects.[128] However, rapid release of Cu^{2+} ions from HKUST-1 can lead to non-physiological concentrations, posing a risk of ion poisoning and cytotoxicity if not properly controlled.[123] HKUST-1 may degrade in aqueous environments, limiting its long-term efficacy in wound healing applications. Stabilization strategies (*e.g.*, biotin modification) are required to address this issue.[123] The synthesis of HKUST-1 often requires precise conditions, such as specific copper salt precursors and solvothermal methods, which can be time-consuming and costly.[118]

1.5. Comparison of HKUST-1 with Other MOFs

ZIF-8 is highly biocompatible and releases Zn^{2+} ions, which promote cell proliferation and collagen deposition. It is also easier to synthesize compared to HKUST-1 (Table 1).[129] However, ZIF-8 lacks the strong antibacterial properties of HKUST-1, making it less effective in infected wound environments.[129] MIL-101 exhibits excellent drug-loading capacity and can be used for synergistic therapies, such as photothermal and chemodynamic therapy, enhancing wound healing in complex cases.[118,129] However, iron-based MOFs may cause oxidative stress due to Fenton reactions, potentially damaging healthy tissues.[129] PCN-224 is highly stable and can be used for photodynamic therapy (PDT) to kill bacteria and promote tissue regeneration. It is also pH-sensitive, enabling targeted drug release.[129] However, the synthesis of PCN-224 is complex, and its high cost limits its widespread application in wound care. Ag-based MOFs have shown excellent antimicrobial properties due to silver release but potential cytotoxicity and high cost limit clinical translation. Bimetallic MOFs obtained by combining different metal ions (*e.g.*, Zn/Cu or Fe/Ag) can provide synergistic antibacterial and wound-healing effects, but their synthesis and stability remain challenging. Mg-based MOFs are highly biocompatible with anti-inflammatory effects, but show a weaker antibacterial performance compared to Cu- or Ag-based MOFs.[49,80,130]

HKUST-1 stands out for its strong antibacterial and angiogenic properties, making it highly effective in treating infected and chronic wounds. However, its potential toxicity and stability issues require careful modification and controlled release strategies. Compared to other MOFs like ZIF-8, MIL-101, and PCN-224, HKUST-1 offers unique advantages in wound healing

Table 1 Comparison of HKUST-1 with other MOFs for wound healing

MOF	Advantages	Challenges
HKUST-1 (Cu-based MOF)	Strong antibacterial effects due to Cu^{2+} release Promotes angiogenesis for tissue regeneration High porosity enables drug loading and sustained release	Stability issues in aqueous environments lead to rapid degradation Potential cytotoxicity at high Cu^{2+} concentrations
ZIF-8 (Zn-based MOF)	Highly biocompatible and promotes cell proliferation and collagen deposition Easy and cost-effective synthesis Good structural stability prevents premature degradation	Lacks strong antibacterial properties and less effective for infected wounds Limited angiogenic potential
MIL-101 (Fe-based MOF)	Exceptional drug-loading capacity for multifunctional therapy Enables photothermal and chemodynamic therapy Iron release mimics enzyme activity, aiding bacterial killing	Potential oxidative stress from Fenton reactions may damage healthy tissues Stability and Fe^{3+} release require optimization
PCN-224 (Zr-based MOF)	High stability and biocompatibility for long-term use Photodynamic therapy (PDT) effectively kills bacteria and promotes tissue regeneration pH-sensitive drug release for targeted therapy	Complex synthesis increases production cost Requires additional modifications for strong antibacterial effects
Ag-based MOFs	Excellent antimicrobial properties due to silver release Effective against antibiotic-resistant bacteria	Potential cytotoxicity and high production cost Stability issues in physiological environments
Bimetallic MOFs (*e.g.*, Zn/Cu and Fe/Ag)	Synergistic antibacterial and wound-healing effects Can combine multiple therapeutic mechanisms	Complex synthesis process Stability and controlled release require further research
Mg-based MOFs	Highly biocompatible and anti-inflammatory Promote cell proliferation and wound healing	Weaker antibacterial performance compared to Cu- or Ag-based MOFs - Require modification for enhanced therapeutic efficiency

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but also presents challenges that need to be addressed for clinical translation. Future research should focus on optimizing HKUST-1's stability and biocompatibility while exploring its integration with other MOFs for synergistic effects.[49,80,130]

2. HKUST's potential for drug delivery and synergistic effects

2.1. HKUST-1's drug loading capabilities

HKUST-1 possesses a highly porous structure that makes it particularly well-suited for the encapsulation and delivery of a wide range of bioactive molecules.[118,131–138] Its extensive internal surface area allows for the efficient loading of therapeutic agents, providing a versatile platform for drug delivery in wound care applications. The material's porous architecture facilitates the storage of molecules such as antibiotics, growth factors, and anti-inflammatory agents, enabling the controlled and sustained release of these compounds at the wound site.[47,49,139–142] One of the primary advantages of HKUST-1 in wound management is its capacity to carry multiple therapeutic agents simultaneously.[49,140,143] For instance, antibiotics can be loaded into the framework to prevent or treat bacterial infections, a common issue that can severely impede wound healing.[80,126,144–146] At the same time, HKUST-1 can be loaded with growth factors—proteins that stimulate cellular proliferation and tissue regeneration—helping to accelerate the formation of new tissue and blood vessels.[47,53,147,148] Furthermore, the incorporation of anti-inflammatory agents can mitigate swelling and reduce prolonged inflammation, which often hinders the healing process, especially in chronic wounds.[47,149,150] In addition to its drug delivery capabilities, HKUST-1 offers another key therapeutic benefit: the controlled release of copper ions.[91,113,140] Copper ions are known for their antimicrobial properties and their role in promoting angiogenesis and collagen synthesis.[86,112,115,151–156] The gradual release of copper from HKUST-1 enhances its overall therapeutic effect by providing effective microbial protection and promoting the biological processes necessary for wound healing. This dual-action capability—delivering both copper ions and other therapeutic agents—makes HKUST-1 particularly advantageous in advanced wound care, where multiple factors often contribute to delayed or impaired healing. The tunable nature of HKUST-1 also allows for the precise control of drug release kinetics.[61,157–162] By modifying the material's structure or surface chemistry, HKUST-1 can be designed to release drugs in response to specific environmental triggers, such as changes in pH, temperature, or enzymatic activity at the wound site.[163–166] This responsiveness ensures that therapeutic agents are delivered when they are most needed, optimizing treatment efficacy while minimizing potential side effects.

Overall, HKUST-1's drug-loading capacity and ability to deliver a combination of therapeutic molecules and copper ions position it as a promising candidate for advanced wound care applications. By enabling the controlled release of antibiotics, growth factors, and anti-inflammatory agents, alongside the antimicrobial and pro-healing properties of copper, HKUST-1 provides a comprehensive approach to managing wounds, particularly those that are chronic or otherwise difficult to heal.

2.2. Synergy with other therapies

HKUST-1's therapeutic potential can be further enhanced when used in combination with other advanced wound healing strategies, such as hydrogels, biocompatible polymers, or specialized wound dressings.[91,92,120,125,167] These hybrid systems offer the advantage of integrating the unique properties of HKUST-1 with the structural and functional benefits of other materials, creating multifunctional platforms that provide sustained, controlled, and targeted release of therapeutic agents.

One promising approach is the incorporation of HKUST-1 into hydrogels, which are good absorbents and biocompatible materials commonly used in wound care.[91,92,125] Hydrogels provide a moist environment conducive to wound healing, while also protecting the wound from external contaminants.[168] By embedding HKUST-1 into a hydrogel matrix, it is possible to combine the hydrophilic properties of the gel with the porous nature of HKUST-1. This hybrid system allows for the gradual release of bioactive molecules, such as antibiotics or growth factors, extending their therapeutic effect over time. Additionally, the slow release of copper ions from HKUST-1 within the hydrogel could provide continuous antimicrobial protection, making it particularly effective for treating wounds prone to infection.[91,92,125] Similarly, integrating HKUST-1 into specialized wound dressings or biocompatible polymers can enhance the material's therapeutic capabilities.[120,126,167] These dressings act as physical barriers that protect the wound while also delivering therapeutic agents in a controlled manner. When combined with HKUST-1, these materials can be engineered to release drugs or copper ions over extended periods, ensuring that the wound receives a consistent supply of healing-promoting compounds. This is especially beneficial in the treatment of chronic wounds, where prolonged antimicrobial activity and sustained stimulation of tissue regeneration are critical for successful healing. The combination of HKUST-1 with other therapies creates a synergistic effect by addressing multiple facets of the wound healing process simultaneously.[119,123,125] For example, a hybrid system incorporating HKUST-1 into a bioactive dressing could simultaneously control infection through the release of antimicrobial copper ions, promote angiogenesis and tissue repair through growth factor delivery, and reduce inflammation with anti-inflammatory agents. By tackling several aspects of wound healing at once—such as infection control, tissue regeneration, and inflammation reduction—these integrated systems offer a more comprehensive approach to wound management, potentially accelerating healing times and improving patient outcomes. In summary, the synergy between HKUST-1 and other therapeutic materials, such as hydrogels and specialized dressings, holds great promise for advancing wound care technologies. These hybrid systems enable the controlled and sustained release of therapeutic agents, enhancing the overall effectiveness of treatment and addressing the complex challenges posed by chronic and non-healing wounds.

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Table 2 Characterization and efficacy of various HKUST-1 based nanoplatforms in wound healing and antibacterial Applications

Nanoplatform	Particle size	Concentrations	Release mechanism	Antibacterial mechanism	Efficacy	*In vivo* results	*In vitro* results	Other results	Ref.
HKUST-1/chitosan/PVA fibers	518 nm	0.10 g HKUST-1	Gradual release of Cu^{2+} ions	Synergistic effect of HKUST-1 and chitosan	99% antibacterial efficiency	99.1% wound closure on the 12th day	99% kill ratio against *E. coli* and *S. aureus*	Enhanced cell adhesion and proliferation	167
HKUST-1	2 μm	4%	NIR light-triggered	Photothermal and NO release	100% inhibition of *S. aureus* and *E. coli*	90% bacterial reduction in wound	Significant reduction in biofilm biomass	Enhanced cell proliferation and angiogenesis	119
TAX@HKUST-1	71.61 ± 21.59	41.94 ± 2.60%	Oxygen-releasing	Antimicrobial, anti-oxidative stress	90% inhibition rate against *S. aureus* and *E. coli*	Promotes epidermal neogenesis, angiogenesis, and collagen deposition	Good CAT enzyme activity and promotes O_2 generation from H_2O_2	—	126
QHKUST-1	Not specified	100 μg mL^{-1}	Catalyzes H_2O_2 to generate hydroxyl groups	Antibacterial therapy	3.95% survival rate for MRSA and 10.6% survival rate for *E. coli*	Facilitates bacteria-infected diabetic wound healing	Promotes cell migration more effectively than HKUST-1	Enhanced moisture stability and catalytic capabilities	172
Cur/MH/HKUST-1@Gel	Not specified	Not specified	pH-dependent	Not specified	Enhanced effects against oxidative stress and promotion of granulation tissue cells	Significantly accelerated wound healing of diabetic mice	Enhanced cell migration and growth of granulation tissue cells	Bio-stability and dual drug load efficiency	125
B-HKUST-1	~267.2 nm	0.5 mM	Sustained release of Cu^{2+}	Upregulation of TGF-β, VEGF, and α-SMA	Promotes MSC adhesion, proliferation, and endothelial differentiation	Wound closure rate: 65.68% on day 5 and 96.46% on day 16	MSC proliferation: 26.3% increase over 8 days; endothelial differentiation: 52% adipogenesis, 106% chondrogenesis, and 182% osteogenesis	Improved stability and hydrophobicity	123
HKUST-1 NPs	285.6 ± 2.7 nm	0.1 m	Sustained release	Copper ion release	Enhanced wound healing	Wounds treated with H-HKUST-1 were almost completely healed by day 21, whereas wounds treated with PBS, PPCN, and HKUST-1 NPs healed by day 39, 39, and 37 on average. Blood vessel density in H-HKUST-1-treated wounds was 54.0 ± 14.4 vessels per mm^2, compared to 11.3 ± 8.0 vessels per mm^2 in PBS-treated wounds	H-HKUST-1 showed a much lower toxicity against HEKa and HDF cells, especially at high concentration (1×10^{-3} M) compared to $CuSO_4$ and HKUST-1 NPs. H-HKUST-1 induced 10.7 ± 2.5% cell apoptosis in HEKa and 17.0 ± 5.4% cell apoptosis in HDF cells, compared to 75.9 ± 3.2% and 90.3 ± 6.5% respectively for $CuSO_4$. H-HKUST-1 promoted the highest migration rate of HEKa cells (91.7 ± 3.5%) and HDF cells (71.4 ± 3.8%) compared to other treatments	Stability in protein solution and antioxidant properties	91
CaO2/HKUST-1@L-Arg	86.1 ± 6.3	40 μg mL^{-1}	Acid-responsive release of Cu^{2+} ions and L-Arg	Generation of H_2O_2, $^{\bullet}OH$, NO, and $ONOO^-$	6.6-log reduction for MRSA, 5.5-log reduction for *P. aeruginosa*	2.3-log reduction in bacterial count and 97.0 ± 2.5% wound healing rate on Day 9	Complete biofilm destruction, near-total bacterial eradication	Low cytotoxicity and minimal hemolysis	121
F-HKUST-1	Not specified	0.5 mM	Slow release of Cu^{2+}	Induces angiogenesis and promotes collagen deposition and re-epithelialization	Improved wound healing in diabetic mice	Wound closure rates: 14 days for 50% closure; body weight constant; granulation tissue thickness: 107.8 ± 18.1 μm; epithelial gap: 37.9 ± 44.7 μm; vascular density: 9.8 ± 0.3 vessels per mm	Lower toxicity to HEKas and HDFs at high concentrations; enhanced cell migration; and the largest number of tubule junctions	Higher stability in protein solutions and increased hydrophobicity	90
HKUST-1	Not specified	0.5 mM	Rapid release of Cu^{2+}	Induces angiogenesis and promotes collagen deposition and	Improved wound healing in diabetic mice	Wound closure rates: 19 days for 50% closure; body weight decreased; granulation tissue thickness: 73.1 ± 17.4 μm;	Higher toxicity to HEKas and HDFs at high concentrations; enhanced cell migration; and a large number of tubule junctions	Lower stability in protein solutions and lower hydrophobicity	90

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Table 2 (*continued*)

Nanoplatform	Particle size	Concentrations	Release mechanism	Antibacterial mechanism	Efficacy	*In vivo* results	*In vitro* results	Other results	Ref.
				re-epithelialization		epithelial gap: 396.8 ± 248.7 μm; vascular density: 7.1 ± 0.6 vessels per mm			
HKUST-1/CS film	Not specified	6.06 μmol mg−1	Slow release of Cu^{2+} ions	Electrostatic attraction to bacteria	Significant antibacterial activity against *S. aureus* and *E. coli*	Enhanced wound closure rate over 21 days and promoted vessel regeneration	Efficient antibacterial activity, significant reduction in bacterial count within 120 minutes, reduced cytotoxicity (cell viability above 80% at concentrations up to 0.4 mg mL^{-1})	Low cytotoxicity and durable antibacterial performance	171
HKUST-1	100-300 nm	0.5 wt %	Controlled release	Copper ions and NO	High	Wound healing rate: 97.80% after 11 days, 99.57% after 13 days; new blood vessels: highest total length of new blood vessels among all groups	Cell proliferation: highest cell proliferation efficiency among all groups on the 7th day; cell migration: a significantly larger number of migrated cells compared to other groups; and tube formation: significantly highest tube length compared to other groups	Improved angiogenesis, collagen deposition, and anti-inflammatory properties	89
HKUST-1	1–3 μm	Not specified	Peroxidase (POD)-like activity	Generation of •OH from H_2O_2 for bacterial inhibition	Effective against *E. coli* and MRSA	Accelerated wound healing with a closure rate of 90% at day 7	Significant reduction in bacterial colonies: *E. coli* (high inhibition rate) and MRSA (marked decrease in bacterial counts)	Good biocompatibility	127
Cu-TCPP	Ultrathin 2D nanosheets	Not specified	Peroxidase (POD)-like activity	Generation of •OH from H_2O_2 for bacterial inhibition	Less effective than HKUST-1	Not specified	Effective bacterial inhibition	Higher surface area	127

2.3. Case studies

2.3.1. Drug delivery platforms. In this subsection, we explore the potential of metal–organic frameworks (MOFs), particularly the copper-based HKUST-1, as versatile drug delivery platforms for wound healing applications (Table 2). By leveraging the inherent properties of HKUST-1, such as its high surface area, tunable porosity, and the ability to be modified with bioactive molecules (*e.g.*, folic acid), researchers have developed systems that enable the controlled release of copper ions and therapeutic agents. This controlled release not only facilitates key wound-healing processes, such as angiogenesis, collagen deposition, and re-epithelialization, but also minimizes cytotoxicity, making these platforms particularly promising for treating chronic wounds, including diabetic ulcers. Metal–organic frameworks (MOFs) such as HKUST-1 can be modified to release copper ions slowly, which aids in wound healing by promoting angiogenesis, collagen deposition, and re-epithelialization. The incorporation of folic acid (Vitamin B9) into HKUST-1 enhances its stability and reduces toxicity. Vitamins, including folic acid, play a crucial role in wound healing. Folic acid supports cell proliferation and tissue repair, making it particularly beneficial when combined with HKUST-1 for treating chronic wounds, especially in diabetic patients. Folic acid-modified HKUST-1 (F-HKUST-1) demonstrates improved stability in protein solutions, sustained copper ion release, and reduced cytotoxicity, leading to better wound healing outcomes in diabetic mice. In diabetic wound models, F-HKUST-1 has been shown to significantly accelerate wound closure, promote angiogenesis, and enhance collagen deposition, indicating its potential as a therapeutic agent for chronic non-healing wounds.[169] A hybrid composite (Cur/MH/HKUST-1@Gel) combining metformin hydrochloride (MH) and curcumin (Cur) in copper-based MOFs (HKUST-1) within a thermosensitive hydrogel was developed to improve diabetic foot ulcer (DFU) healing by reshaping the wound microenvironment. The hybrid system achieved high drug loading efficiencies: curcumin (38.35 ± 1.18%) and metformin hydrochloride (26.84 ± 1.05%), totaling 65.19%. The system showed sustained release of drugs under different pH conditions, with significant release percentages of Cu ions: 27.6% (pH 6.0), 66.8% (pH 7.4), and 44.7% (pH 8.0) within 24 hours. In diabetic mice, the wound closure rate reached 94.10 ± 2.79% after 20 days of treatment with Cur/MH/HKUST-1@Gel, significantly higher than those of control groups.[125,170] The HKUST-1/CS film demonstrated significant antibacterial activity against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. This film showed a slow release of copper ions, contributing to its antibacterial effectiveness. *In vivo* experiments on mice revealed that the HKUST-1/CS film not only killed bacteria but also promoted vessel regeneration, leading to an enhanced wound closure rate. The film exhibited better wound healing performance compared to other treatments. Moreover, the controlled release of copper ions resulted in reduced cytotoxicity, making the film safer for wound-healing applications.[171]

The use of biotin-stabilized HKUST-1 nanoparticles (B-HKUST-1) combined with an acellular dermal matrix (ADM) scaffold was also investigated to enhance diabetic wound healing. The B-HKUST-1 nanoparticles were synthesized by modifying HKUST-1

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with biotin to improve stability and hydrophobicity. The ADM scaffold was provided as a biological "niche" for cell attachment and growth. The composite scaffold, ADM–B-HKUST-1, was designed to release copper ions (Cu^{2+}) and mesenchymal stem cells (MSCs) to promote angiogenesis and endothelial differentiation. The results indicated that B-HKUST-1 nanoparticles exhibited a hexahedral structure and were more stable than HKUST-1 in protein solutions. Stability was confirmed through X-ray diffraction (XRD) and transmission electron microscopy (TEM) analyses. The release of Cu^{2+} from B-HKUST-1 was sustained over 210 hours, with 33.93% released in 72 hours and 73.95% in 210 hours. The ADM–B-HKUST-1 scaffold supported MSC adhesion, proliferation, and endothelial differentiation, as evidenced by scanning electron microscopy (SEM) and two-photon excited fluorescence (TPEF) imaging. *In vivo* experiments using a diabetic mouse model demonstrated that the ADM–B-HKUST-1 scaffold significantly improved wound healing. The scaffold promoted angiogenesis, collagen deposition, and re-epithelialization, leading to faster wound closure. Histological and immunofluorescence analyses confirmed the enhanced expression of vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and alpha-smooth muscle actin (α-SMA). These findings suggested that use of the ADM–B-HKUST-1 scaffold could be an effective strategy for diabetic wound healing by providing a sustained release of Cu^{2+} and a conducive environment for MSCs.[123] Another study demonstrated that the NO-loaded HKUST-1 nanoparticles, incorporated into a core–shell nanofiber scaffold, could release nitric oxide (NO) at an average rate of 1.74 nmol L^{-1} h^{-1} for over 14 days. This controlled release significantly improved diabetic wound healing by promoting endothelial cell growth, angiogenesis, and collagen deposition and reducing inflammation. The NO@HPG scaffold showed a wound-healing rate of 97.80% after 11 days and 99.57% after 13 days, significantly higher than those of other groups. The HKUST-1 nanoparticles, with copper ions as the metal center and trimesic acid as the organic ligand, exhibited an octahedral structure. These particles were modified with secondary amino groups to enhance NO loading. The NO-loaded HKUST-1 particles were then incorporated into the core of coaxial nanofibers, with polycaprolactone (PCL) as the core material and gelatin (Gel) as the shell. This structure allowed for a controlled release of NO and copper ions, which synergistically promoted wound healing. The effectiveness of the NO@HPG scaffold in wound healing was attributed to the controlled release of NO and copper ions. NO played a crucial role in inhibiting inflammation, promoting angiogenesis, and stimulating collagen deposition. Copper ions further enhanced these effects by stabilizing NO and promoting endothelial cell growth. The scaffold's micropatterned structure provided high porosity and hydrophilicity, facilitating cell growth and nutrient exchange, which are essential for effective wound healing.[89]

In summary, the diverse range of HKUST-1-based drug delivery platforms—from folic acid-modified nanoparticles and hybrid composite gels to advanced films and nanofiber scaffolds—demonstrate high therapeutic potential for accelerating wound healing. These systems exemplify how the integration of controlled drug release, antibacterial activity, and regenerative support can synergistically address the multifaceted challenges of wound repair. The promising *in vitro* and *in vivo* results underscore the clinical relevance of these platforms and pave the way for future research aimed at optimizing and translating these innovative treatments into practical, patient-centered therapies.

2.3.2. Synergistic composite systems. In this section, we delve into synergistic composite systems that integrate HKUST-1 with various biocompatible matrices to amplify wound-healing outcomes (Table 2). These systems combine the inherent antibacterial and catalytic properties of HKUST-1 with the structural and functional benefits of polymeric substrates such as chitosan/PVA fibers, hydrogels, and acellular dermal matrix scaffolds. By incorporating HKUST-1 into these composites, researchers have achieved a controlled release of copper ions alongside enhanced mechanical properties, water uptake, and biocompatibility. This integration not only intensifies the antibacterial efficacy, often reaching up to a 99% kill ratio against common pathogens, but also promotes cell adhesion, proliferation, and angiogenesis, thereby accelerating wound closure and tissue regeneration.

Incorporating HKUST-1 into chitosan/PVA fibers also significantly enhanced antibacterial properties, achieving a 99% kill ratio against both *Escherichia coli* and *Staphylococcus aureus*. In animal studies, these HKUST-1/chitosan/PVA fibers demonstrated superior wound healing capabilities compared to commercial chitosan dressings, resulting in less inflammation and faster healing rates. The fibers supported cell adhesion and proliferation, indicating good biocompatibility, which is crucial for effective wound healing applications. Additionally, the fibers exhibited excellent mechanical properties, water uptake, and water vapor transmission rates, making them suitable for wound dressing applications.[167] Chronic diabetic foot ulcers (DFUs) were found to lead to over 73 000 nontraumatic lower limb amputations annually and cost between $9 to $13 billion in addition to diabetes-related expenses. Current treatments were largely ineffective. Copper was identified as essential for wound healing processes, including angiogenesis and antimicrobial activity. However, it was noted that high levels of copper ions could be toxic. An innovative hydrogel system incorporating copper metal–organic framework nanoparticles (HKUST-1 NPs) embedded in an antioxidant hydrogel (PPCN) was explored to reduce copper toxicity and enhance wound healing in diabetic mice. The results showed that the hydrogel system had reduced cytotoxicity, enhanced cell migration, and improved wound healing, suggesting its potential as a novel dressing for chronic wounds. HKUST-1 nanoparticles were synthesized using copper acetate monohydrate and H3BTC, which were purified and characterized using 1H NMR and FTIR spectroscopy. The prepared HKUST-1 NPs were added to the PPCN solution to form H-HKUST-1, with detailed characterization provided. The release of copper ions from H-HKUST-1 and H-$CuSO_4$ was assessed in different media using ICP-MS, showing 56.5% copper ion release in PBS and 61.5% in 10% FBS within 24 hours for H-HKUST-1, compared to 88.7% and 89.5% for H-$CuSO_4$. The stability and morphology of PPCN after loading HKUST-1 NPs were investigated and visualized

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using SEM and TEM. H-HKUST-1 showed significantly lower cytotoxicity and apoptosis rates in HEKa and HDF cells compared to $CuSO_4$ and HKUST-1 NPs, promoting the highest cell migration rates in HEKa (91.7% at 30 hours) and HDF cells (71.4% at 54 hours). Wounds treated with H-HKUST-1 healed almost completely by day 21, outperforming other treatments with PBS, PPCN, and HKUST-1 NPs.[91]

Another study focused on developing a multifunctional hydrogel composed of poly(vinyl alcohol) (PVA), sodium alginate (SA), and carboxymethyl chitosan (CMCS), incorporating HKUST-1 nanoenzymes loaded with taxifolin (TAX) and calcium peroxide (CaO_2). The hydrogel aimed to promote diabetic wound healing by providing oxygen release, anti-bacterial, and anti-inflammatory properties. HKUST-1 exhibited catalase-like activity, promoting the decomposition of hydrogen peroxide into oxygen. TAX was loaded into HKUST-1 to enhance its anti-inflammatory and antioxidant properties, while CaO_2 was included to generate oxygen, crucial for wound healing. The FT-IR spectra confirmed the presence of characteristic peaks for HKUST-1 and TAX, while XRD patterns validated the successful synthesis of HKUST-1 and its loading with TAX. BET analysis revealed a significant surface area reduction upon TAX loading, indicating successful incorporation. The hydrogel's swelling properties, rheological behavior, oxygen release, and mechanical properties were also evaluated, demonstrating its suitability as a wound dressing. *In vitro* and *in vivo* experiments demonstrated the hydrogel's efficacy in promoting wound healing. The hydrogel exhibited high antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, with a bacterial inhibition rate of 90%. *In vivo* studies on diabetic mice showed that the hydrogel significantly reduced inflammation, promoted collagen deposition, and enhanced angiogenesis and epidermal regeneration. The hydrogel's ability to release oxygen and TAX in a controlled manner contributed to its effectiveness in treating diabetic wounds, making it a promising candidate for future wound healing applications.[126] Quasi-HKUST-1 (QHKUST-1) nanostructures were also synthesized by calcining HKUST-1 at 250 °C for different durations, enhancing peroxidase activity in wound healing. The optimal calcination time was determined to be 1 hour, which preserved the MOF structure while enhancing peroxidase activity and water stability. QHKUST-1 exhibited a porous structure with improved catalytic capabilities, enabling the effective catalysis of hydrogen peroxide (H_2O_2) to generate hydroxyl radicals ($^{\bullet}OH$) for antibacterial therapy. The structural stability and catalytic performance were confirmed through various analyses. *In vitro* experiments demonstrated that QHKUST-1 exhibited superior antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli* (*E. coli*) compared to HKUST-1. The survival rates of MRSA and *E. coli* were significantly reduced to 3.95% and 10.6%, respectively, when treated with QHKUST-1 and H_2O_2. Additionally, cell migration experiments indicated that QHKUST-1 promoted the migration of RAW 264.7 cells more effectively than HKUST-1, achieving a migration rate of 80.5% after 24 hours. *In vivo* studies on diabetic mice with bacteria-infected wounds revealed that QHKUST-1, combined with H_2O_2, significantly accelerated wound healing. The treated wounds showed complete epidermis formation and reduced inflammation, with a higher presence of new granulation tissue and blood vessels. Histological analyses confirmed the enhanced healing effects, indicating that QHKUST-1 could effectively facilitate wound healing by preventing bacterial growth and promoting tissue regeneration. The biocompatibility of QHKUST-1 was also confirmed, showing no significant toxicity *in vivo*.[172]

In summary, the synergistic composite systems leveraging HKUST-1 present a promising and multifaceted approach to wound healing. By uniting the catalytic, antibacterial, and regenerative functions of HKUST-1 with supportive polymer matrices, these platforms address critical challenges such as infection control, inflammation reduction, and tissue repair in chronic wounds. The positive results observed in both *in vitro* and *in vivo* studies underscore the potential of these composites to offer safer, more effective treatments for conditions like diabetic foot ulcers. This integrated strategy not only optimizes therapeutic outcomes but also paves the way for future innovations in advanced wound care therapies.

2.3.3. Treatment mechanisms based on reactive species and photothermal effects. Studies illustrate how the strategic use of reactive species such as $^{\bullet}OH$, H_2O_2, and NO can be harnessed in innovative Cu-MOF-based materials to address complex medical challenges, particularly in combating bacterial infections and enhancing wound healing (Table 2). In the last decade, the antibacterial properties of copper-based metal–organic frameworks (Cu-MOFs) were investigated. Two types of Cu-MOFs, HKUST-1, and Cu-TCPP, were synthesized and characterized. HKUST-1, with its three-dimensional structure, demonstrated a higher peroxidase-like activity compared to the two-dimensional Cu-TCPP. This activity enabled the decomposition of hydrogen peroxide into toxic hydroxyl radicals, which effectively killed both Gram-negative *Escherichia coli* and Gram-positive methicillin-resistant *Staphylococcus aureus*. The antibacterial performance of these Cu-MOFs was evaluated through various experiments. HKUST-1 showed superior antibacterial activity due to its ability to generate more hydroxyl radicals, which damaged bacterial cells. Animal experiments confirmed that HKUST-1 accelerated wound healing with good biocompatibility, making it a promising candidate for antibacterial therapy. They highlighted the potential of Cu-MOFs in biomedical applications, particularly in fighting bacterial infections and promoting wound healing. The unique properties of HKUST-1, such as its high surface area and catalytic efficiency, were emphasized as key factors in its effectiveness. The findings suggested that Cu-MOFs could be further developed for targeted antibacterial treatments in the future (Fig. 3).[127]

Recently, a multifunctional nanoplatform was developed to enhance chemodynamic therapy (CDT) for biofilm eradication by self-supplying hydrogen peroxide (H_2O_2) and generating nitric oxide (NO). This nanoplatform responded to the acidic microenvironment within biofilms, triggering reactions that produced reactive species such as NO, hydroxyl radicals, and peroxynitrite, which effectively dispersed biofilms and reduced bacterial viability. *In vitro* assays demonstrated significant antibiofilm efficacy against both Gram-positive methicillin-resistant *Staphylococcus aureus* and Gram-negative *Pseudomonas aeruginosa*, reducing

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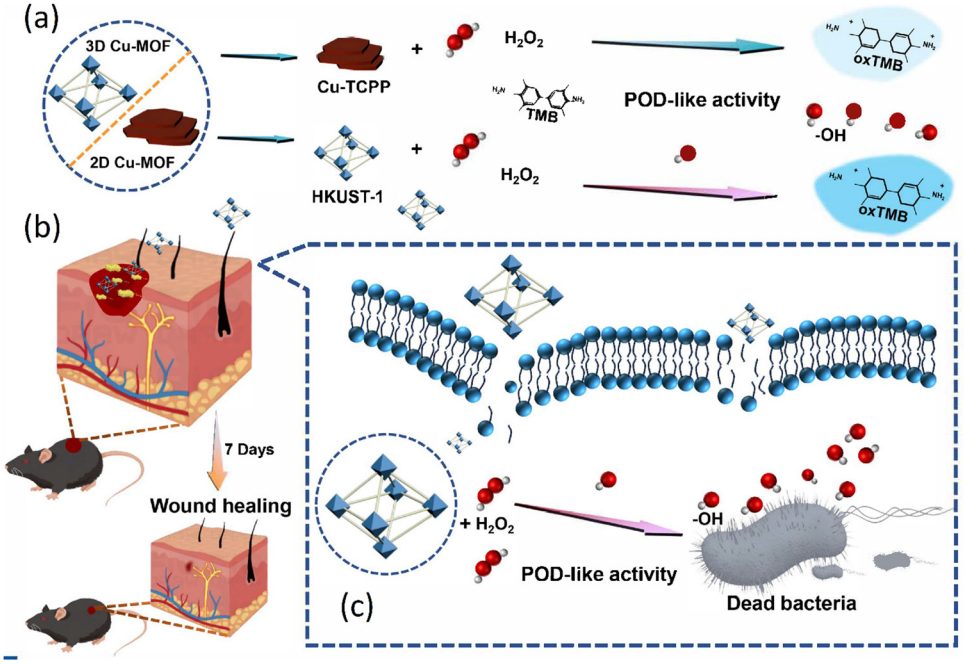

Fig. 3 The synthesis and application of a MOF for antibacterial purposes. (a) The synthesis process shows the transition from a 2D Cu-MOF to a 3D Cu-MOF (HKUST-1), highlighting the structural changes involved. (b) The MOF's effectiveness is demonstrated on a mouse model, showing significant wound healing for seven days. In terms of antibacterial activity (c), the 3D Cu-MOF is combined with H_2O_2 to achieve peroxidase (POD)-like activity, which effectively leads to the killing of bacteria (under the terms and conditions of the Creative Commons Attribution (CC BY) license).[127]

bacterial viability and extracellular polymeric substance (EPS) content. The nanoplatform comprised several key components: calcium peroxide (CaO_2), HKUST-1 (a copper-based metal–organic framework), and L-arginine (L-Arg). Each component served a specific purpose. CaO_2 provided sustained H_2O_2 production, crucial for initiating the production of reactive species. HKUST-1 encapsulated CaO_2 and released Cu^{2+} ions under acidic conditions to catalyze reactions. L-Arg acted as a natural NO donor, producing NO that dispersed biofilms and reacted with other reactive species to enhance bactericidal effects. The measured particle sizes were as follows: CaO_2 nanoparticles averaged 65.3 ± 3.2 nm, CH nanoparticles (after HKUST-1 coating) averaged 79.5 ± 4.7 nm, and CHA nanoparticles (after adding L-arginine) averaged 86.1 ± 6.3 nm. The zeta potential of these particles also varied with each stage, indicating stability in various environments. *In vivo* experiments performed using mouse models confirmed the nanoplatform's effectiveness in eliminating biofilms and promoting wound healing without adverse effects. The key numerical data highlighted the nanoplatform's capability to generate over 60 μM H_2O_2 within 24 hours under acidic conditions and achieve a 6.6-log reduction for MRSA and a 5.5-log reduction for *P. aeruginosa*. Additionally, cell viability remained above 85% after a 24-hour co-culture period with CHA nanoparticles, and the hemolysis rate was approximately 2.7%, well below the safety threshold of 5%. This study represented a breakthrough in overcoming traditional CDT limitations, offering a promising therapeutic strategy for biofilm-associated infections.[121]

In another study, a smart electrospun fibrous membrane incorporating nitric oxide (NO)-loaded HKUST-1 particles was developed. Near-infrared (NIR) light was used by this membrane to control NO release, effectively eliminating bacterial biofilms and promoting wound healing. The dual functionality of NO, with high concentrations for antimicrobial action and low concentrations for tissue regeneration, was leveraged to enhance the healing process. It was demonstrated by the study that the NO-loaded HKUST-1 particles, when exposed to NIR light, could precisely control the release of NO. This controlled release was effective in both eliminating bacterial biofilms and promoting angiogenesis, which was crucial for wound healing. Significant antibacterial activity against both Gram-positive and Gram-negative bacteria was shown by the composite fibrous membranes, and the antibacterial effects were enhanced by the photothermal properties of HKUST-1. Additionally, the gradual degradation of the fibrous membrane facilitated sustained NO release, further aiding the healing process. HKUST-1 was chosen for its high porosity, large surface area, and excellent NO loading capacity. The photothermal properties of HKUST-1 also allowed for precise control of NO release under NIR light, making it an effective dual-function agent for both antimicrobial treatment and wound healing. The release of copper ions during the degradation of HKUST-1 also contributed to the antibacterial and angiogenic effects, enhancing the overall wound-healing process.[119] A novel porous metal–organic framework (MOF) microneedle (MN) patch was also developed for photothermal-responsive nitric oxide (NO) delivery to promote diabetic wound healing (Fig. 4). This patch incorporated a NO-loadable copper-benzene-1,3,5-tricarboxylate (HKUST-1) MOF, encapsulated with graphene oxide (GO), creating NO@HKUST-1@GO microparticles (NHGs). These NHGs were embedded

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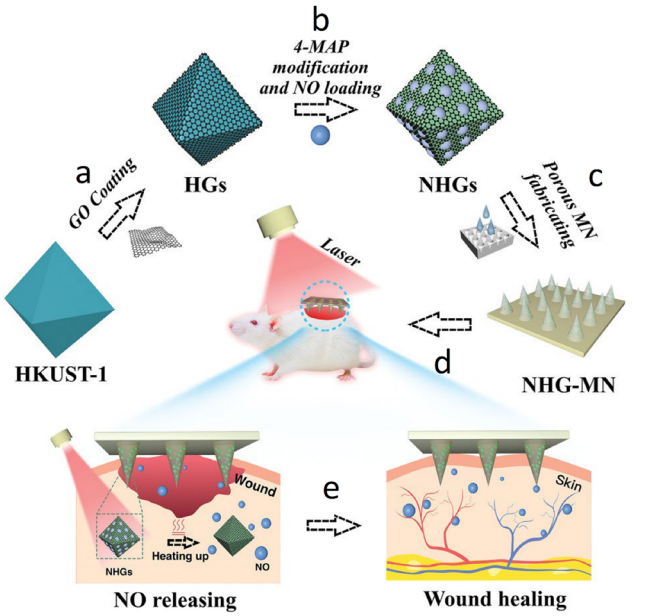

Fig. 4 Schematic illustration of nitric oxide (NO)-loaded HKUST-1-based systems for photothermal-controlled antibacterial and wound-healing applications. (a) and (b) A smart electrospun fibrous membrane incorporating NO-loaded HKUST-1 particles, which utilizes near-infrared (NIR) light to precisely control NO release. High NO concentrations eliminate bacterial biofilms (Gram-positive and Gram-negative), while low concentrations promote angiogenesis and tissue regeneration. HKUST-1's high porosity, photothermal properties, and sustained copper ion release enhance antibacterial and healing efficacy. (c)–(e) A porous metal–organic framework (MOF) microneedle (MN) patch (NHG-MN) for diabetic wound healing, comprising NO@HKUST-1@GO microparticles (NHGs) embedded in a polyethylene glycol diacrylate (PEGDA) matrix. Under NIR irradiation, the patch achieves photothermal-triggered NO release (≈ 3× higher cumulative release *vs.* non-NIR groups), stabilizes temperatures at ≈40 °C, and delivers NO deeper into wounds. The NHG-MN + NIR group achieves 99% diabetic wound closure in 13 days, with enhanced collagen deposition, vascularization, and tissue regeneration. Both systems highlight HKUST-1's dual functionality as a NO carrier and photothermal agent, leveraging copper ions for synergistic antibacterial and angiogenic effects (under the terms of the Creative Commons CC BY license).[124]

in a porous polyethylene glycol diacrylate (PEGDA)-MN patch, facilitating controlled release and deeper delivery of NO molecules into wound sites. The NHG-MN patch significantly accelerated wound healing in a type I diabetic rat model, achieving a 99% wound closure rate within 13 days for the NHG-MN + NIR group. Histological analysis revealed improved vascularization, tissue regeneration, and collagen deposition. The patch exhibited an excellent photothermal response, with temperatures stabilizing around 40 °C under near-infrared (NIR) irradiation, aiding in controlled NO release. The study demonstrated the superior mechanical strength and biocompatibility of the porous MN patch. The Young's modulus of the patch varied with PEGDA concentrations, ensuring adequate mechanical strength for transdermal delivery. The cumulative NO release in the NHG-MN + NIR group was approximately three times higher than that in the NHG-MN group, highlighting the effectiveness of NIR-triggered NO delivery. These findings suggested that the NHG-MN patch held great potential for diabetic wound healing and other therapeutic applications.[124]

In conclusion, the studies reviewed in this section underscore the promising potential of integrating reactive species generation with photothermal control in Cu-MOF-based platforms. By harnessing the controlled production of hydroxyl radicals, hydrogen peroxide, and nitric oxide, these systems achieve potent antibacterial effects while simultaneously promoting key regenerative processes such as angiogenesis, collagen deposition, and re-epithelialization. Moreover, the precise control afforded by photothermal triggers—whether through near-infrared light or other mechanisms—further enhances the efficacy of these materials by enabling on-demand therapeutic action and sustained release of bioactive agents. This dual-action strategy not only addresses the challenges of biofilm eradication and infection control but also fosters an optimal wound microenvironment for accelerated healing. Collectively, these findings pave the way for the development of next-generation, multifunctional wound care therapies that can be tailored to combat chronic and diabetic wounds effectively.

3. Integrated discussion on the mechanisms of nanoplatforms in wound healing

The studies collectively reveal a multifaceted strategy for wound management that leverages the intrinsic properties of copper-based metal–organic frameworks (MOFs) and related composites. Here, we provide an overarching narrative that connects the mechanistic insights of these nanoplatforms.

3.1. Synergistic antibacterial and catalytic activities

At the core of several studies is the catalytic activity of HKUST-1, a three-dimensional Cu-MOF, which exhibits high peroxidase-like (POD-like) activity. By catalyzing the decomposition of low-concentration H_2O_2 into hydroxyl radicals ($^{\bullet}OH$), HKUST-1 directly attacks bacterial cell membranes, achieving significant antibacterial effects against pathogens such as *E. coli* and MRSA.[172] This mechanism is not isolated; it forms the foundation for several composite systems where antibacterial efficacy is enhanced by additional functionalities. For instance, the NO-loaded HKUST-1 particles and NO@HKUST-1@GO microparticles introduce an extra layer of bacterial inhibition through nitric oxide (NO) release, which further disrupts biofilms and modulates the local inflammatory response.[119,124] Thus, the combination of ROS generation and NO release provides a dual-action antimicrobial strategy, creating a robust barrier against infection.

3.2. Controlled ion release and the role of copper

Beyond their direct bactericidal properties, these nanoplatforms are designed to manage the release of copper ions (Cu^{2+}) in a controlled manner. Copper ions are well known for their ability to stimulate angiogenesis, promote cell migration, and facilitate collagen deposition—processes essential for tissue repair. Conventional HKUST-1 nanoparticles release Cu^{2+} in a sustained manner, avoiding the cytotoxicity associated with a sudden burst of ions while ensuring an environment conducive to accelerated wound healing.[173–176] Innovations such as the quasi-HKUST-1

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(QHKUST-1) further improve upon this by enhancing peroxidase activity and water stability, thereby optimizing the balance between antibacterial action and regenerative support.[172]

3.3. Enhancing the microenvironment through oxygen and reactive species modulation

A key insight emerging from our synthesis is that a well-regulated wound microenvironment requires both oxidative control and sufficient oxygen supply. For example, while CaO_2 nanoparticles produce sustained H_2O_2 to exert antibiofilm activity, they also risk generating excessive reactive oxygen species (ROS) if left unchecked.[167] To counterbalance this, composite systems have been developed where HKUST-1 or its derivatives (*e.g.*, CH and CHA formulations) encapsulate CaO_2. These systems not only moderate the release of H_2O_2 but also harness its decomposition into $^{\bullet}OH$ for controlled bacterial killing. Furthermore, hydrogel formulations such as the PVA/SA/CMCS hydrogel with TAX@HKUST-1 utilize oxygen release from CaO_2 to relieve hypoxic conditions in the wound bed, thereby promoting healing and reducing oxidative stress.[121] This dual modulation of ROS and oxygen availability underlines a central theme: the necessity of orchestrating a delicate balance between antimicrobial activity and tissue regeneration.

3.4. Incorporation of bioactive agents for multifunctionality

A further step in the evolution of these nanoplatforms is the incorporation of additional bioactive molecules, such as L-arginine in the CHA system. L-arginine serves as a precursor for NO, enhancing both the bactericidal effects and biofilm dispersal, while also contributing to the signaling pathways that stimulate angiogenesis and cell proliferation.[167] Biotin-HKUST-1 similarly illustrates how surface modifications can promote angiogenesis and support mesenchymal stem cell (MSC) proliferation and migration, leading to enhanced collagen deposition and overall wound repair.[123] These modifications demonstrate that by integrating multiple bioactive components, nanoplatforms can be tailored to simultaneously address infection control, inflammation modulation, and tissue regeneration.

3.5. Overarching mechanistic integration

Collectively, the evidence suggests that the effectiveness of these nanoplatforms does not lie in a single isolated mechanism but rather in their synergistic integration. The coordinated release of antibacterial agents ($^{\bullet}OH$, NO, and Cu^{2+}) and oxygen, combined with the modulation of the wound's microenvironment, creates a cascade of events that transition the wound from an inflammatory state to a regenerative phase. This holistic approach underscores the value of combining catalytic activity, controlled ion release, and bioactive surface modifications. Moreover, the diversity in particle sizes and release profiles across the various platforms indicates that tailoring these parameters can further optimize therapeutic outcomes. Hence, the interconnected mechanisms—from ROS-mediated bacterial eradication and controlled copper ion release to oxygen supply and NO generation—form an integrated strategy that not only combats infection but also actively promotes tissue repair. Such a comprehensive understanding bridges the gap between individual study conclusions and offers a robust framework for the development of next-generation wound healing materials.

4. Innovative comparison between HKUST-1 and other copper-based nanomaterials in wound healing

In advanced wound care, copper-based nanomaterials have garnered significant attention due to their antimicrobial and pro-healing properties.[98,177,178] Among these, HKUST-1 stands out for its unique structural and functional attributes. Traditional copper-based nanomaterials, such as copper oxide (CuO) and copper sulfide (CuS) nanoparticles, have been widely studied for their antibacterial properties.[98,179,180] These nanoparticles typically exert their effects through the direct release of Cu^{2+} ions, which disrupt bacterial cell membranes and interfere with essential cellular processes. Although effective in eliminating pathogens, these materials often suffer from limitations including uncontrolled ion release and potential cytotoxicity.[98,176,179–182] As stated before, in contrast, HKUST-1 possesses a highly ordered, porous crystalline structure that allows for the controlled and sustained release of copper ions. This controlled release is critical in maintaining therapeutic copper levels within the wound microenvironment, reducing the risk of toxicity while promoting angiogenesis and collagen synthesis—key processes in tissue repair. One of the hallmark features of HKUST-1 is its exceptionally high surface area and porosity. These structural characteristics not only facilitate high loading capacities for therapeutic agents but also provide ample active sites for catalytic reactions. HKUST-1 exhibits peroxidase-like (POD-like) activity, catalyzing the decomposition of low concentrations of hydrogen peroxide (H_2O_2) into hydroxyl radicals ($^{\bullet}OH$). This catalytic behavior enhances its antibacterial performance by generating reactive oxygen species (ROS) that can effectively disrupt biofilms and inactivate pathogenic bacteria (Table 2). In contrast, conventional copper salts or CuO nanoparticles lack such intrinsic catalytic properties. Their antimicrobial action relies solely on the ionic toxicity of copper, which may be less effective against biofilm-associated infections and often results in rapid, uncontrolled release of ions.[183–186] Thus, the built-in catalytic functionality of HKUST-1 offers a dual-action approach that combines both controlled ion release and localized ROS generation, leading to more effective bacterial eradication. Another significant advantage of HKUST-1 is its adaptability to form composite systems and smart wound dressings. In previous sections, HKUST-1 integrated into hydrogels or electrospun nanofiber matrices, where it not only provides a controlled release of copper ions but also enhanced the mechanical properties and biocompatibility of the dressing. These composites can be engineered to be stimuli-responsive, releasing therapeutic agents in response to environmental triggers such as pH changes, temperature fluctuations, or even near-infrared (NIR) light. This level of responsiveness is not typically achievable with conventional copper-based nanoparticles, which are generally static in their release

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profiles. The ability of HKUST-1-based systems to adapt to the dynamic wound environment enables a more targeted and efficient healing process, particularly in chronic wounds where conditions can fluctuate dramatically over time. Moreover, in terms of practical applications, HKUST-1 exhibits superior integration capabilities. Its modular structure allows for post-synthetic modifications, which can tailor the material's surface chemistry for improved biocompatibility and targeted therapeutic delivery (Table 2). For instance, modifications with biotin or other biocompatible ligands have been shown to enhance the stability of HKUST-1 in biological environments, further reducing the risk of rapid degradation and excessive copper release. These enhancements are particularly important when compared to simpler copper-based nanomaterials, which may require additional surface coatings or modifications to achieve similar levels of biocompatibility and stability (Table 2).

5. Current challenges and limitations

5.1. Stability under physiological conditions

While HKUST-1 holds great promise for biomedical applications, one of the primary challenges is its long-term stability under physiological conditions (Fig. 5).[47,187] In environments such as bodily fluids (*e.g.*, blood, lymph, or intracellular fluids), HKUST-1 is susceptible to degradation, which can significantly affect its performance. The porous framework that gives HKUST-1 its remarkable drug-loading capacity and therapeutic potential is also a point of vulnerability when exposed to moisture, ions, and varying pH levels typical of biological environments.[188–190] The key issue arises from the sensitivity of HKUST-1 to water and other ions, such as chloride and bicarbonate, which are abundant in physiological fluids.[191,192] These factors can induce hydrolysis, where water molecules break down the bonds between the metal ions (copper in the case of HKUST-1) and the organic linkers, compromising the structural integrity of the framework. This degradation weakens the material, reducing its ability to maintain its porous architecture, and thereby diminishing its drug delivery capacity, antimicrobial properties, and overall therapeutic effectiveness.[189,190,193] Furthermore, the loss of structural integrity can lead to the premature release of therapeutic agents, preventing sustained or controlled drug delivery—a crucial requirement in many medical applications, such as wound healing or targeted cancer therapies. The breakdown of the framework may also result in the uncontrolled release of copper

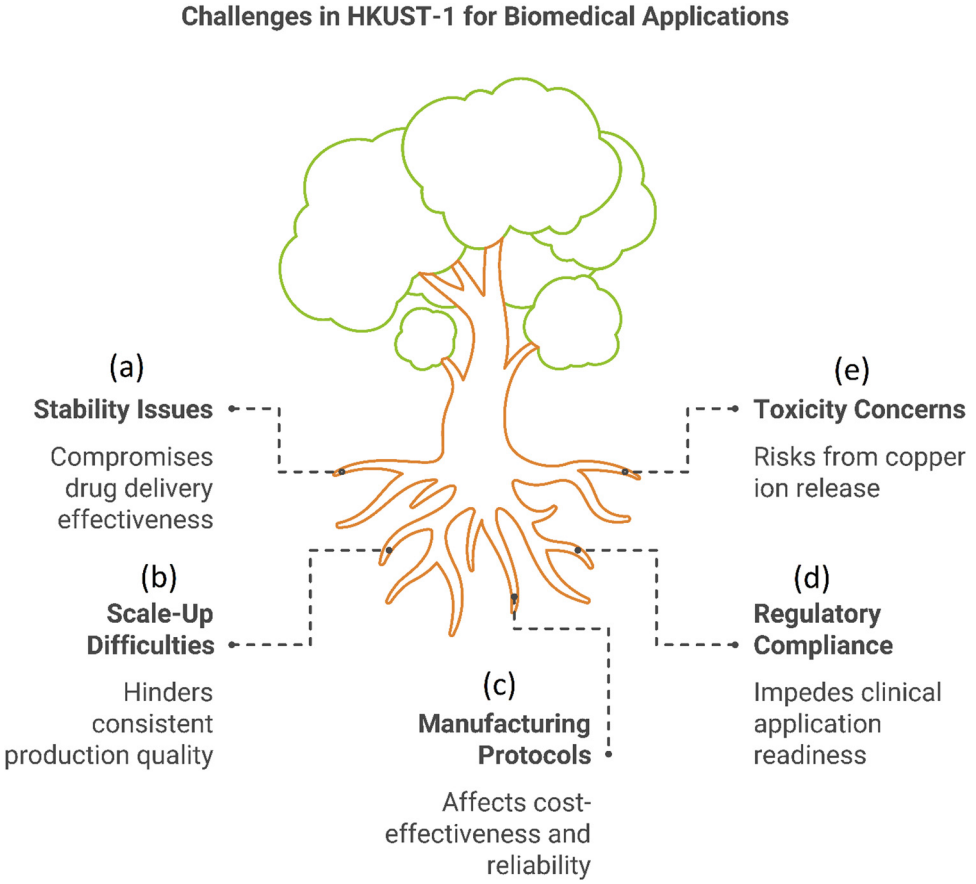

Fig. 5 Challenges in utilizing HKUST-1 for biomedical applications: (a) stability issues and copper-related risks compromising drug delivery effectiveness; (b) scale-up difficulties and regulatory compliance hindrances; and (c) manufacturing inconsistencies and protocol limitations affecting clinical readiness, cost-effectiveness, and reliability.

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ions, potentially leading to cytotoxic effects if copper levels exceed safe thresholds.[134,194].

To fully harness HKUST-1's potential in medical applications, improving its stability in physiological environments is essential. Strategies being explored to address this issue include surface modification of the MOF particles, encapsulation within protective materials, or designing composite materials that integrate more stable components. For instance, coating HKUST-1 with biocompatible polymers or embedding it within hydrogels could help shield the MOF from direct exposure to moisture, thereby enhancing its stability while maintaining its therapeutic function. Ultimately, overcoming the challenge of stability under physiological conditions is critical for the successful translation of HKUST-1 into practical medical applications. Enhanced stability would not only preserve its structural robustness but also ensure that it can provide sustained therapeutic effects over extended periods, making it a more reliable and effective option for drug delivery, wound healing, and other biomedical uses.

5.2. Potential toxicity concerns

A significant concern in the application of HKUST-1 in biomedical contexts is the potential toxicity associated with its copper content.[195] Copper is an essential trace element in the human body, involved in a variety of biological processes, including enzymatic activities, mitochondrial function, and the regulation of oxidative stress.[196] However, when copper ions are released in excessive amounts, they can lead to cytotoxic effects, resulting in damage to cells and tissues. This dual nature of copper—as both a vital nutrient and a potential toxin—presents a major challenge in the clinical use of copper-based materials like HKUST-1.[196] The controlled release of copper ions from HKUST-1 is critical for balancing its therapeutic benefits with the risk of toxicity.[197] While the antimicrobial and pro-healing properties of copper ions are advantageous for wound care and other medical applications, an uncontrolled or rapid release of copper can overwhelm the body's regulatory mechanisms.[198,199] Excessive copper accumulation can induce oxidative stress by generating reactive oxygen species (ROS), which can damage cellular components such as lipids, proteins, and DNA.[200] This oxidative damage not only impairs the healing process but can also exacerbate inflammation and lead to tissue necrosis.[198,200]

In clinical settings, the safe use of HKUST-1 hinges on maintaining a precise balance between copper's beneficial and harmful effects. Achieving this balance requires a deep understanding of the safe dosage limits for copper ion release, which can vary depending on the type of tissue, the duration of exposure, and the specific medical condition being treated. Additionally, the rate at which copper ions are released from HKUST-1 must be carefully controlled to ensure that therapeutic levels are sustained over time without reaching toxic concentrations. Further research is essential to optimize the parameters governing copper ion release from HKUST-1. Strategies to mitigate potential toxicity include modifying the MOF's structure to slow the release of copper ions, incorporating additional biocompatible materials to buffer copper levels, or designing composite systems that combine HKUST-1 with other therapeutic agents to reduce the required copper dosage. Preclinical studies and toxicity assessments are necessary to identify safe operational windows for copper ion release, ensuring that HKUST-1 can deliver its therapeutic effects without causing harm to surrounding tissues. In summary, while HKUST-1 holds significant promise for medical applications due to its therapeutic properties, particularly in wound healing, addressing the potential toxicity concerns related to copper ion release is crucial. By fine-tuning copper release rates and dosage, researchers can enhance the material's biocompatibility, paving the way for its safe and effective use in clinical settings.

5.3. Scale-up and manufacturing challenges

The successful translation of HKUST-1 nanostructures from laboratory research to clinical use requires overcoming significant scale-up and manufacturing challenges. While HKUST-1 has shown great promise in preclinical studies, its large-scale production for biomedical applications poses several practical obstacles that must be addressed to ensure its safe and effective use in clinical settings.[118,201] One of the primary challenges in scaling up the production of HKUST-1 is ensuring consistency in particle size, shape, and composition during synthesis. In the laboratory, these properties can be carefully controlled on a small scale, but achieving the same level of precision in large-scale manufacturing is considerably more difficult.[201,202] Even slight variations in particle size or morphology can have a substantial impact on the material's performance, particularly in medical applications where drug release rates, stability, and biocompatibility are critical factors.[202,203] For example, inconsistencies in the size of HKUST-1 particles could lead to uneven drug loading or unpredictable copper ion release, which could compromise both efficacy and safety.[202] Moreover, large-scale production must be cost-effective to be commercially viable, especially in the pharmaceutical and biomedical industries where cost constraints are stringent. The synthesis of HKUST-1 involves the use of copper salts and organic ligands, and scaling up these processes requires careful consideration of raw material costs, energy input, and the efficiency of the reactions. Any inefficiencies in the production process could make HKUST-1 prohibitively expensive for widespread use in wound care or other therapeutic applications.[204–206] In addition to cost, reproducibility and quality control are essential factors in the manufacturing of HKUST-1 at scale. Inconsistent batches could lead to variability in therapeutic outcomes, which is unacceptable in clinical settings where patient safety is paramount. Developing robust protocols for reproducible synthesis, alongside stringent quality control measures, will be critical to ensure that each batch of HKUST-1 meets the necessary standards for clinical use. This includes ensuring that the material's structure, purity, and therapeutic properties remain consistent across large production runs.[118,207–209] Another consideration in scaling up HKUST-1 for clinical applications is regulatory compliance. Manufacturing processes must adhere to Good Manufacturing Practice (GMP) standards, which require strict documentation, validation, and control of production processes. Ensuring that HKUST-1 production is not

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only scalable and cost-effective but also compliant with regulatory requirements will be crucial for gaining approval from agencies such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). In conclusion, the transition from laboratory research to large-scale production of HKUST-1 presents a range of challenges, including maintaining uniformity in particle characteristics, ensuring cost-effectiveness, and establishing reproducible and controlled manufacturing processes. Addressing these challenges will be essential for the successful commercial and clinical implementation of HKUST-1 in wound care and other biomedical applications.

6. Future directions

6.1. Enhancing stability and biocompatibility

We believe that enhancing the stability and biocompatibility of HKUST-1 within biomedical contexts is crucial for advancing its application (Fig. 6). Its structural integrity can deteriorate under physiological conditions, which hampers its potential for clinical applications. Consequently, enhancing its stability and biocompatibility is vital for realizing its therapeutic potential. Stability in biological environments is a primary concern for nanoparticles.[210–214] Exposure to biological fluids can compromise its structural integrity, as physiological conditions characterized by moisture, varying pH levels, and the presence of ions can lead to its degradation. Addressing this issue involves several strategies. Researchers should explore various surface modification techniques to improve HKUST-1's resistance to degradation. These modifications may include applying protective coatings that shield the framework from harsh environmental conditions while ensuring biocompatibility. Encapsulation techniques are also being investigated to protect HKUST-1 from environmental stressors by embedding it within a protective matrix or coating that preserves its stability while allowing for the controlled release of therapeutic agents. Additionally, developing composite materials that integrate HKUST-1 with other more stable substances represents another promising approach. By hybridizing HKUST-1 with materials possessing superior stability, we aim to enhance its overall resilience to biological environments.

Ensuring the biocompatibility of HKUST-1 is equally important. While the inherent properties of HKUST-1, such as the release of copper ions, provide antimicrobial benefits, the same properties raise concerns regarding cytotoxicity and overall safety in biological applications. Balancing therapeutic efficacy with biocompatibility involves minimizing cytotoxicity through advanced bioengineering techniques. This includes careful

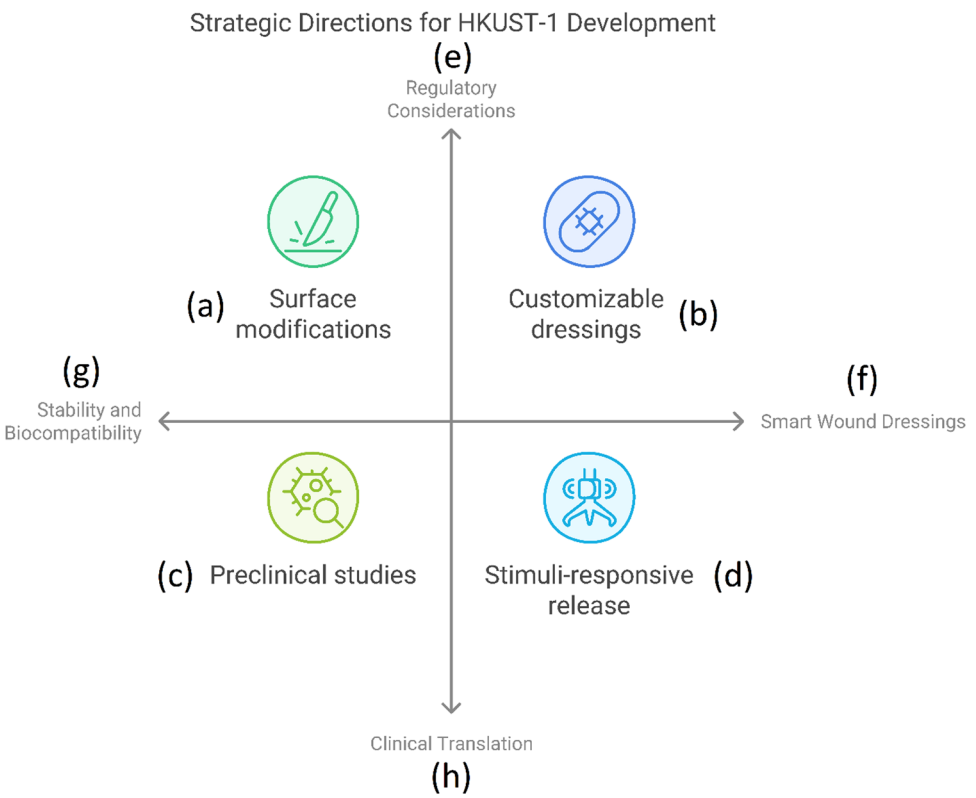

Fig. 6 Strategic directions for HKUST-1 development in wound healing: this framework highlights key areas for advancing HKUST-1 applications in biomedical settings. The four quadrants represent essential aspects: (a) surface modifications to enhance stability and biocompatibility, (b) customizable dressings integrating HKUST-1 into smart wound care materials, (c) preclinical studies for safety and efficacy validation, and (d) stimuli-responsive release for controlled therapeutic action. The axes illustrate the balance between stability/biocompatibility and smart wound dressing integration, as well as regulatory considerations and clinical translation, essential for HKUST-1's progression from research to medical applications.

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modification of HKUST-1's surface and structure to ensure it does not elicit harmful biological responses while retaining its antimicrobial properties. Implementing controlled release mechanisms can help manage the release of copper ions and other therapeutic agents, enhancing therapeutic efficacy while mitigating potential cytotoxic effects. Comprehensive safety profiling, including *in vitro* and *in vivo* studies, is essential to assess the biocompatibility of HKUST-1. These studies help determine safe concentration levels and potential interactions with biological systems.

Hence, addressing the dual challenges of stability and biocompatibility is critical for advancing HKUST-1's application in biomedical fields. By employing strategies such as surface modifications, encapsulation, and the development of composite materials, we aim to enhance its stability in biological environments. Concurrently, efforts to minimize cytotoxicity and ensure the safe and controlled release of therapeutic agents are pivotal for achieving biocompatibility. These advancements will pave the way for HKUST-1's successful integration into drug delivery systems, wound care, and other therapeutic applications.

6.2. Integration with smart wound dressings

We believe that the integration of HKUST-1 into smart wound dressings represents a cutting-edge advancement in wound care technology. Smart wound dressings are designed to adapt and respond to various environmental stimuli, such as changes in pH, temperature, or infection markers. By incorporating HKUST-1, particularly its copper ions, into these advanced dressings, we could aim to enhance the precision and efficacy of wound treatment, especially in complex cases like chronic wounds and burns.

Smart wound dressings are engineered to respond dynamically to the conditions of the wound environment. This adaptability can be crucial for effective wound management, as chronic wounds or burns often experience fluctuations in their healing conditions. Key features of these smart systems include the ability to detect and respond to specific changes in the wound environment. For instance, they might release therapeutic agents in response to shifts in pH, temperature variations, or the presence of infection markers. This real-time responsiveness ensures that treatment is tailored to the current state of the wound. By integrating HKUST-1 into these dressings, the release of copper ions can be controlled based on environmental triggers. For example, if the dressing detects an increase in pH indicating an infection, it can release copper ions to combat microbial growth. This on-demand release not only maximizes the therapeutic effect but also minimizes the exposure of healthy tissue to potentially harmful agents. The ability to deliver therapeutic agents precisely when and where they are needed represents a significant advancement in wound care. HKUST-1's integration allows for the targeted release of copper ions, which can accelerate the healing process and reduce the risk of complications. By ensuring that therapeutic agents are released only under specific conditions, smart wound dressings reduce unnecessary exposure to these compounds. This controlled delivery helps minimize potential side effects and adverse reactions, contributing to improved patient safety and comfort. The adaptive functionality of smart wound dressings can lead to more effective management of chronic and difficult-to-heal wounds. By addressing fluctuations in the wound environment and delivering targeted treatments, these advanced dressings can improve healing rates and patient outcomes.

The development and refinement of smart wound dressings with HKUST-1 hold significant promise for transforming wound care. Continued research and innovation in this area could lead to improved materials and technologies. Advances in materials science and bioengineering could enhance the integration of HKUST-1 into smart dressings, optimizing their performance and stability. As the technology matures, smart wound dressings could become standard in treating a wider range of wounds, including complex chronic wounds, diabetic ulcers, and severe burns. Future developments may enable even greater customization of wound care, allowing dressings to be tailored to individual patient needs and specific wound characteristics. Hence, integrating HKUST-1 into smart wound dressings represents a transformative approach to wound care. By leveraging the adaptive functionality of these dressings and the antimicrobial properties of copper ions, we can achieve more precise, effective, and safer treatment of chronic and difficult-to-heal wounds. This innovative technology has the potential to significantly improve patient outcomes and revolutionize modern wound care practices.

6.3. Clinical translation and regulatory considerations

Our efforts to transition HKUST-1 from a promising research material to a clinically approved product could involve navigating a complex landscape of scientific validation, regulatory scrutiny, and economic feasibility. To achieve successful clinical translation, HKUST-1 must undergo comprehensive evaluation processes to establish its safety, efficacy, and suitability for medical applications. First, the scientific validation process necessitates extensive preclinical testing. HKUST-1 must undergo *in vitro* studies to assess its interactions with various biological tissues, such as cell cultures and tissue models. These studies help determine the material's biocompatibility, cytotoxicity, and potential for causing allergic reactions or other adverse effects. Following *in vitro* testing, *in vivo* studies are essential to evaluate the material's behavior within a living organism. These studies involve animal models to investigate how HKUST-1 integrates with biological systems, its impact on wound healing, and any long-term effects on overall health. *In vivo* testing provides insights into the material's efficacy and safety in a more complex and realistic biological environment. Understanding the long-term effects of HKUST-1 on human health is crucial, including assessing potential chronic toxicity, accumulation in tissues, and any delayed adverse effects. Long-term studies help ensure that HKUST-1 remains safe and effective throughout its intended duration of use. Next, regulatory approval is critical. HKUST-1 must gain approval from regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) to be used in medical

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applications. These agencies will review comprehensive data from preclinical and clinical studies to evaluate the material's safety profile, therapeutic benefits, and potential risks. Clinical trials are a critical component of the approval process, conducted in phases starting with small-scale Phase I studies to assess safety in healthy volunteers, followed by Phase II and III studies to evaluate efficacy, optimal dosing, and safety in larger patient populations. Successful completion of these trials is necessary for regulatory approval. Manufacturers must prepare detailed documentation demonstrating compliance with regulatory standards and providing data on material synthesis, quality control, and manufacturing processes. Ensuring that all documentation meets regulatory requirements is essential for obtaining approval. Economic feasibility is also paramount. The synthesis process for HKUST-1 must be scalable to meet commercial demands. We need to develop methods for producing the material in large quantities while maintaining consistent quality and performance. Economic considerations are crucial for the widespread adoption of HKUST-1-based products. The cost of production should be balanced with the technological benefits to ensure that the final product is affordable for healthcare systems and patients. This includes evaluating the costs of raw materials, synthesis, quality control, and distribution. Conducting a thorough market analysis helps determine the commercial viability of HKUST-1 products, assessing market needs, potential competition, pricing strategies, and reimbursement options to ensure that HKUST-1-based wound care solutions are both economically viable and accessible. Hence, the successful clinical translation of HKUST-1 into medical applications, particularly in wound care, requires overcoming significant scientific, regulatory, and economic challenges. Rigorous preclinical and clinical testing is essential to establish safety and efficacy. Securing regulatory approval involves thorough documentation and compliance with standards set by agencies like the FDA or EMA. Additionally, ensuring the scalability and cost-effectiveness of production processes is crucial for commercial viability. Addressing these challenges comprehensively will be key to advancing HKUST-1 from a research novelty to a widely adopted medical product.

7. Conclusion

This review highlights the therapeutic potential of HKUST-1-based nanoplatforms in wound healing, demonstrating their ability to integrate antibacterial activity, oxidative stress modulation, angiogenesis promotion, and biofilm disruption. Unlike conventional wound treatment materials, HKUST-1 leverages copper ion release, catalytic activity, and smart composite systems to create an advanced, multifunctional wound care approach. The findings emphasize that HKUST-1 provides a dual benefit: antibacterial action through peroxidase-like (POD) activity and regenerative properties by releasing Cu^{2+} ions, which promote angiogenesis, fibroblast proliferation, and ECM remodeling. These attributes make HKUST-1 a promising candidate for treating both acute and chronic wounds. One of the most significant advantages of HKUST-1-based platforms is their ability to modulate the wound microenvironment by balancing oxidative stress and oxygen supply. Several HKUST-1-integrated hydrogels and nanofiber scaffolds have demonstrated the capability to relieve hypoxia while simultaneously delivering antibacterial agents in a controlled manner. The incorporation of calcium peroxide (CaO_2) and NO-releasing HKUST-1 formulations further promotes vascularization and wound closure, making them particularly valuable for treating diabetic wounds and infection-prone injuries. Another key finding is the potential for smart wound care applications. Stimuli-responsive photothermal HKUST-1 composites enable controlled NO release under near-infrared (NIR) light, allowing for on-demand antibacterial and regenerative action. Additionally, bioengineered wound dressings incorporating HKUST-1 with biopolymers such as chitosan or collagen have shown promise in enhancing cell migration, collagen deposition, and rapid tissue remodeling. These findings pave the way for next-generation wound dressings that dynamically respond to infections, pH variations, and inflammatory markers, optimizing wound healing based on real-time conditions. Despite these promising advancements, several challenges must be addressed before HKUST-1 can be translated into clinical practice. One major limitation is its stability under physiological conditions. HKUST-1 is prone to structural degradation in aqueous environments, leading to uncontrolled Cu^{2+} release and potential cytotoxicity. To overcome this, future research should focus on surface functionalization, polymer encapsulation, or hybridization with biocompatible carriers to enhance its stability and control therapeutic release. Long-term biocompatibility studies are also essential to identify safe Cu^{2+} concentration thresholds and minimize potential side effects. Another challenge is the scalability and cost-effectiveness of HKUST-1 production. While laboratory synthesis methods such as solvothermal and hydrothermal techniques provide high-quality HKUST-1, they are time-consuming and expensive for large-scale manufacturing. The development of green, solvent-free, or microwave-assisted synthesis techniques could significantly reduce costs and improve reproducibility, making HKUST-1 more viable for commercial biomedical applications. Additionally, standardized protocols for toxicity assessments and regulatory approvals must be established to facilitate its clinical translation. Looking ahead, the integration of HKUST-1 with biosensors and wearable wound-monitoring technologies could revolutionize personalized medicine. Smart wound dressings equipped with biosensors to detect bacterial infections, inflammation markers, or oxidative stress levels could provide real-time feedback, allowing clinicians to adjust treatment dynamically based on individual patient needs. This level of customized wound management could significantly improve healing outcomes in complex, non-healing wounds. Future research should also explore multi-therapeutic approaches, combining HKUST-1 with growth factors, anti-inflammatory agents, or stem cell-derived exosomes to enhance regenerative outcomes. Co-delivery systems, such as HKUST-1 loaded with VEGF for enhanced angiogenesis, could provide a multifaceted treatment strategy for patients suffering from chronic wounds, burns, or diabetic ulcers. Additionally, combining HKUST-1 with MOF-based photodynamic and photothermal therapies could create

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next-generation antimicrobial dressings with light-triggered drug release mechanisms, improving their efficacy against multi-drug-resistant bacterial infections. Hence, developing HKUST-1-based nanoplatforms represents a transformative approach to wound healing, addressing bacterial infections, inflammation, oxygen supply, and tissue regeneration in a single system. However, bridging the gap between fundamental research and clinical applications requires advancements in materials engineering, toxicity regulation, and scalable production methods. By enhancing HKUST-1's stability, improving its controlled release properties, and integrating it into smart wound dressings, these nanoplatforms could pave the way for highly efficient, responsive, and personalized treatment strategies in modern wound care. With continued interdisciplinary collaboration, HKUST-1-based technologies have the potential to revolutionize the future of wound healing, offering faster recovery, lower infection rates, and improved patient outcomes.

Data availability

All data supporting the findings of this study are available within the manuscript.

Conflicts of interest

There are no conflicts to declare.

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