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Photo-Responsive Blood Clot Hydrogel for Wound Healing

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ABSTRACT: Wound healing remains a major clinical challenge, placing a substantial burden on healthcare resources and imposing considerable socioeconomic costs. Here, we developed a blood clot delivery platform loaded with the antibiotic minocycline for enhanced wound healing. The blood clot gel, formed through the natural coagulation process of autologous blood, serves as an endogenous and biocompatible biomaterial. Its fibrin-rich network provides a porous three-dimensional matrix capable of entrapping abundant red blood cells (RBCs), which can serve as an endogenous oxygen reservoir and facilitate oxygen release upon near-infrared (NIR) irradiation. Furthermore, minocycline was incorporated within the pores of the blood clot gel, enabling sustained antibacterial activity and effectively suppressing bacterial proliferation. Given these functional properties, this blood clot gel platform delivers antibacterial efficacy and facilitates both collagen deposition and granulation tissue formation throughout the wound healing process. These findings indicate that the blood clot gel platform possesses considerable clinical potential for applications in wound repair and related biomedical fields.

KEYWORDS: Hydrogel; blood clot; photo-responsive; red blood cell; wound healing

1 Introduction

Acute skin injuries represent a widespread clinical issue in everyday contexts, typically originating from traumatic damage, severe thermal burns, or surgical procedures. In the absence of standardized wound care, these lesions can trigger a series of complications, most notably local infections and the transition from acute to chronic non-healing wounds [1–5]. The healing process, a dynamic multi-step biological cascade consisting of inflammatory, proliferative, and tissue remodeling phases, poses a sophisticated and multifactorial therapeutic challenge [6–10]. Hence, effective therapeutic strategies are highly desired to expedite the wound healing process. To address this unmet clinical need, researchers have developed a wide array of wound dressings endowed with varied biological functionalities, among which hydrogel-based dressings stand out as a particularly notable category [11–15]. These hydrogel-based dressings exhibit favorable biocompatibility and mechanical flexibility, and exert beneficial therapeutic effects on wound healing by maintaining a moist wound microenvironment and acting as carriers for bioactive substances [16–21].

Despite these advances, most existing hydrogel systems still face notable limitations that restrict their clinical translation. First, the majority of reported multifunctional hydrogels rely on synthetic polymer

matrices or exogenous biomacromolecules, which require complex fabrication protocols and may elicit foreign body responses. Second, conventional hydrogel dressings typically target only one facet of wound pathology, most commonly bacterial infection, while overlooking the critical role of local oxygen tension in tissue repair. Third, although photothermally mediated oxygen delivery has gained traction as a therapeutic strategy, most platforms depend on exogenous photothermal agents such as metallic nanoparticles or 2D nanomaterials, which carry potential biosafety risks and raise concerns over prolonged tissue retention. As a result, the development of innovative multifunctional hydrogel dressings continues to be a central research priority in the field of wound repair.

In this work, drawing on the natural physiological mechanisms of blood coagulation, we developed a minocycline loaded blood clot hydrogel platform for wound management, as schematically shown in Fig. 1. As a native biological process, coagulation converts liquid blood into a gelatinous matrix. During this process, fibrin is generated and interlaced into a hydrated fibrous network, which enmeshes blood cells to assemble the three dimensional blood clot scaffold [22–25]. Within this scaffold, red blood cells (RBCs) constitute the most prevalent cellular component. Beyond their structural contribution, RBCs serve a key physiological function by maintaining continuous and adequate oxygen delivery throughout all stages of wound healing, thus supporting normal cellular metabolic activity [26–29]. Given these inherent biological features, developing multifunctional wound dressings based on the physiological characteristics of RBCs represents a rational and promising direction. This novel design approach exhibits considerable promise for alleviating the pathological status of acute wounds.

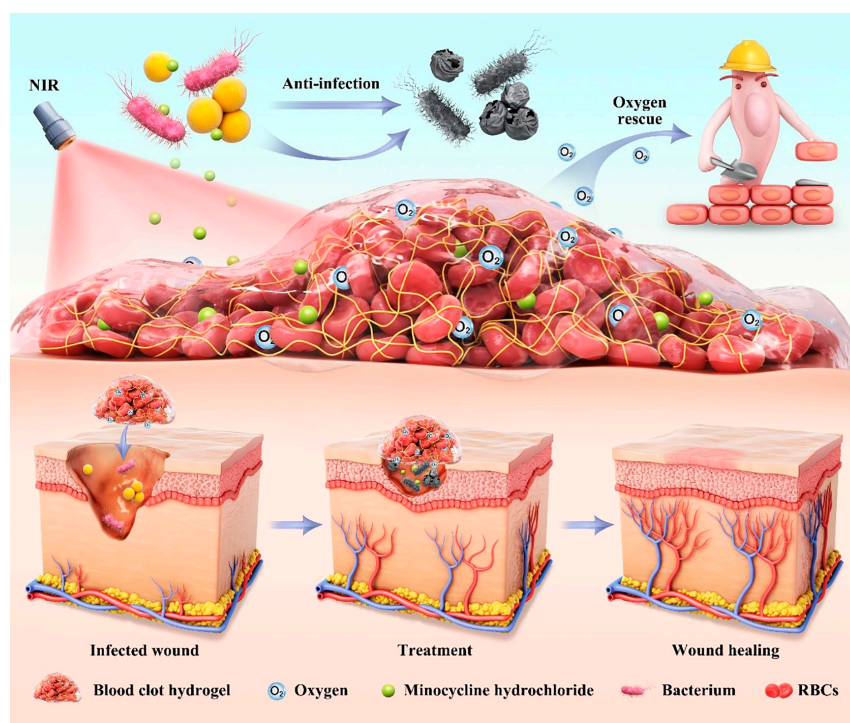


Figure 1: Schematic illustration of the preparation and application process of the MH@BC hydrogel. Blood formed a fibrin scaffold that trapped RBCs to support oxygen supply and cellular metabolism, loaded with minocycline to inhibit bacterial growth in infected wounds. Mild hyperthermia under NIR irradiation further promoted oxygen release. The hydrogel simultaneously inhibited bacterial proliferation, promoted angiogenesis, and supported granulation tissue formation, accelerating wound healing.

Here, the multifunctional blood clot hydrogels loaded with the minocycline were developed and employed for skin wounds repair. Minocycline serves as the key ingredient of MHO (minocycline hydrochloride ointment). This formulation is characterized by its extensive coverage against diverse bacterial pathogens, marked inhibitory strength, high therapeutic efficiency, and enduring effects over time. [30,31]. In this work, we first mixed freshly collected *ex vivo* blood with minocycline in a custom-designed reaction model, then initiated the endogenous coagulation cascade to form minocycline-loaded blood clots. Additionally, when subjected to near-infrared (NIR) irradiation, the induced mild localized hyperthermia can further facilitate oxygen release and accelerate cutaneous tissue regeneration. This biofabrication strategy exhibits broad potential for subsequent clinical translation. *In vivo* data from this study verified that these blood clot hydrogels drive wound tissue regeneration by restricting bacterial propagation and boosting angiogenic responses across the full wound healing cascade. Collectively, these advantageous properties underline the promising clinical application prospects of blood clot-based hydrogels.

2 Methods

Materials, cell lines and animals: Blood was collected from the retrobulbar venous plexus of mice. Minocycline hydrochloride was purchased from YuanYe Corp. NIH-3T3, HaCaT, and HUVECs were provided by the Chinese Academy of Sciences. Cell culture reagents—including Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), penicillin–streptomycin, and trypsin—were obtained from Gibco (USA). Six-week-old male BALB/c mice were supplied by Vital River Laboratory. All animal procedures were approved by the Animal Ethics Committee of Drum Tower Hospital, Nanjing University School of Medicine (Approval No. 2025AE01080).

Preparation and characterization of MH@BC hydrogels: Blood clot scaffolds were fabricated by triggering spontaneous coagulation of freshly drawn murine whole blood without anticoagulant, followed by controlled vacuum dehydration. In brief, 200 μ L of fresh whole blood was harvested from the ocular fundus venous plexus of mice and immediately transferred into sterile, customized cylindrical polydimethylsiloxane (PDMS) molds. For the preparation of MH@BC, minocycline hydrochloride solution (dissolved in PBS) was gently mixed with the blood sample by repeated pipetting for 5 times prior to molding, yielding a final minocycline concentration of 0.2% (w/v). Samples were left to clot undisturbed at 25°C for 10 min, and then dried under vacuum for 2 h to form stable hydrogel constructs. Blank blood clot hydrogels were prepared using the identical coagulation and drying procedure, with an equal volume of sterile PBS substituted for the minocycline solution to maintain consistent total liquid volume.

The rheological behavior of the hydrogels was characterized using a hybrid rheometer (Discovery HR-1, TA Instruments, USA) equipped with a 10 mm parallel plate. Cylindrical hydrogel specimens (10 mm in diameter, 5 mm in height) were prepared to fit the measuring geometry. For dynamic frequency sweep measurements, a constant strain of 1% was applied while the oscillatory frequency was varied from 0.1 to 10 Hz. To identify the linear viscoelastic range, strain sweep experiments were carried out at a fixed frequency of 1 Hz.

Cylindrical hydrogel samples (10 mm in diameter, 5 mm in height) were prepared for compression tests. Prior to mechanical testing, the samples were soaked in PBS at 37°C for 1 h to reach equilibrium under conditions simulating the physiological environment. Uniaxial compression tests were then performed using a universal testing machine, during which stress–strain curves were recorded continuously. Each test was repeated three times to guarantee data reliability.

NIR-triggered photothermal behavior: Hydrogel samples were irradiated with an NIR light source (3.5 W) positioned 50 mm above the surface. Temperature changes were monitored at 12 s intervals throughout the

experiments. In cyclic on/off tests, irradiation was applied until the hydrogel reached its peak temperature, after which the laser was turned off and the next cycle was initiated once the sample had cooled back to room temperature.

Oxygen release tests: Oxygen release was assessed in four experimental groups: PBS, BC, MH@BC hydrogel, and MH@BC hydrogel combined with NIR irradiation. Prior to gel formation, red blood cells were incubated under oxygen-rich conditions for 6 h. Dissolved oxygen concentrations were determined using a portable oxygen meter (JPB-607A, Leici, China). To minimize gas exchange with the atmosphere, 1 mL of liquid paraffin was gently layered on the surface of each PBS sample. For the NIR-treated group, irradiation was applied intermittently for 10 min at half-hour intervals. Measurements of dissolved oxygen were performed at 0, 1, 2, 4, 8, 12, and 24 h for all groups.

Antibacterial activity: Antibacterial activity was evaluated following previously reported protocols with slight modifications. Bacterial suspensions (2×10^6 CFU mL⁻¹) were incubated with hydrogel samples at 37°C for 4 h, with NIR (3.5 W) irradiation applied to the designated groups. After treatment, bacterial viability was assessed using a SYTO9/propidium iodide (PI) live/dead assay. Stained suspensions were kept under dark conditions and imaged by confocal laser scanning microscopy.

In vivo wound healing study: Twenty healthy male BALB/c mice were anesthetized, and the dorsal hair was carefully removed. A full-thickness excisional wound measuring 0.6 cm in diameter was generated on the back of each animal, followed by administration of 25 μ L of *E. coli* suspension (1×10^6 CFU mL⁻¹). The mice were randomly divided into four groups and treated with PBS, BC, MH@BC hydrogel, or MH@BC hydrogel coupled with NIR irradiation. In the last group, NIR exposure was performed five times per day for 10 min each session. All mice were housed individually and allowed to recover under standard conditions. Wound closure was assessed on days 0, 3, 5, and 7. At the endpoint, animals were sacrificed, and wound tissue samples were harvested for histological and immunohistochemical analysis.

Statistical analysis: All statistical analyses were performed using GraphPad Prism 9.0 software. Differences between experimental groups were assessed with two-tailed Student's *t*-tests. **p* < 0.05; ***p* < 0.01; ****p* < 0.001 considered a statistically significant, and NS represents not significant.

3 Results and Discussion

In a typical experiment, skin defect dimensions were assessed, and corresponding molds were customized via 3D printing to replicate the wound morphology. MH@BC hydrogels were fabricated by incorporating minocycline hydrochloride into freshly collected blood, followed by casting into a pre-designed mold and gentle drying to maintain structural integrity (Fig. 2a). Prior to incubation, RBCs were uniformly dispersed in the liquid phase mixture, as shown in Fig. S1. Upon incubation at 37°C, a coagulation cascade was triggered, transforming the liquid blood into a gel-like scaffold and entrapping RBCs within a fibrous network, as visualized by scanning electron microscopy (SEM) (Fig. 2b,c). To demonstrate the adaptability of MH@BC hydrogels to diverse wound sites, customized molds with varying shapes and sizes were fabricated via 3D printing (Fig. S2), and employed to produce hydrogels with corresponding morphologies, as illustrated in Fig. 2d. To evaluate the gelation behavior of MH@BC hydrogels, rheological measurements were conducted using a rotational rheometer. As shown in Fig. 2e,f, the storage modulus (*G'*) was consistently higher than the loss modulus (*G''*) across the tested range, demonstrating the formation of a stable crosslinked viscoelastic network. This elastic-dominant property ensures the hydrogel maintains structural integrity when applied to irregular wound beds. In addition, compression tests further demonstrated that MH@BC hydrogels withstood moderate stress without structural failure, supporting their mechanical robustness (Fig. S3). In Fig. 2g, MH@BC hydrogels were incubated in phosphate-buffered

saline (PBS) at 37°C for *in vitro* degradation assessment, showing slight degradation over the 7 days period. Collectively, these findings demonstrate that MH@BC hydrogels exhibit desirable formability, mechanical stability, and *in vitro* durability, supporting their suitability as a customizable and stable platform for subsequent therapeutic applications.

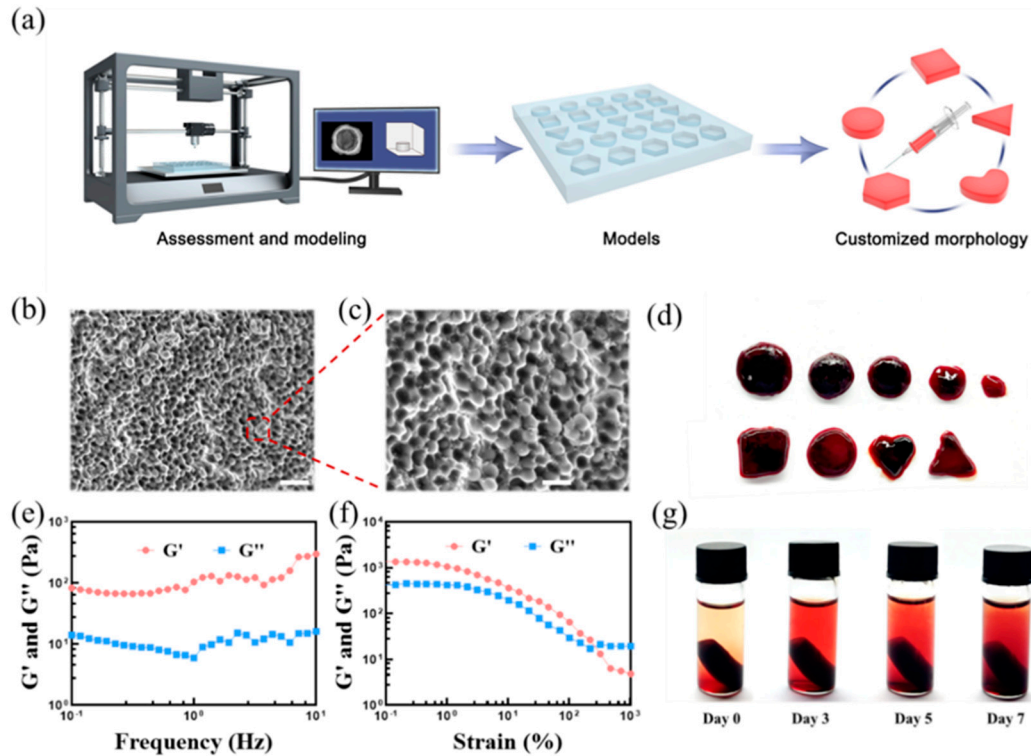


Figure 2: Construction and property characterization of the MH@BC hydrogel system. (a) Schematic illustration of the preparation procedure of MH@BC hydrogels using customized 3D printed molds to replicate wound morphology. (b) SEM image of MH@BC hydrogels. Scale bar is 10 μm. (c) The magnified view of the red framed region. Scale bar is 5 μm. (d) MH@BC hydrogels exhibiting morphology tailored by distinct models. (e,f) Rheology analysis of MH@BC hydrogels on frequency sweeps (e) and strain sweeps (f). (g) The degradation of MH@BC hydrogels *in vitro*.

To investigate the multifunctional properties of MH@BC hydrogels, we next evaluated their photothermal responsiveness and oxygen release behavior. The deep red coloration of the RBC based matrix indicated its potential to serve as a novel photothermal agent for generating mild hyperthermia in skin tissue under NIR irradiation, motivating further exploration of its thermal conversion performance (Fig. 3a). To assess the photothermal behavior of MH@BC hydrogels, NIR laser irradiation was applied at three power levels (1.6, 1.8, and 2.0 W). As shown in Fig. 3b, the temperature of the blood clot rose with increasing laser intensity, exceeding 55°C at 2.0 W. In contrast, the temperature elevation at 1.6 W was relatively slow and insufficient for therapeutic heating. Considering both photothermal conversion efficiency and safety, 1.8 W was selected as the optimal irradiation condition, under which the hydrogel could steadily reach a mild hyperthermia range of approximately 41–43°C. Furthermore, to examine the structural effects of NIR irradiation on the RBC based hydrogel, the samples used in the aforementioned photothermal experiments were subjected to SEM for morphological evaluation. As shown in Fig. 3d, the hydrogel irradiated at a laser power of 1.8 W retained an interconnected porous network and morphology that was well preserved, indicating its structural integrity under mild thermal stimulation. Notably, RBCs remained morphologically

intact within the fibrous matrix under this condition, which is essential for preserving their functional properties including oxygen release. In contrast, excessive thermal input at 2.0 W led to obvious structural collapse, pore distortion, and disruption of the RBC morphology. Hence, 1.8 W was chosen for further studies. To evaluate the photothermal stability of MH@BC hydrogels, five successive NIR on/off cycles were performed. Upon each irradiation cycle, the hydrogel rapidly heated to approximately 40°C and returned to ambient temperature when the laser was turned off, demonstrating consistent and reversible thermal responsiveness (Fig. 3c). Upon NIR irradiation, MH@BC hydrogels exhibited effective *in vivo* photothermal conversion, raising the temperature of both the hydrogel and adjacent dorsal skin tissue in mice from 25°C to around 38°C within 100 s, as verified by thermal imaging (Fig. 3e). This highlights their suitability for localized photothermal applications. Building on this photothermal effect, we investigated the possibility that mild heating could promote oxygen release from RBCs within the hydrogel. Since the oxygen binding affinity of RBCs is dependent on temperature, heating induced by NIR was expected to facilitate oxygen dissociation. To investigate this effect, MH@BC hydrogels were incubated in an oxygen deficient medium, and dissolved oxygen concentrations were monitored over time. As shown in Fig. 3f, the hydrogel group exhibited a rapid rise in oxygen tension during the first 8 h, followed by a gradual plateau after approximately 12 h. Both the BC and MH@BC hydrogel groups achieved significantly higher oxygen concentrations than the PBS control via spontaneous oxygen diffusion from RBCs, while the NIR-treated group showed further accelerated release kinetics and greater cumulative oxygen output, as mild hyperthermia reduces hemoglobin-oxygen binding affinity and facilitates oxygen dissociation. These findings underscore the hydrogel's potential to act as a photo responsive oxygen delivery platform under mild thermal stimulation.

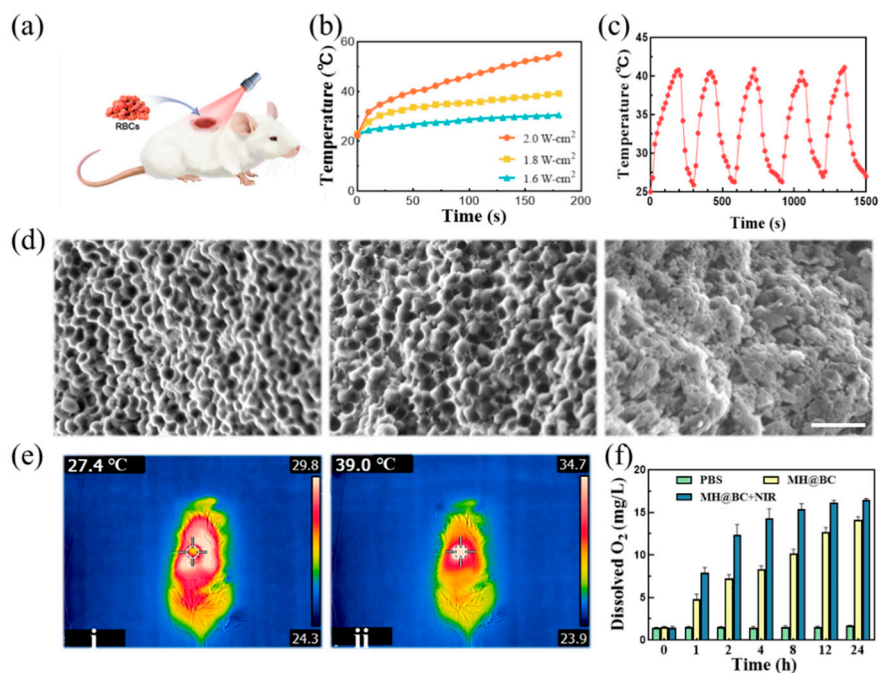


Figure 3: Photothermal performance and oxygen release of MH@BC hydrogels. (a) Schematic illustration of NIR laser irradiated MH@BC hydrogel for skin defect treatment. (b) Temperature rising profiles of MH@BC hydrogels under different NIR power levels. (c) Temperature response of MH@BC hydrogels throughout five switching cycles. (d) SEM images of MH@BC hydrogels after NIR irradiation at different power levels. Scale bar is 10 μm . (e) Thermal response of MH@BC hydrogels on mouse dorsal skin before and after NIR irradiation. (f) Oxygen release profiles of different groups.

To assess the biocompatibility and antimicrobial efficacy of the drug loaded MH@BC hydrogels, a series of cellular and microbiological experiments were conducted, including cytocompatibility evaluation on murine fibroblasts (3T3), human epidermal keratinocytes (HaCaTs), and human umbilical vein endothelial cells (HUVECs). To assess cellular viability, Calcein-AM staining was carried out on the samples after they had been incubated with the hydrogels for 24 h. As shown in Fig. 4a–c,f, the MH@BC and MH@BC + NIR groups exhibited green fluorescence intensity comparable to the untreated control, indicating negligible cytotoxicity. Collectively, these findings support the favorable biocompatibility of MH@BC hydrogels and their potential for biomedical applications. Beyond biosafety, the antibacterial properties of MH@BC hydrogels were subsequently investigated to evaluate their potential in infection control. *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*), representing Gram-negative and Gram-positive bacteria respectively, were selected for *in vitro* assays. The MH@BC and MH@BC + NIR groups exhibited substantial red fluorescence (signifying bacterial impairment), as shown in Fig. 4d,e. In sharp contrast, the control counterparts showed predominantly bright green fluorescence, pointing to a high survival rate of bacteria. Furthermore, NIR irradiation did not noticeably alter the bactericidal performance of the hydrogel. The quantitative image analysis corroborated the fluorescence observations, confirming that MH@BC hydrogels exerted potent and broad-spectrum antibacterial activity (Fig. 4g,h).

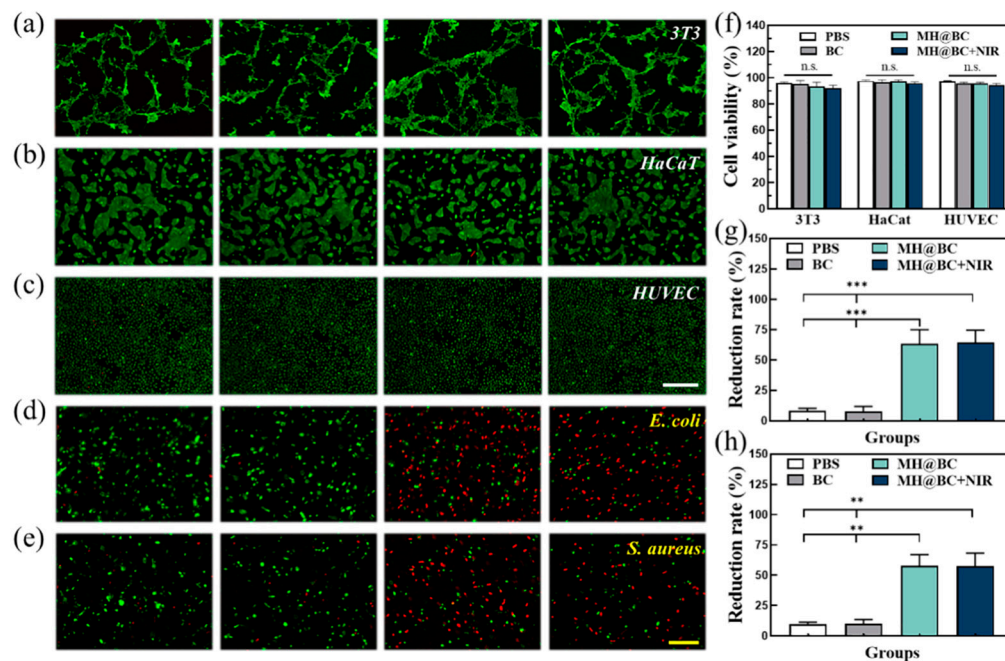


Figure 4: Biocompatibility and antibacterial evaluation of MH@BC hydrogel. (a–c) Cells were labeled with Calcein-AM following 24 h of incubation. Green fluorescence indicates viable cells. Scale bar is 500 μm . (d,e) Fluorescence images of *E. coli* and *S. aureus* after 4 h treatment with various groups. Scale bar is 20 μm . (f–h) Statistical analysis of cell viabilities (f) and bacterial reduction rates for *E. coli* (g) and *S. aureus* (h) under different treatments. n.s., not significant; ** $p < 0.01$; *** $p < 0.001$. Groups: PBS (i), BC hydrogel (ii), MH@BC hydrogel (iii), MH@BC hydrogel + NIR (iv).

Subsequent to thorough *in vitro* characterization of the MH@BC hydrogel, its *in vivo* therapeutic performance was further investigated using a full-thickness cutaneous wound model, where mice were randomized into four groups: PBS, BC hydrogel, MH@BC hydrogel, and MH@BC hydrogel in combination with NIR light irradiation. During treatment, the mice exhibited stable growth and good overall health during the healing process, supporting the favorable biocompatibility of the hydrogel platform and NIR

irradiation (Fig. S4). Subsequently, wound closure was monitored throughout the treatment period (Fig. 5a). In the context of wound healing, oxygen is a key determinant, as it provides the necessary metabolic support for tissue regeneration and concurrently promotes the deposition of granulation tissue, thereby facilitating overall structural integrity. Accordingly, hydrogels delivering oxygen significantly accelerated wound repair compared with the PBS control. The MH@BC hydrogel group outperformed the BC group due to its antibacterial effect, and the MH@BC hydrogel + NIR group showed nearly complete closure by day 7 (Fig. 5b,d), benefiting from the synergistic effects of sustained oxygen supply and oxygen release enhanced by NIR. To evaluate regenerative responses under distinct therapeutic regimens, hematoxylin and eosin (H&E) staining was further carried out on the specimens. As shown in Fig. 5c,e, the MH@BC hydrogel + NIR group exhibited the greatest granulation tissue thickness, surpassing all other groups including PBS and BC controls. This enhancement could be ascribed to NIR irradiation, which accelerated oxygen release through photothermal effects.

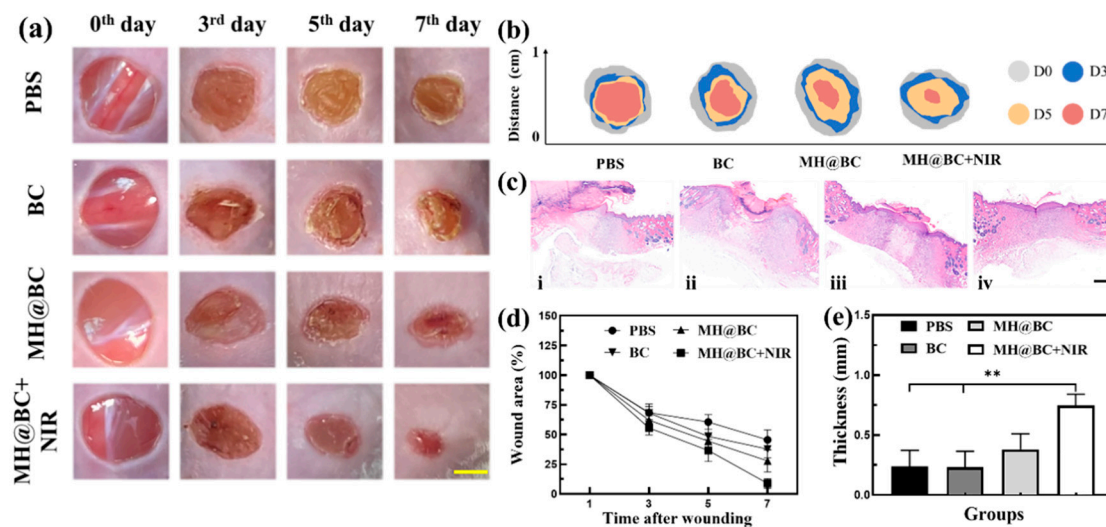


Figure 5: Therapeutic potential of the MH@BC hydrogel in wound healing. (a) Representative macroscopic images of wound healing progression on days 0, 3, 5, and 7. Scale bar is 2.5 mm. (b) Quantitative tracing analysis of relative wound area over time. (c) Histological micrographs of wound tissues on day 7. Scale bar is 400 μ m. (d,e) Quantitative analysis of the wound defect area and the thickness of granulation tissue. ** $p < 0.01$. Groups: PBS (i), BC hydrogel (ii), MH@BC hydrogel (iii), MH@BC hydrogel + NIR (iv).

To further assess the reparative effect of the MH@BC hydrogel, we evaluated angiogenesis, collagen deposition, and inflammatory responses across different groups. Functional angiogenesis is indispensable for tissue regeneration, as it supports the delivery of nutrients, oxygen, and cytokines. To evaluate neovascular formation within the wound defect, we performed immunofluorescence staining for CD31 and α -SMA, which label endothelial cells and smooth muscle cells respectively. As illustrated in Fig. 6a, oxygen intervention resulted in a notable rise in microvessel density within the wound bed, and the combination of MH@BC hydrogel and NIR irradiation delivered the strongest therapeutic effect across all groups. Collagen production and organized alignment are key indicators of effective wound healing, reflecting improved extracellular matrix reconstruction and tissue remodeling. To quantify the extent of collagen deposition, Masson's trichrome staining was accordingly carried out on the tissue sections. This assay yielded blue signals for collagen, with the cytoplasm, myofibrils, and red blood cells exhibiting red hues instead. Minimal collagen was detected in the PBS group, whereas substantial collagen deposition accompanied by cellular

infiltration was evident in the MH@BC hydrogel group and most pronounced in the MH@BC + NIR group (Fig. 6b). Moreover, immunohistochemical staining of interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) was carried out to assess inflammatory responses at the wound sites (Fig. 6c,d). The hydrogel treated groups exhibited a pronounced increase in IL-6 and TNF- α expression compared with PBS and blank controls. Inflammatory cell infiltration was evident across all samples, but the number of infiltrating cells was markedly reduced in the MH@BC + NIR group compared with controls. Taken together, the findings indicate that MH@BC hydrogels hold promise as a safe and effective approach for promoting wound repair.

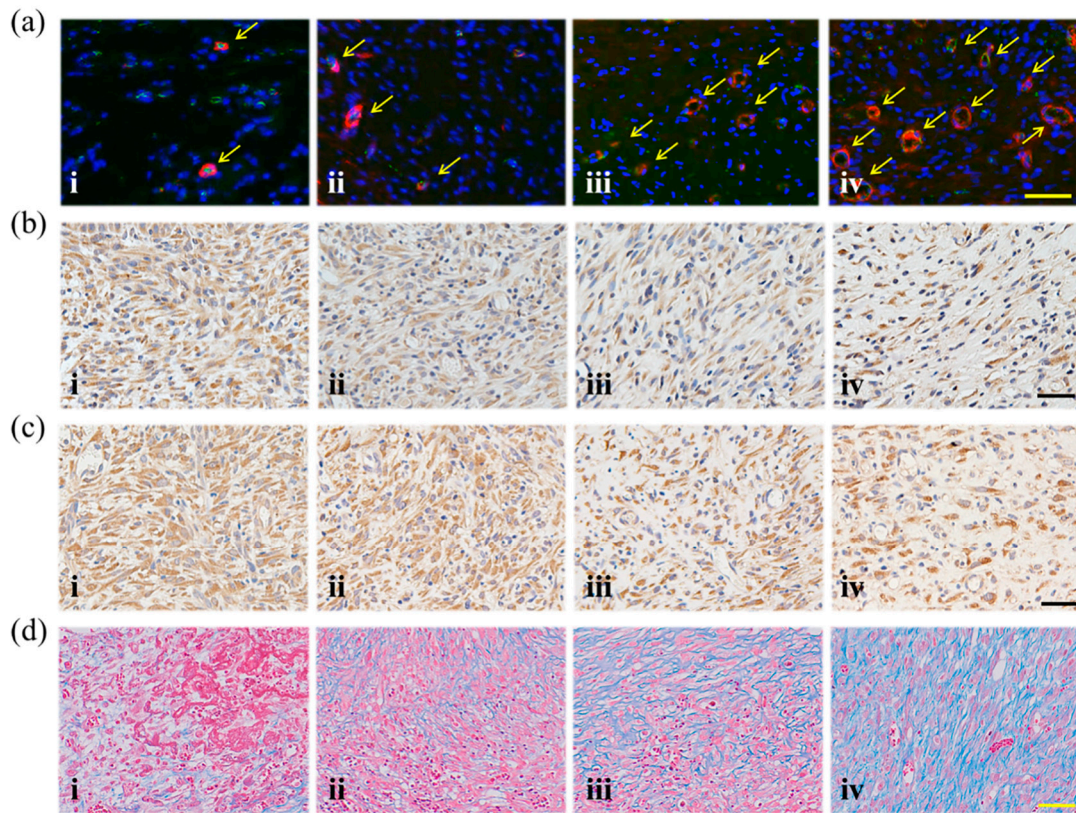


Figure 6: Histological assessment of wound tissues. (a) Immunofluorescence staining of CD31 (red) and α -SMA (green) in wound beds; yellow arrows mark vessels. (b) Masson's trichrome staining of wound sections on day 7. (c,d) Immunostaining for IL-6 (c) and TNF- α (d) at day 7. Scale bars: 50 μ m (a,b), 25 μ m (c,d). Groups: PBS (i), BC hydrogel (ii), MH@BC hydrogel (iii), MH@BC hydrogel + NIR (iv).

4 Conclusion

In conclusion, we developed a photoresponsive blood clot hydrogel by incorporating red blood cells and minocycline into a fibrin scaffold. This hydrogel exhibited stable structural properties, favorable biocompatibility, and regulated oxygen release upon NIR irradiation. This hydrogel further demonstrated robust bactericidal action and significantly boosted *in vivo* angiogenesis, collagen synthesis, and granulation tissue proliferation. Taken together, these observations support the translational potential of this multifunctional platform for accelerating the healing process and improving prognosis in infected cutaneous injuries.

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Availability of Data and Materials: The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials.

Ethics Approval: All animal procedures were approved by the Animal Ethics Committee of Drum Tower Hospital, Nanjing University School of Medicine (Approval No. 2025AE01080).

Conflicts of Interest: The authors declare no conflicts of interest.

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