

MXene-based hydrogel disrupts bacterial biofilms and reprograms immune cell metabolism via photothermal-electron transfer effects to reverse bone resorption in periodontitis

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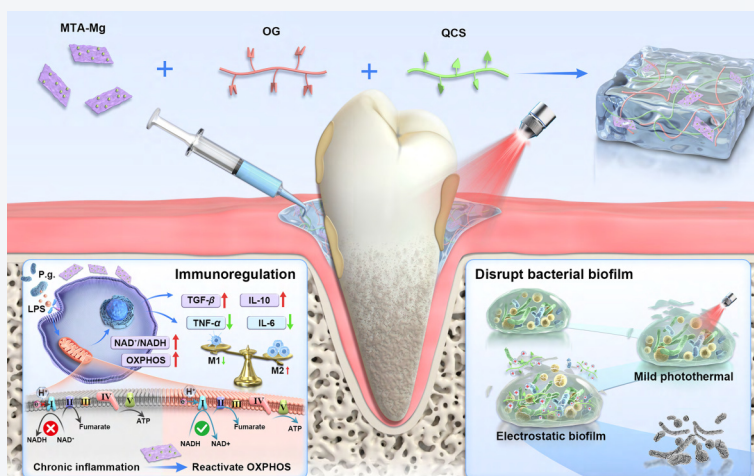
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ABSTRACT: Bacterial biofilm colonization and persistent chronic inflammation in periodontitis cause periodontal tissue destruction and eventual tooth loss. Bacterial biofilms disruption and immune cell metabolism reprogramming are critical for the treatment of periodontitis. Herein, we developed an injectable MXene-based hydrogel (GQM), composed of oxidized gellan gum, quaternized chitosan, and magnesium-tannic acid-modified MXene nanosheets (MTA-Mg), which serves as a flexible scaffold for targeted delivery of MTA-Mg within periodontal pockets. The GQM hydrogels can be injected into periodontal pockets and targetedly deliver MTA-Mg, which disrupts the dense biofilm efficiently by photothermal effect, while the bacteria are killed through the electrostatic interaction and charge neutralization from quaternized chitosan. MTA-Mg nanosheets serve as interfacial electron transfer to activate oxidative phosphorylation pathway, while delivering the magnesium and tannic acid to improve mitochondrial function, which reprogram the immune cell metabolism by inducing macrophage toward the M2 phenotype. The rat periodontitis model demonstrated that the GQM hydrogel effectively eradicates bacterial biofilms, alleviates inflammation, and reverses alveolar bone resorption, thereby treating periodontitis efficiently. All in all, the GQM hydrogel achieves a synergistic effect of "biofilm disruption-immune metabolic reprogramming" and offers a novel strategy for the reversal of inflammatory bone resorption in periodontitis.

Keywords: injectable hydrogel, periodontitis, bacterial biofilm, immune cell reprogramming



1 Introduction

Periodontitis is a highly prevalent chronic inflammatory disease worldwide [1]. Periodontitis results in alveolar bone resorption and

tooth loss, severely reducing the oral function and quality of life of patients [2, 3]. Due to its high prevalence and close association with various systemic inflammatory diseases, periodontitis has emerged as a critical global public health issue [4].

Bacterial biofilms in periodontitis are formed by *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, which establish highly organized microbial communities within periodontal pockets [5]. Bacteria are encapsulated in an extracellular polymeric substances (EPS) matrix, thereby making it difficult for antibiotics to exert their bactericidal effects [6]. Due to the narrow and irregular morphology

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of periodontal pockets and the high tolerance of bacterial biofilms, current clinical strategies involving mechanical debridement and antimicrobial therapy often fail to completely eradicate these biofilms [7, 8]. Furthermore, chronic biofilm stimulation causes immune cells to release excessive reactive oxygen species (ROS), which directly damages periodontal tissues and amplifies inflammatory signaling cascades, creating a persistent chronic inflammatory microenvironment [9, 10]. Recent researches have shown that the chronic inflammatory microenvironment induces immune cells such as macrophages to shift from mitochondrial oxidative phosphorylation to glycolysis [11–14]. Dysregulation of redox and energy metabolism drives the polarization of macrophages toward the inflammatory M1 phenotype and further participates in inflammatory alveolar bone resorption [15, 16]. Significantly, the inflammatory storm driven by metabolic dysregulation will be difficult to resolve after the bacteria are eliminated [17, 18]. Bacterial biofilms and the metabolic dysregulation of immune cells trigger an inflammatory storm, leading to the irreversible destruction of periodontal tissues [19]. Therefore, effective treatment for periodontitis requires not only the disruption of bacterial biofilms but also the metabolic reprogramming of immune cells.

Two-dimensional MXene nanomaterials have attracted increasing attention in biomedical applications due to their unique physicochemical properties, including high electrical conductivity, tunable surface chemistry, and excellent photothermal capabilities [20–22]. MXene nanosheets have been reported to disrupt bacterial membranes and interfere with biofilm architecture, owing to their good photothermal antibacterial activity [23]. Besides antibacterial properties, MXene can also participate in redox modulation and electron-transfer processes, enabling the regulation of intracellular oxidative stress and redox homeostasis [24, 25]. At the same time, the reversible phenol–quinone redox cycling of tannic acid (TA) has been recognized as an effective molecular mechanism for facilitating electron exchange and stabilizing redox-active interfaces [26, 27]. Metal–polyphenol networks offer additional stability and redox buffering capacity, providing a promising platform for electron transfer biomaterials [28]. Meanwhile, recent researches have shown that restoring the mitochondrial NAD^+/NADH balance and reactivating oxidative phosphorylation (OXPHOS) are key factors to shift macrophages from M1 phenotype to M2 phenotype [29, 30]. However, no existing therapeutic system integrates MXene-mediated photothermal effect with electron-transfer capabilities to regulate immune–metabolic reprogramming in periodontitis. A biomaterial capable of both disrupting biofilms and reprogramming immune metabolism would represent a novel strategy for the treatment of periodontitis.

The narrow structure of periodontal pockets and continuous salivary washout make the application of nanomaterials in periodontitis therapy remain challenged by insufficient local delivery and retention [31]. These limitations restrict the distribution and duration of action of nanomedicines in periodontitis [32]. Hydrogels have been widely used in drug delivery and tissue regeneration because of their good biocompatibility, porous network structure, and tunable microenvironmental responsiveness [33]. Among them, injectable hydrogels possess shear-thinning properties, self-healing abilities, adaptability to irregular spaces, and the capacity for local drug release [34]. Therefore, injectable hydrogels can fill and conform to the complex geometry of periodontal pockets, which facilitates the

precise delivery of nanomaterials to the lesion site within the periodontal pocket [35]. The injectable hydrogels delivery system may be an ideal solution to address the challenge.

In order to treat periodontitis, we constructed an injectable MXene-based hydrogel GQM, which is composed of quaternized chitosan (QCS), oxidized gellan gum (OG), and magnesium ions and tannic acid modified MXene nanosheets (MTA-Mg). In GQM hydrogels, G stands for OG, Q stands for QCS, and M stands for MTA-Mg nanosheets. With near infrared light, the MTA-Mg nanosheets generate photothermal effect causing the dense biofilm structure to loosen and disintegrate. Meanwhile, the cationic quaternary ammonium groups on the quaternized chitosan segments engage in electrostatic interactions with the anionic groups on bacterial cell membranes [36]. This interaction alters bacterial membrane permeability, thereby further eliminating *P. gingivalis* and *F. nucleatum* [37]. GQM also exhibits profound immunomodulatory functions. The Ti-based conductive network on MTA-Mg acts as an efficient electron acceptor and transport channel, while tannic acid facilitates electron transfer via reversible phenol quinone redox cycles to stabilize the local redox environment. Upon coordination with divalent metal ions like magnesium, tannic acid forms a metal polyphenol network with superior structural stability and redox buffering capabilities. MTA-Mg utilizes its excellent electron transfer capability to restore the NAD^+/NADH balance. This process reactivates the mitochondrial respiratory chain and boosts OXPHOS levels within immune cells. Such metabolic reprogramming facilitates the polarization of macrophages from the inflammatory M1 phenotype toward the reparative M2 phenotype, which improves local inflammation and mitigates bone loss induced by excessive inflammation. In conclusion, the GQM hydrogel achieves a dual effect of biofilm eradication and immune metabolic reprogramming through its photothermal effect and electron transfer capability. This provides a novel strategy for reversing alveolar bone resorption in periodontitis.

2 Experimental

2.1 Materials

Gellan gum (GG) and QCS (degree of substitution 90%) were purchased from Shanghai Yuanye Bio-Technology Co., Ltd. Sodium periodate was obtained from Sigma Aldrich. TA was acquired from Shanghai Aladdin Biochemical Technology Co., Ltd. Ethylene glycol and magnesium sulfate (MgSO_4) were purchased from Sinopharm Chemical Reagent Co., Ltd. MAX phase (Ti_3AlC_2) was purchased from 11 Technology Co., Ltd.

2.2 Preparation of MTA-Mg nanosheets

To prepare the nanosheets, 1 g of lithium fluoride (LiF) was added to a 9 mol/L hydrochloric acid solution to obtain a clear solution. Subsequently, 1 g of Ti_3AlC_2 black powder was added, and the mixture was stirred in a water bath at 35 °C for 26 h to produce a black solution. The precipitate was collected by centrifugation at 3500 rpm and washed repeatedly with deionized water until the pH of the supernatant approached 6. The precipitate was then re-dispersed in an appropriate amount of deionized water and subjected to ultrasonic oscillation under an argon atmosphere for 1 h. Finally, the supernatant was collected via low-speed centrifugation and lyophilized to obtain MXene nanosheets [38].

Then, 10 mg of MXene nanosheets were dissolved in 1 mL of deionized water to create a 10 mg/mL dispersion. Separately, 30 mg of tannic acid powder was dissolved in a Tris-HCl buffer solution (pH = 8.5), to which 1 mL of the MXene dispersion was added. The mixture reacted in the dark for 4 h. Then, 30 mg of MgSO₄ powder was added to the mixture and allowed to react for an additional 4 h. After ultrasonic oscillation, the precipitate was collected by centrifugation at 8000 rpm, washed with deionized water, and lyophilized to obtain the composite MTA-Mg nanosheets.

2.3 Preparation of oxidized gellan gum

Oxidized gellan gum (OG) was prepared using the sodium periodate oxidation method. The aldehyde content of the oxidized gellan gum was measured using the Schiff reagent, and the oxidation degree of the oxidized gellan gum was calculated to be 36%. The detailed experimental methods are provided in the Electronic Supplementary Material (ESM).

2.4 Preparation of Gel, GQ and GQM hydrogel

To prepare the Gel hydrogel, 8% OG and 3% carboxymethyl chitosan were mixed at a volume ratio of 1:3. To prepare the GQ hydrogel, 8% OG and 3% QCS were mixed at a volume ratio of 1:3. To prepare the GQM hydrogel, a specific amount of multifunctional MTA-Mg nanosheets was added to a 2 wt.%–10 wt.% OG aqueous solution to form Solution A. A 3 wt.% QCS aqueous solution was prepared as Solution B. Solution A and Solution B were mixed thoroughly at a volume ratio of 1:3 and allowed to react for 5 min to obtain the multifunctional injectable GQM hydrogel.

2.5 Material characterization

Ultraviolet-visible (UV-Vis) absorption spectra were collected using a Lambda 800 UV-Vis spectrophotometer. X-ray photoelectron spectroscopy (XPS) data were measured using a Thermo Scientific K-ALPHA spectrometer with monochromatic Al K α excitation (1486.68 eV). Dynamic light scattering (DLS) was measured using a Zetasizer Nano ZS. Fourier transform infrared (FTIR) spectra were obtained using a Nicolet Avatar 360. The pore morphology of the hydrogel was observed using a JEOL JSM-6700F scanning electron microscope (SEM). The morphology of the MTA-Mg nanosheets was characterized using a transmission electron microscope (TEM, JEM-2100F) and an atomic force microscope (AFM, Bruker ICON-XR). The rheological properties of the GQM hydrogel were analyzed using a rheometer (TA Discovery DHR-2). The detailed experimental methods are provided in the ESM.

2.6 Antibacterial experiments

Bacterial suspensions of *Porphyromonas gingivalis* (*P. g.*) and *Fusobacterium nucleatum* (*F. n.*) were adjusted to 1×10^8 colony-forming units (CFU)/mL. Sterile circular glass coverslips were placed at the bottom of a 24-well plate. Biofilms were cultured in tryptic soy broth (TSB) containing conditioned medium at 37 °C under anaerobic conditions for 96 h, with the medium refreshed every 24 h. The detailed experimental methods are provided in the ESM.

2.7 In vitro anti-inflammatory assay

RAW264.7 cells were seeded in 6-well plates (3×10^6 cells/well) and cultured for 24 h. Cells were stimulated with lipopolysaccharide (LPS) (1 μ g/mL) for 3 h. The medium was then replaced with

conditioned medium for the Gel, GQ, GQM, and GQM + NIR groups, or normal medium for the Control group. The detailed experimental methods are provided in the ESM.

2.8 Animal experiments

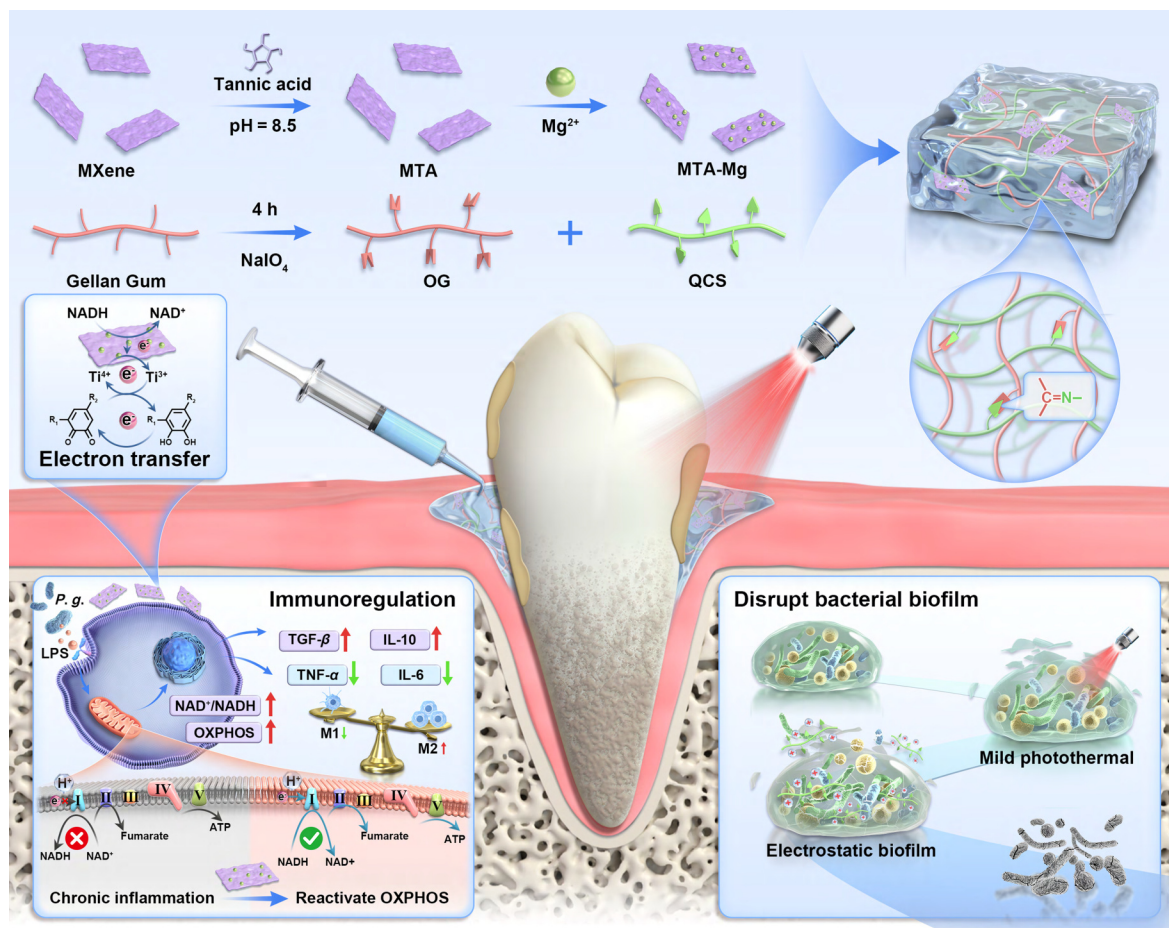
A rat periodontitis model was established by ligating the left maxillary second molar with a 0.25-mm wire under anesthesia and injecting a mixed suspension of *P. gingivalis* and *F. nucleatum* every other day for 7 injections. After 2 weeks, rats were randomized into six groups: Blank, Periodontitis, Gel, GQ, GQM, and GQM + NIR. The treatment groups received an injection of the hydrogel (200 μ g/mL) into the periodontal pocket every 3 days. The NIR groups were irradiated (0.5 W/cm², 5 min) every 3 days for 28 days. The detailed experimental methods are provided in the ESM.

3 Results and discussion

3.1 Synthesis and characterization of MTA-Mg nanosheets and the GQM hydrogel

We constructed an injectable hydrogel consisting of QCS, OG, and MTA-Mg nanosheets to adapt to the narrow and complex anatomy of periodontal pockets (Scheme 1). First, tannic acid was modified to the MXene surface at pH 8.5 driven by electrostatic and hydrogen bonding interactions. Following this, magnesium ions were modified to the MXene surface through chelation with the catechol groups of the tannic acid. The modified MTA-Mg nanosheets were incorporated into an injectable hydrogel network composed of QCS and OG, which was designated as GQM. Attributed to the reversible dynamic covalent bonds formed between the amino groups of QCS and the aldehyde groups of OG, the GQM hydrogel is capable of fully filling irregular periodontal pockets and achieving prolonged retention at the lesion site. Consequently, this enables the tight encapsulation of biofilms. Under near infrared irradiation, the mild photothermal effect generated by MTA-Mg reduces the viscoelasticity and structural stability of the EPS. This causes the dense biofilm to gradually transform into a loose and porous state. The strong cationic surface endowed by QCS engages in electrostatic adsorption and charge neutralization with anionic groups on bacterial membranes and within the biofilm matrix. This process induces the aggregation and structural collapse of the EPS, thereby further eliminating pathogenic bacteria within the periodontal pocket. MTA-Mg nanosheets exhibit superior surface charge transport capabilities. The Ti-based conductive network within the MXene layers serves as an efficient electron acceptor and transport channel. Through reversible redox reactions between surface Ti-O/Ti-OH groups and the phenol-quinone groups on tannic acid, MTA-Mg nanosheets function as an electron donor. Furthermore, the coordination structure of magnesium ions further stabilizes this electron migration process. The continuous electron transport pathway formed at the material interface accelerates the reoxidation of nicotinamide adenine dinucleotide (NADH), enabling the restoration of the NAD⁺/NADH ratio. This process reactivates the mitochondrial electron transport chain and enhances oxidative phosphorylation levels, thereby promoting the transition of macrophages toward a low-inflammation and reparative metabolic state.

To verify the successful modification of tannic acid and magnesium ions, we characterized the UV absorption spectra of



Scheme 1 The illustration of GQM treatment for periodontitis.

MXene and MTA-Mg. As shown in Fig. S1 in the ESM, MTA-Mg exhibited characteristic peaks corresponding to the benzene ring and catechol groups at 212 and 276 nm, confirming the successful modification with tannic acid. Subsequently, we measured the zeta potentials of MXene, MTA, and MTA-Mg using the zeta mode of DLS. The values were -31.2 , -52.8 , and -36.6 mV, respectively (Fig. 1(a)). The decrease in potential to a more negative value for MTA is due to the increased electron cloud density from the tannic acid modification. Then, the zeta potential increased when magnesium ions were modified onto the MXene surface through chelation. These results demonstrate the successful modification involving tannic acid and magnesium ions. We characterized the MTA-Mg nanosheets by AFM and TEM. AFM images revealed that MTA-Mg exhibits a nanosheet structure with a thickness of approximately 15 nm (Figs. 1(b) and 1(c)). The TEM images further confirmed the nanosheet structure of MTA-Mg. Additionally, elemental mapping results showed that Ti, Mg, and O elements were uniformly distributed on the MXene surface, confirming the successful modification of Mg onto the MXene surface (Fig. 1(d)). In the XPS spectrum of MTA-Mg, the peaks at 455.2, 456.2, and 457.3 eV in the Ti 2p plot correspond to the $2p_{3/2}$ peaks of Ti-C, Ti-O, and Ti-F. Meanwhile, the peaks at 461.1, 461.6, and 462.7 eV correspond to the $2p_{1/2}$ peaks of Ti-C, Ti-O, and Ti-F, demonstrating that the MXene was successfully etched by HCl and LiF (Fig. 1(e)). The Mg 2p peak at 50.3 eV confirms the modification of Mg onto the MXene surface, which is consistent with the previous results (Fig. 1(f)).

Traditional nanomaterials struggle to maintain long-term retention in periodontal pockets due to the narrow structure and constant saliva washout, which reduces their therapeutic efficacy [39]. To overcome this limitation and enable MTA-Mg to function continuously at the periodontitis site, the nanosheets were loaded into an injectable hydrogel constructed by QCS and OG. As illustrated in Fig. 1(g), mixing Solution A containing OG and MTA-Mg with Solution B containing QCS at a volume ratio of 1:3 for 2 min, the GQM hydrogel transforms from sol into a gel state, which makes the hydrogels exist stably in the periodontal pocket. SEM was then used to investigate the microstructure of the GQM hydrogel. SEM images revealed that the GQM hydrogel exhibited a porous architecture with a pore size of approximately 100 μm . As observed from the energy dispersive spectroscopy (EDS) mapping of the hydrogel, Mg, Ti, C, and O elements are distributed evenly throughout the sample. This provides evidence that the MTA-Mg nanosheets are uniformly incorporated into the hydrogel (Fig. 1(h)). The presence of the Mg 2p characteristic peak in the XPS spectrum of the GQM hydrogel further substantiates this result (Figs. 1(i) and 1(l)). In the N 1s spectrum, the peak located at 402.4 eV is attributed to the N^+ of the quaternary ammonium structure in QCS, while the peak at 399.8 eV is assigned to the C-N-H of the amino groups. The peak at 398.8 eV corresponds to $-\text{N}=\text{C}$, which validates the formation of imine bonds within the GQM hydrogel (Fig. 1(j)). The FTIR spectrum also confirms this result, showing a stretching vibration peak for the imine group ($\text{C}=\text{N}$) at 1685 cm^{-1} (Fig. S2 in the ESM). In the C 1s spectrum, the

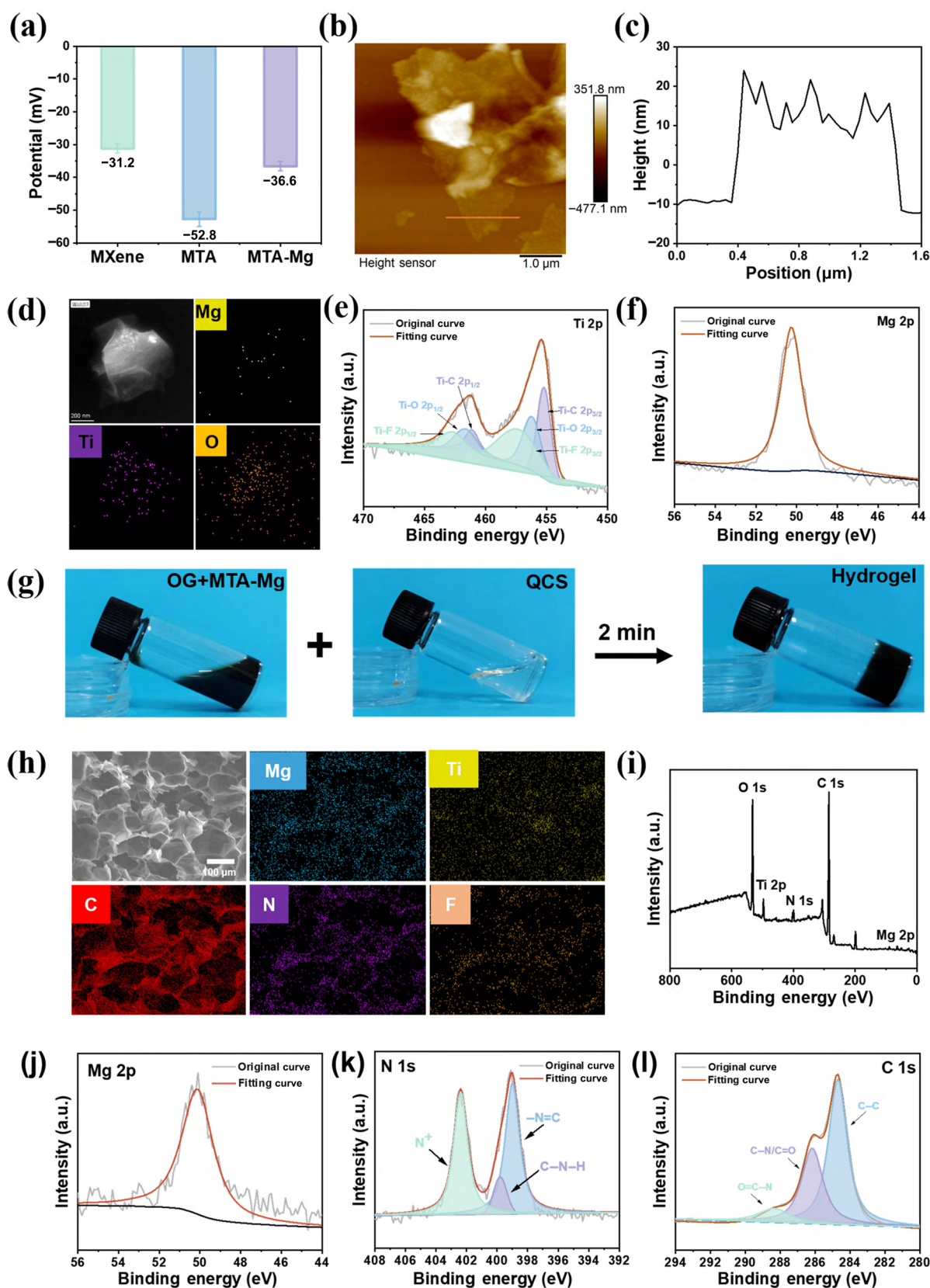


Figure 1 (a) The zeta potential of MXene, MTA and MTA-Mg. (b) The AFM image of MTA-Mg nanosheets. (c) Sample height diagram corresponding to the line drawing of MTA-Mg nanosheets in the AFM image. (d) TEM and mapping images of MTA-Mg nanosheets. (e) The Ti 2p XPS spectra of MTA-Mg nanosheets. (f) The Mg 2p XPS spectra of MTA-Mg nanosheets. (g) The photographs illustrate gelation process of GQM hydrogels. (h) The SEM and EDS images of the GQM hydrogels. (i) The XPS spectrum of GQM hydrogel. (j) The Mg 2p XPS spectra of GQM hydrogel. (k) The N 1s XPS spectra of GQM hydrogel. (l) The C 1s XPS spectra of GQM hydrogel.

peak at 288.4 eV represents O=C from the aldehyde groups of OG, and the C–N bond in the hydrogel is identified at 286.1 eV (Fig. 1(k)). In summary, we have successfully modified tannic acid and magnesium ions to the MXene surface and synthesized MTA-Mg nanosheets, and we incorporated MTA-Mg into an injectable hydrogel formed by imine bonds.

3.2 The properties of GQM hydrogels

The treatment progress of periodontitis involves stages that include biofilm disruption, inflammation control, and bone regeneration [40, 41]. Under the continuous washing of gingival crevicular fluid, existing commercial clinical ointments often exhibit rapid burst release of drugs and poor local retention, making them inadequate for completely filling deep periodontal pockets with highly complex anatomical structures [42]. In contrast, GQM hydrogels exhibit excellent injectability and self-healing activity, enabling them to tightly conform to irregular periodontal defects and achieve prolonged local retention. Meanwhile, the photothermal functionality of GQM hydrogels enables effective bacterial biofilm disruption, and the ROS-scavenging capacity contributes to anti-inflammatory property. To obtain a composite hydrogel capable of meeting the mechanical requirements, we investigated the composition ratios of the system. The results show that GQM hydrogels with broadly tunable mechanical properties can be prepared by adjusting the concentration of OG (Fig. 2(a)). With the rise in OG concentration, the hydrogels showed a significant increase in both storage modulus (G') and loss modulus (G''). Considering the requirements for adaptability and convenience associated with *in vivo* injection, the composite hydrogel containing 8% OG with 509 Pa G' and 89 Pa G'' was selected for subsequent experimental studies. With the increasing concentration of MTA-Mg nanosheets, the G' and G'' of the hydrogel initially increased and subsequently decreased (Fig. 2(b)). This is attributed to the ability of MTA-Mg to form non-covalent interactions, such as hydrogen bonds and electrostatic interactions, with the hydrogel network, thereby increasing the modulus. However, at excessive MTA-Mg concentrations, the nanosheets hindered the formation of imine bonds, which resulted in a decrease in the modulus of the hydrogel. Degradation experiments demonstrated that the GQM hydrogel degraded by 40% within 3 days and reached 80% degradation by 15 days (Fig. S3(a) in the ESM). This indicates excellent biodegradability of GQM hydrogels, ensuring that the hydrogel maintains sufficient structural integrity to eradicate bacterial biofilms and reverse the inflammatory microenvironment in the first 15 days and does not impose an additional burden on the periodontal site. Furthermore, the hydrogel reaches swelling equilibrium at approximately 12 h with a final swelling ratio of 177% (Fig. S3(b) in the ESM). This rapid and moderate swelling behavior allows the hydrogel to adapt to the irregular geometry of the periodontal pocket and exist stably.

Because the periodontal pocket is narrow and has an irregular shape, the injectability of the GQM hydrogel is an essential property for treating periodontitis. We verified this injectability through shear thinning experiments by testing the viscosity change of the hydrogel at shear rates ranging from 0.05 to 100 s^{-1} . Under high shear rates, GQM showed low viscosity, enabling the hydrogel to be injected into the periodontal pocket through a syringe (Fig. 2(c)).

Continuous saliva flushing and mechanical interference in the oral cavity make materials prone to fracture in the periodontal pocket. Therefore, self-healing properties are essential for the

effective application of this injectable hydrogel *in vivo*. As shown in Fig. 2(d), the hydrogels were dyed pink and blue, respectively, to create two hydrogels of different colors. Afterwards, we cut these two hydrogels in half, took one half from each, and joined them together. After 30 min, the two halves of the hydrogel self-healed into an integrated whole. Subsequently, we subjected the hydrogel to rheological testing under strains ranging from 0.1% to 500%. The results indicated that the hydrogel underwent a transition from a gel state to a sol state at a strain of approximately 300% (Fig. 2(e)). We then confirmed the self-healing ability of GQM through four cycles of rheological measurement switching between low and high strain. At low strain, the storage modulus was higher than the loss modulus, keeping the hydrogel stable as a gel. At high strain, the loss modulus became greater than the storage modulus, making the hydrogel transform to a sol state. When the strain was switched from 500% to 1%, the G' and G'' of GQM returned to the gel state (Fig. 2(f)). This sol–gel transition under alternating high and low strain cycles remained stable for 4 cycles, further confirming the self-healing properties of the hydrogel. To further characterize the ability of the hydrogel to adapt to the mechanical stimulation of chewing within the periodontal pocket, we tested the compressibility and cyclic compression properties of the GQM hydrogel. The results showed that the hydrogel can be compressed by 80% without breaking (Fig. S4(a) in the ESM). During the 10 compression cycles, the hydrogel gradually deformed under the repeated pressure from above, and the compressive stress of GQM hydrogels decreased gradually (Fig. S4(b) in the ESM). This result is attributed to the injectable properties of GQM hydrogels, which make the hydrogels easily change shape when mechanical force is applied. The findings above indicate that the hydrogel can withstand the squeezing forces of chewing without cracking and can smoothly adjust to the mechanical forces during chewing and continuously fit the complex shape of the periodontal pocket. The excellent self-healing capability of GQM is attributed to the dynamic imine bonds and complex non-covalent interactions within GQM. When exposed to external stress, GQM dissipates energy initially via non-covalent interactions, such as hydrogen bonds and electrostatic interactions, and then through dynamic imine bonds. When the external stress is removed, these non-covalent interactions and the ruptured imine bonds can reform, thereby endowing the hydrogel with excellent self-healing capability.

MTA-Mg endows GQM with excellent photothermal capabilities, enabling the effective treatment of periodontitis through localized photothermal therapy. As the MTA-Mg concentration increased from 0 to 0.9 mg/mL, the temperatures of the hydrogels containing 0.6 and 0.9 mg/mL of MTA-Mg rose rapidly to 44.3 and 49.1 °C, respectively (Fig. 2(g)). Meanwhile, the temperature of the hydrogel without MTA-Mg exhibited negligible rising. Thermal infrared images of GQM hydrogels with different MTA-Mg contents after 0 to 240 s of irradiation also verified this result (Fig. 2(h)). As shown in Fig. 2(i), when the laser power density was increased from 0.25 to 0.75 W/cm², the hydrogel temperature significantly increased from 20 to 36.7, 44.6, and 64.7 °C within 300 s, respectively. Previous research suggests that mild photothermal therapy (< 45 °C) effectively kills bacterial biofilms in periodontal pockets while avoiding damage to oral tissues. Therefore, we selected the hydrogel with 0.6 mg/mL MTA-Mg and a laser power of 0.5 W/cm² for the following experiments. As illustrated by the photothermal cyclic experiment in Fig. 2(j), the

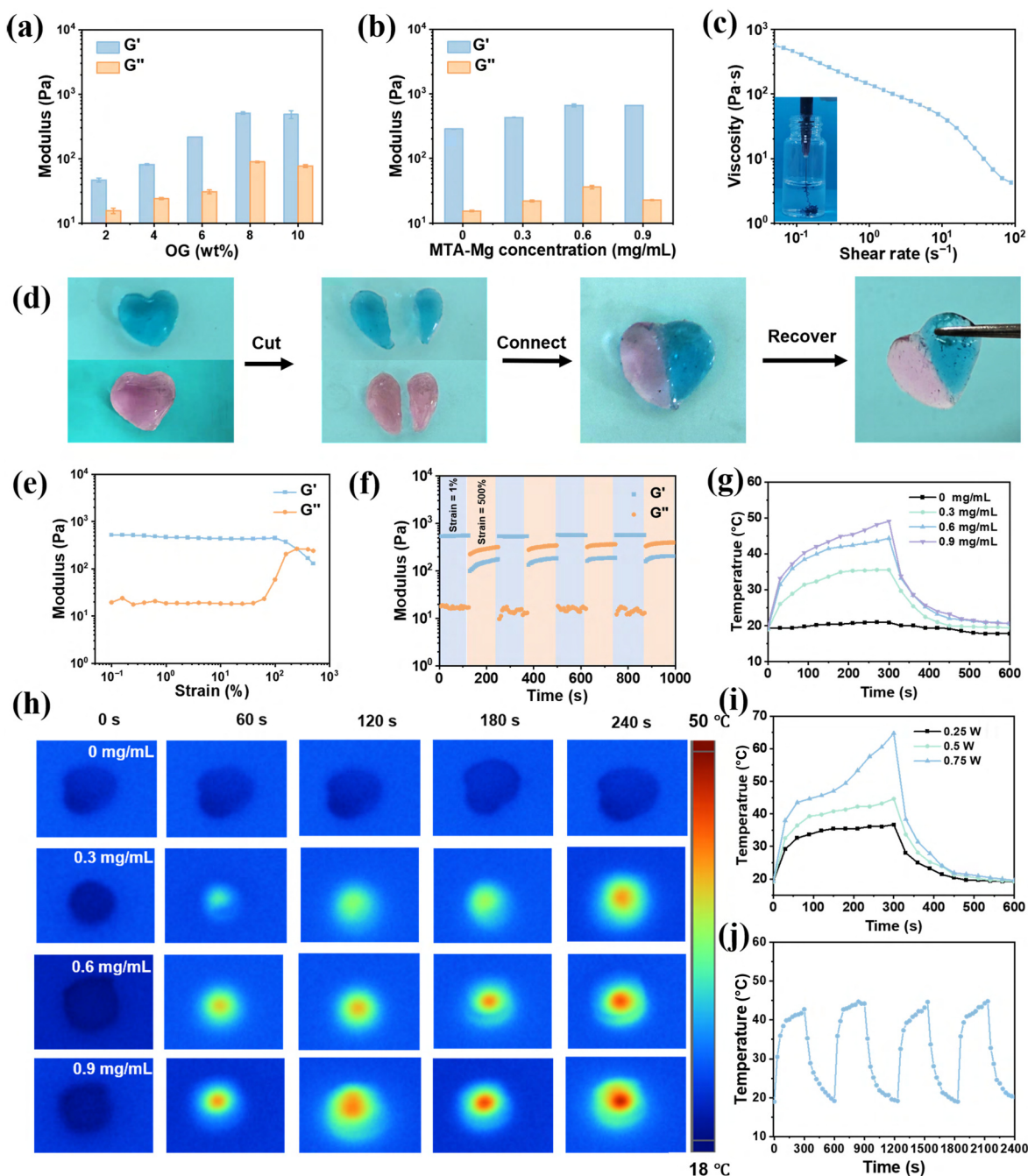


Figure 2 The modulus of GQM hydrogels with different contents of (a) OG and (b) MTA-Mg. (c) Viscosity of GQM hydrogel with shear rate increased from 0.05 to 100 s^{-1} . (d) The photographs of self-healing processes in GQM hydrogels. (e) Strain amplitude sweep measurements of the GQM hydrogel. (f) Cyclic rheological measurement of the GQM hydrogels. (g) Temperature curves of GQM hydrogels containing different concentrations of MTA-Mg under 0.5 W/cm^2 . (h) Thermal infrared images of hydrogels with different contents of MTA-Mg under 0.5 W/cm^2 for different time. (i) Temperature curves of GQM hydrogels with 0.6 mg/mL MTA-Mg at different powers. (j) Photothermal cycling curves of the GQM hydrogels.

temperature changes remained consistent across four repeated cycles. These results demonstrate the excellent photothermal stability of the GQM hydrogel.

To verify the cytocompatibility of the synthesized GQM hydrogel, we exposed L929 cells to varying contents of MTA-Mg nanosheets. Quantitative analysis revealed an inverse correlation between nanosheet density and cell proliferation over 24 and 72 h (Fig. S5(a) in the ESM). Despite this minor reduction in proliferative activity at higher loadings, the hydrogels demonstrated low toxicity and viability remained above 80% at 0.6 mg/mL. These

quantitative findings align with the qualitative Live/Dead fluorescence microscopy (Fig. S5(b) in the ESM), collectively confirming that the GQM platform exhibits excellent biocompatibility.

The GQM hydrogel also possesses excellent ROS scavenging ability to alleviate inflammation in periodontitis. The ROS scavenging ability of GQM hydrogels with different MTA-Mg contents was first analyzed by using 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) ammonium radical (ABTS $\cdot^-$) and 1,1-diphenyl-2-picrylhydrazyl radical (DPPH $\cdot$) as the

representative reactive nitrogen species. The DPPH $\cdot$ and ABTS $\cdot^-$ had their absorbances recorded at 519 and 734 nm, respectively (Figs. S6(a) and S6(c) in the ESM). The significantly lowered absorbance levels of both DPPH and ABTS after treatment by GQM hydrogels confirm the substantial ROS scavenging efficacy. The results showed that the clearance efficiency of GQM hydrogel with 0.6 mg/mL MTA-Mg against ABTS $\cdot^-$ can reach 57.9% (Fig. S6(b) in the ESM), while its scavenging ratio against DPPH $\cdot$ can reach 51.2% (Fig. S6(d) in the ESM). The observed data indicate the robust ROS scavenging capacity of the GQM hydrogels, which is due to the synergistic effect of tannic acid and the absorption of electrons by MXene nanosheets.

The GQM hydrogel exhibits good biocompatibility, injectability, and self-healing ability, allowing it to adapt to the complex structure of the periodontal pocket. Additionally, through its excellent photothermal capability and ROS scavenging ability, the hydrogel provides long-term antibacterial and anti-inflammatory properties in the treatment of periodontitis.

3.3 *In vitro* antibacterial activity of GQM hydrogels

Dental plaque is the initiating factor of periodontitis [43]. *P. g.* is a key driver of disease progression, while *F. n.* is an early colonizer in periodontal biofilms [44]. Because bacteria play a central role in this disease, biomaterials for periodontal therapy must exhibit strong antibacterial properties. Traditional clinical formulations primarily rely on the local release of antibiotics, which have very limited penetration capabilities into mature biofilm matrix barriers, and long-term use faces a significant risk of bacterial resistance [45]. Therefore, by combining the cationic disruption effect of QCS with the photothermal effect of MTA-Mg nanosheets to disrupt bacterial biofilms, we provide a novel non-antibiotic antibacterial strategy. To evaluate the antibiofilm activity of GQM *in vitro*, we used biofilms formed by *P. gingivalis* and *F. nucleatum* as model systems. Biofilm clearance has a direct impact on the therapeutic outcome of periodontitis. Five groups were established including a control group and four treatment groups (Gel, GQ, GQM, and GQM+NIR), which were treated by Gel, GQ, GQM hydrogels and GQM hydrogels with near-infrared light. Specifically, the Gel hydrogels were synthesized from OG and carboxymethyl chitosan (CMCS), whereas the GQ hydrogels were composed of OG and QCS. The GQM hydrogels consisted of OG, QCS and MTA-Mg nanosheets. Biofilm disruption to two different bacteria was assessed across these designated treatment groups. After the materials were introduced, the GQM+NIR group received 5 min of mild photothermal treatment.

This study evaluated the disruption of mature biofilms of the key periodontal pathogens *P. gingivalis* and *F. nucleatum* in each treatment group. The hydrogel was co-incubated with both species (Figs. 3(a) and 3(b)). CFU counts were recorded after each treatment (Figs. 3(c) and 3(d)). Compared with the Control group, the Gel group showed only a few dead colonies with no significant change. The GQ group showed an approximately 1-log reduction. The GQM+NIR group showed an additional 2-log decrease. These results indicate that the GQM+NIR hydrogel caused a pronounced reduction in CFU counts of both pathogens. This suggests a strong synergistic effect among membrane disruption, photothermal heating, and MTA-Mg metabolic interference. In order to further characterize the antibacterial effects of each group, the hydrogels were grown together with *P. gingivalis* and *F. nucleatum* for 12 h. The OD₆₀₀ results in Fig. S7 in the ESM showed the largest decrease

in the GQM+NIR group. For *P. gingivalis*, the OD₆₀₀ was 0.79 in the Control group while it was 0.28 in the GQM+NIR group. Similarly, the OD₆₀₀ for *F. nucleatum* went down from 0.82 to 0.23 when treated by GQM+NIR. These results are in agreement with the previous CFU results, clearly showing that the GQM+NIR treatment can strongly reduce the overall growth of these two harmful bacteria.

SEM analysis provided ultrastructural evidence for the antibacterial and antibiofilm mechanisms. SEM imaging revealed clear morphological features of the two pathogens. *P. gingivalis* appeared as short rods. *F. nucleatum* appeared as long fusiform cells. After treatment with the GQM hydrogel, surface depressions appeared on both species. After GQM+NIR treatment, severe damage occurred. The cell membranes showed wrinkles and deformation, which indicated bacterial death (Fig. 3(e)). To further assess the antibacterial activity, live/dead staining was performed. Live bacteria showed green fluorescence. Membrane-damaged bacteria showed red fluorescence. Confocal microscopy was used to evaluate the disruption of mature biofilms of *P. gingivalis* and *F. nucleatum* (Fig. 3(f)). The control group displayed strong green signals, indicating viable biofilms. The GQM and GQM+NIR groups showed increased red fluorescence and reduced biofilm thickness. The GQM+NIR group showed the highest dead-to-live ratio, the smallest biofilm thickness, and the lowest total bacterial load. A similar trend was observed in the *F. nucleatum* biofilm assay. Confocal imaging showed a marked decrease in green signals in both the surface and deep layers of the GQM+NIR group. Red signals from dead bacteria increased significantly (Figs. 3(g) and 3(h)). The continuous three-dimensional structure broke into fragmented sheets and sparse clusters. The quaternized chitosan first disrupted the EPS framework through electrostatic interactions with extracellular DNA and acidic polysaccharides. This created channels for active agents to penetrate the biofilm. The photothermal effect of MXene increased the temperature inside the biofilm, producing direct thermal killing of anaerobic bacteria in low-metabolic zones. MTA-Mg nanosheets inhibit the adhesion and reaggregation of the two bacteria on damaged substrates by suppressing adhesion-associated proteins and persistent oxidative stress. The pattern matched the "red-throughout" signals and structural failure observed in the confocal images. Crystal violet staining in Fig. 3(i) supported these results. While the control and gel groups retained most of their biomass and structural integrity, the GQ, GQM, and GQM+NIR groups disrupted the compact biofilm and caused a marked loss of biomass. Particularly, the GQM+NIR group showed a decrease in absorbance for *P. gingivalis* and *F. nucleatum* biofilms compared with the control group (Figs. 3(j) and 3(k)), indicating a marked reduction in matrix content and adherent bacteria.

To differentiate the contributions of the electrostatic antibacterial effect of QCS and the photothermal film damage effect of MTA-Mg, we constructed several control groups (Gel, GQ, GM, GM+NIR, GQM, and GQM+NIR) by replacing QCS with CMCS. Under the premise of basically maintaining the consistency of the hydrogel structure, we tested the photothermal antibacterial effects of QCS and MTA-Mg respectively. Specifically, Gel consisted of OG and CMCS, GQ consisted of OG and QCS, and GM consisted of OG, CMCS, and MTA-Mg nanosheets, while GQM consisted of OG, QCS and MTA-Mg nanosheets. CFU results in Fig. S8 in the ESM showed that although the GQ group reduced the colony count by 1 log and the GM+NIR group reduced it by 2 log, which

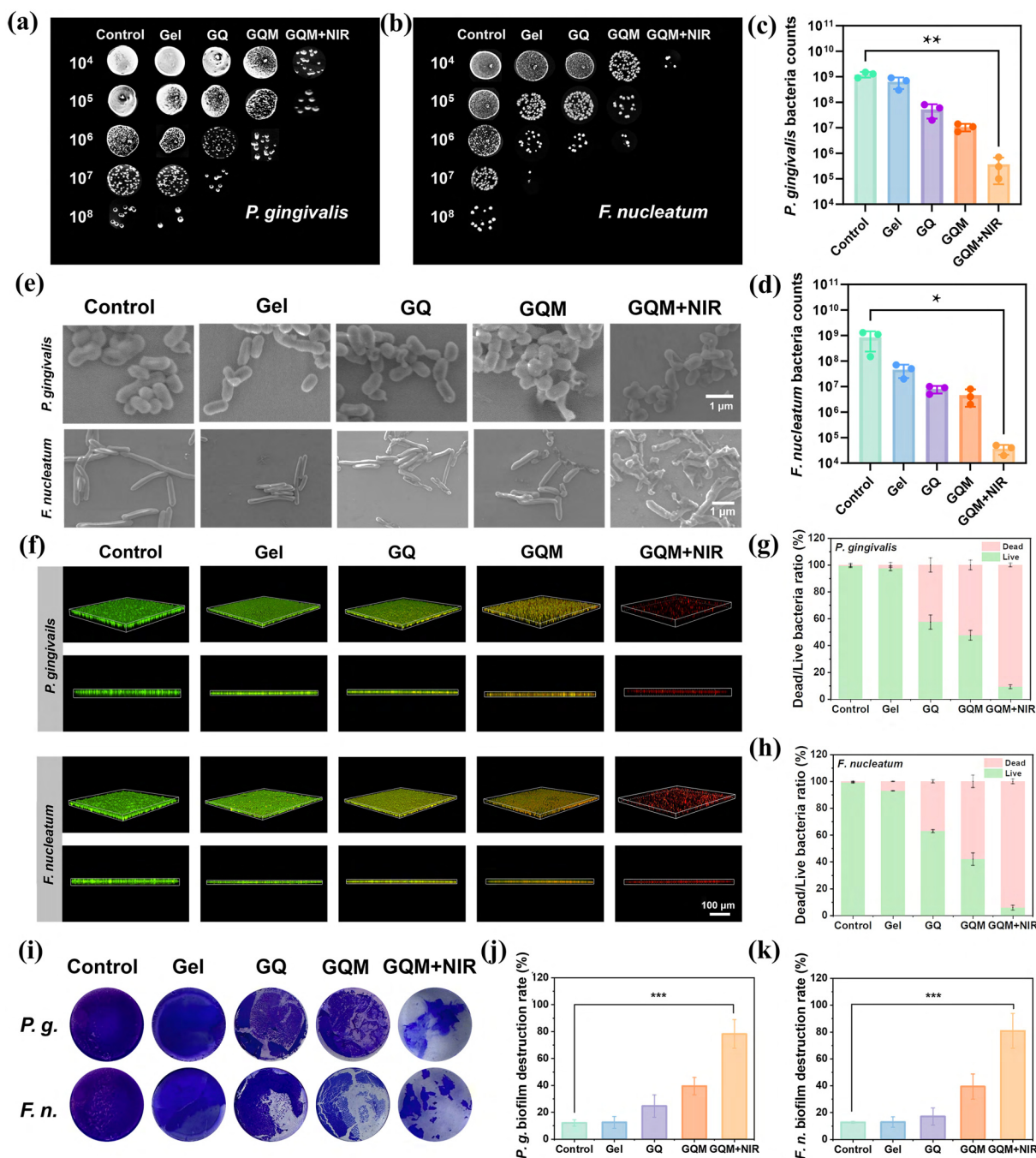


Figure 3 Antibacterial effects of GQM hydrogels. CFU counting photographs (a) *P. gingivalis* and of (b) *F. nucleatum*. CFU counting chart of (c) *P. gingivalis* and (d) *F. nucleatum*. (e) SEM images of *P. gingivalis* and *F. nucleatum*. Scale bars: 1 μm . (f) 3D live/dead staining images of *P. gingivalis* and *F. nucleatum* biofilms. Scale bar: 100 μm . Live/dead rate of (g) *P. gingivalis* and (h) *F. nucleatum* bacteria ratio in biofilm. (i) Crystal violet staining images of bacterial biofilms of *P. gingivalis* and *F. nucleatum*. Biofilm destruction rate of (j) *P. gingivalis* and (k) *F. nucleatum*. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, ns, not significant (compared with the Control group). Group settings: (1) Control group, where bacteria were not subjected to any treatment; (2) Gel group treated by Gel hydrogels consist of OG and CMCS; (3) GQ group treated by GQ hydrogels which consist of OG and QCS; (4) GQM group treated by GQM hydrogels which consist of OG, QCS and MTA-Mg nanosheets; (5) GQM + NIR group treated by GQM hydrogel with near-infrared light (0.5 W/cm², 5 min).

indicated that both the electrostatic interaction of QCS and the photothermal effect of MTA-Mg activated by NIR can independently contribute to the antibacterial effect, neither of them was as good as the antibacterial effect of the GQM+NIR group which had the synergistic effect of the two. These results suggest that the electrostatic interaction of QCS and the photothermal effect of MTA-Mg exhibit complementary enhancement at different

spatial levels, thereby jointly improving the biofilm disruption ability of the GQM+NIR group. QCS caused membrane potential collapse and adenosine triphosphate (ATP) depletion, which rapidly weakened the membrane barrier and the metabolic basis of *P. gingivalis* and *F. nucleatum*. The photothermal effect of MTA-Mg nanosheets induced thermal degradation and detachment of the matrix. It also enhanced membrane phase transitions and

enzyme inactivation. The combination of the two effects is the key to the GQM+NIR group disrupting the biofilm at the periodontitis site. The results above show that the GQM hydrogel not only kills bacteria inside the biofilm but also removes the supporting matrix scaffold. This dual action directly explains the sharp reduction in CFU counts and the collapse of the biofilm structure.

3.4 *In vitro* anti-inflammatory activity of GQM hydrogels

Current clinical drug delivery systems are limited to antibacterial treatment, neglecting the immune metabolic disorders caused by infection [42]. By introducing MTA-Mg nanosheets, the GQM hydrogels can improve mitochondrial redox homeostasis, actively promoting the restoration of macrophages to an anti-inflammatory metabolic phenotype. In the complex immune microenvironment of periodontitis, macrophages, owing to their remarkable phenotypic plasticity, play a central role and constitute a critical link connecting pathogenic assault and host immune responses [10]. Upon stimulation by pathogen-associated molecular patterns, classically activated M1 macrophages highly express pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β). While aimed at clearing infection, this response inevitably exacerbates tissue inflammation and activates osteoclast differentiation, leading to alveolar bone destruction. In contrast, alternatively activated M2 macrophages, through the secretion of regulatory factors like interleukin-10 (IL-10) and arginase-1 (Arg-1), orchestrate the resolution of inflammation and facilitate tissue repair and bone regeneration [46]. As therapeutic strategies evolve from purely antibacterial approaches towards immunomodulation, researchers are focusing on developing novel strategies capable of precisely regulating macrophage polarization [16]. Among these, GQM hydrogels effectively reprogram macrophages from the pro-inflammatory M1 phenotype to the restorative M2 phenotype, thereby reshaping the immune homeostasis in the periodontal region and offering a promising regulatory pathway for achieving true structural and functional regeneration of periodontal tissues (Fig. 4(a)).

To confirm the successful internalization of MTA-Mg nanosheets by macrophages, we first utilized TEM. As shown in Fig. S9 in the ESM, MTA-Mg nanosheets were clearly observed within the treated cells. Building upon this observation, we further evaluated the regulatory effect of the GQM+NIR treatment on the metabolic state of macrophages from the perspective of mitochondrial function by examining mitochondrial membrane potential ($\Delta\Psi_m$), intracellular ROS levels, and the NADH/NAD⁺ ratio. JC-1 staining results (Fig. S10 in the ESM) showed that after LPS stimulation, the red aggregates fluorescence in the Control group was significantly weakened while the green monomer fluorescence was enhanced, whereas the GQM group showed a significant recovery of red fluorescence signal. The red ratio in the GQM+NIR group was further increased, suggesting that this treatment can more effectively improve the damaged mitochondrial membrane potential. 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) staining showed (Fig. S11 in the ESM) that LPS stimulation significantly increased intracellular ROS levels, and the DCF fluorescence signal in the GQM+NIR group was significantly reduced. At the same time, LPS stimulation led to a significant increase in the intracellular NADH/NAD⁺ ratio, while the ratio was significantly decreased after GQM+NIR treatment (Fig. S12 in the ESM), indicating that this treatment helps improve the damaged cellular redox homeostasis under inflammatory conditions. These

results indicate that GQM+NIR can effectively improve LPS-induced macrophage mitochondrial dysfunction and provide direct functional support for promoting macrophage immune metabolic remodeling.

Then, polymerase chain reaction (PCR) results demonstrated that the GQM+NIR combination most effectively suppressed the expression of pro-inflammatory genes (e.g., TNF- α and IL-1 β) while upregulating anti-inflammatory genes (e.g., IL-10 and Arg-1) in macrophages (Figs. 4(b)–4(e)). Subsequent immunofluorescence staining of these key markers further validated, at the protein level, that GQM+NIR optimally promotes the transition of macrophages toward an anti-inflammatory and reparative phenotype, even under bacterially induced inflammatory conditions (Figs. 4(f) and 4(g)). To quantitatively assess the phenotypic modulation by GQM+NIR, flow cytometry was performed on macrophage populations subjected to various treatments. The results revealed that GQM+NIR most significantly enhanced the conversion of macrophages to the M2 phenotype, increasing the proportion of M2 macrophages from 28.9% (control group) to 50.8% (Fig. 5(a)).

Encouraged by these promising findings, we performed transcriptomic sequencing (RNA-seq) to gain deeper insights into the mechanism by which GQM+NIR modulates macrophage polarization. Principal component analysis (PCA) confirmed the robust and distinct therapeutic profile of the GQM+NIR treatment group (Figs. S13(a) and S13(b) in the ESM). Volcano plot analysis identified a total of 2961 differentially expressed genes (DEGs) following GQM+NIR stimulation, comprising 1353 upregulated and 1608 downregulated genes (Fig. 5(b)). A heatmap vividly illustrates the expression patterns of these 2961 DEGs across different experimental conditions (Fig. 5(c)). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis revealed a significant enrichment of DEGs in immune-related signaling pathways, particularly highlighting the suppression of the Toll-like receptor and nuclear factor- κ B (NF- κ B) pathways, which aligns perfectly with the observed downregulation of pro-inflammatory markers (Fig. 5(d)). Furthermore, Gene Ontology (GO) enrichment analysis demonstrated that GQM+NIR not only impacted immune response-related terms but also significantly influenced various metabolic processes (Fig. 5(e)). Integrated pathway analysis ultimately established a hierarchical regulatory relationship, indicating that GQM+NIR primarily reprograms macrophage metabolism, which in turn orchestrates its potent immunomodulatory effects (Fig. 5(f)).

Macrophage immune function is intricately regulated by its metabolic reprogramming, a central paradigm in immunometabolism. Proinflammatory M1 polarization is tightly coupled to aerobic glycolysis, a metabolic shift primarily driven by hypoxia-inducible factor-1 α (HIF-1 α) signaling. This pathway promotes rapid energy production via glycolysis even under normoxic conditions, while lactate—a glycolytic byproduct—further stabilizes HIF-1 α , establishing a feedforward loop that amplifies the production of pro-inflammatory cytokines and ROS, thereby exacerbating inflammatory responses [47]. In contrast, M2 macrophages, which mediate tissue repair and inflammation resolution, predominantly rely on OXPHOS to meet their bioenergetic demands [13]. OXPHOS not only supplies sustainable energy but is also mechanistically linked to the expression of anti-inflammatory genetic programs. Thus, metabolic pathways act not merely as passive energy suppliers but as upstream regulatory switches that dictate macrophage phenotypic fate.

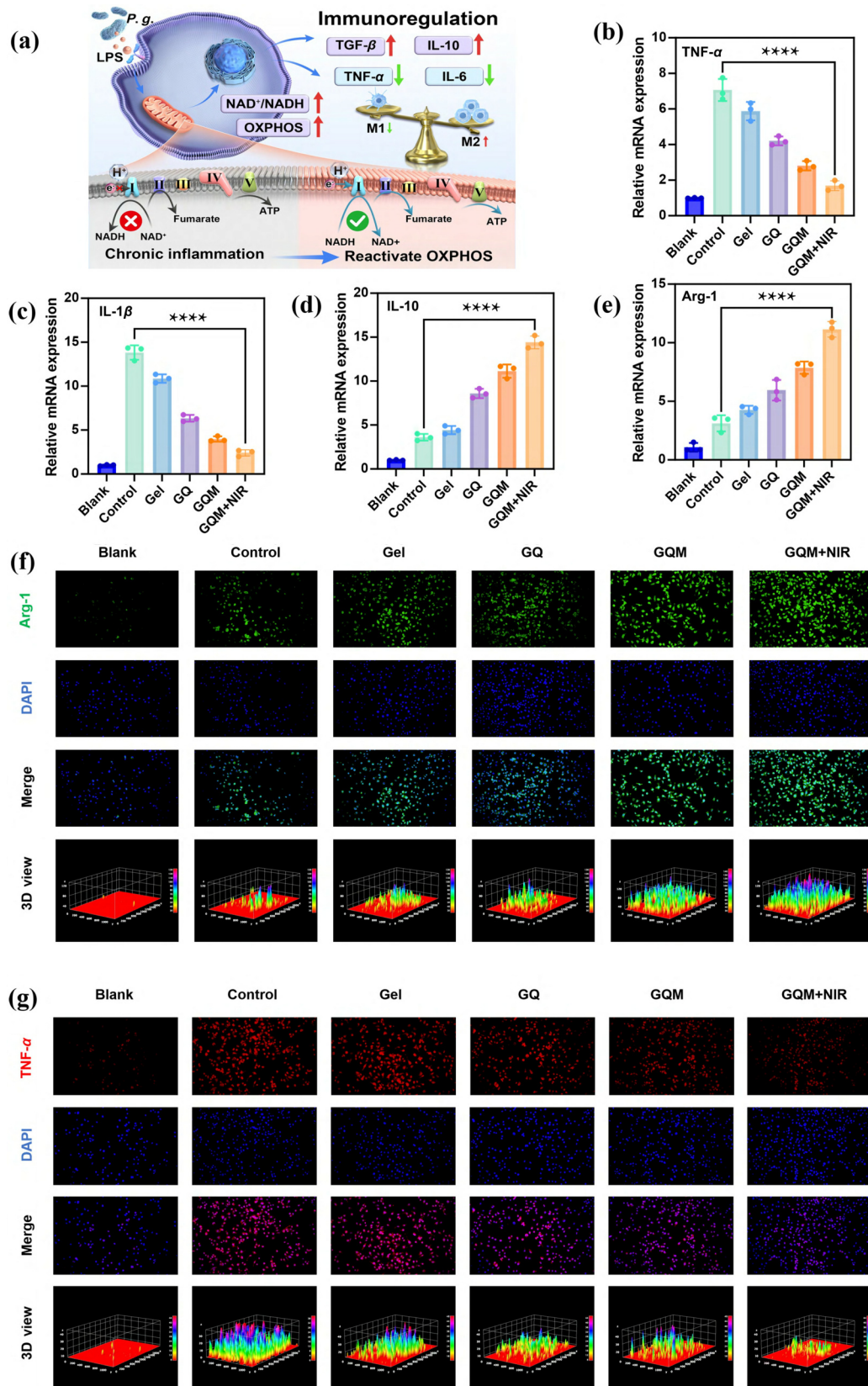


Figure 4 The therapeutic effect of GQM+NIR on inflammation *in vitro*. (a) The illustration of the therapeutic effect of GQM hydrogels on immunoregulation. Expression of inflammation-related genes (b) $\text{TNF-}\alpha$, (c) $\text{IL-1}\beta$, (d) IL-10 , and (e) Arg-1 in macrophages after treatment in different ways. (f) Immunofluorescence staining images of Arg-1 protein expression in macrophages after treatment in different ways. (g) Immunofluorescence staining images of $\text{TNF-}\alpha$ protein expression in macrophages after treatment in different ways. Data were expressed as mean $\pm$ standard deviation (SD) ($n = 3$ per group). Statistical significance was performed by one-way ANOVA with Tukey post hoc test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, ns, not significant.

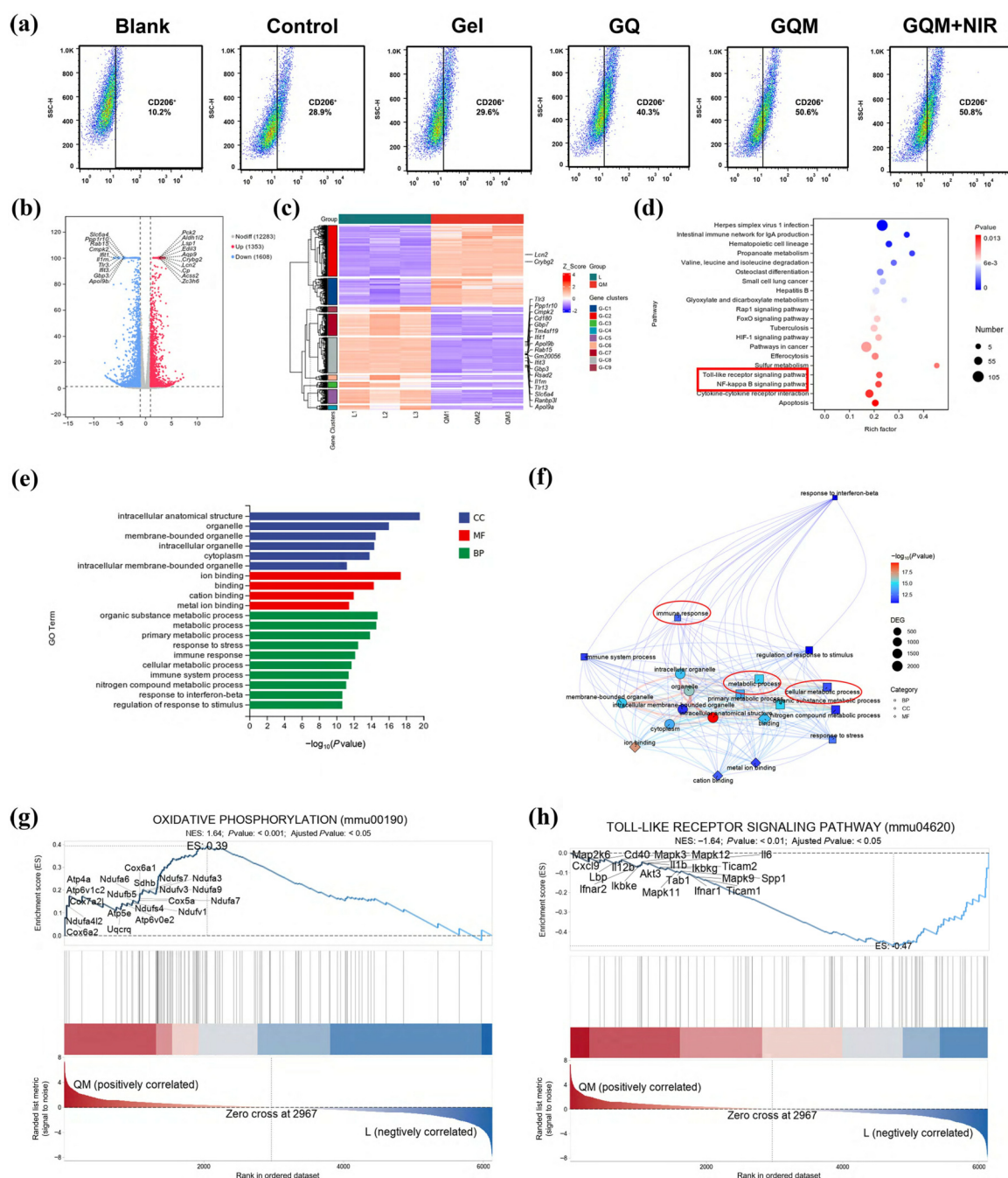


Figure 5 Effect and mechanism of GQM+NIR on macrophage metabolism. (a) The proportion of M2 macrophages after different treatments. (b) Volcano plot of differentially expressed genes. (c) Heat map of differentially expressed genes. (d) KEGG enrichment analysis results of differentially expressed genes. (e) GO enrichment analysis results of differentially expressed genes. (f) Inter-relationships between differentially expressed pathways. (g) GSEA results of macrophage oxidative phosphorylation pathway. (h) GSEA results of macrophage TOLL-like receptor pathway.

Targeting OXPHOS as a key metabolic checkpoint represents a promising therapeutic strategy for periodontitis [48]. Our transcriptomic findings strongly support this concept: gene set enrichment analysis (GSEA) revealed that GQM+NIR treatment significantly upregulates OXPHOS-related pathways while concurrently suppressing pro-inflammatory signaling cascades (Figs. 5(g) and 5(h) and Figs. S13(c)–S13(g) in the ESM).

Based on a more detailed analysis of the OXPHOS pathway, we found that GQM+NIR significantly enhanced mitochondrial respiratory chain activity (Figs. S13(d)–S13(f) in the ESM). This is attributed to the interfacial electron transfer between MTA-Mg and

the mitochondrial inner membrane respiratory chain complexes, particularly complexes I and III. This exogenous material-mediated "extra" electron injection effectively compensates for the relative insufficiency of endogenous electron donors, driving more efficient operation of transmembrane proton pumps and thereby establishing a stronger proton motive force. Ultimately, this photothermal–electron synergistic mechanism significantly accelerates the overall flux of the electron transport chain and enhances global OXPHOS levels. In summary, the photothermal effect activates electron transfer between the MTA-Mg in GQM and macrophage mitochondria, leading to the upregulation of

OXPHOS in macrophages under inflammatory stress and ultimately enabling phenotypic reprogramming.

3.5 *In vivo* evaluation of the therapeutic effect of GQM hydrogel

Blood compatibility is an important safety factor for biomaterials. We evaluated the hemocompatibility of the GQM hydrogels by measuring the hemolysis ratio through direct contact. All hydrogel groups looked pale gray, while the Triton X-100 control group was bright red, which exhibited significant hemoglobin release. The good hemocompatibility of GQM hydrogels with 0.6 mg/mL MTA-Mg groups was quantitatively verified with the hemolysis ratio remaining below 1% at this concentration (Fig. S14 in the ESM). *In vivo* biosafety was further evaluated by harvesting major organs from mice with skin defects that were treated with Gel or GQM hydrogels. Hematoxylin and eosin (H&E)-stained sections showed no discernible pathological alterations in the heart, liver, spleen, lung, or kidney (Fig. S15 in the ESM). Taken together, these results support the high biocompatibility of the GQM hydrogels *in vitro* and *in vivo*.

To evaluate the therapeutic efficacy of the GQM hydrogel in inhibiting periodontitis-associated alveolar bone defects, a 0.2-mm steel wire was firmly placed at the bilateral maxillary second molars (Fig. 6(a)), and a bacterial suspension containing *P. gingivalis* was locally injected to induce the periodontitis model. The constructed rat periodontitis model fully recapitulated the three major pathological processes of bacterial invasion, inflammation amplification, and bone resorption, laying a reliable foundation for verifying the *in vivo* therapeutic efficacy of the material. Following model establishment, the Periodontitis group exhibited distinct gingival redness and swelling. Significant alveolar bone loss was observed in the proximal area between the first and second molars. After hydrogel treatment, CFU counts in the different treatment groups showed varying degrees of reduction. Notably, compared to the Periodontitis group, the GQM + NIR group showed a significant decrease in CFU counts, with a reduction of more than 4 log units (Fig. S16 in the ESM). Due to the complex oral microbial environment and the synergistic effects of multiple microbial communities, the reduction in *in vivo* bacterial colonies was sufficient to effectively alleviate the inflammatory state in the rat's oral cavity (Fig. 6(b)). Four weeks post-ligation, micro-CT images demonstrated the impact of different treatment groups on alveolar bone remodeling (Fig. 6(c)).

We used the distance between the alveolar bone crest (ABC) and the cemento-enamel junction (CEJ) of the first and second molars to measure the degree of alveolar bone resorption. The Periodontitis group showed significant bone loss, indicated by a larger distance from the bone crest to the CEJ compared to the Blank group. After 4 weeks, the CEJ-ABC distance recovered from 0.926 mm in the periodontitis group to 0.323 mm in the GQM + NIR group (Fig. 6(d)). This shows that alveolar bone height was preserved and restored, proving that the GQM hydrogel reversed the inflammatory bone resorption caused by periodontitis. The GQM + NIR group had the smallest difference compared to the Blank group, showing the greatest vertical bone repair. Subsequent morphometric evaluation highlighted the superior osteogenic capability of the GQM+NIR group. Quantitative assessment results are shown in Figs. 6(e)–6(g), which indicated that this treatment method showed a significant reduction in trabecular separation (Tb.Sp) (Fig. 6(g)), while bone volume/tissue volume (BV/TV) (Fig. 6(e)) and trabecular thickness (Tb.Th) (Fig. 6(f)) achieved

maximum recovery. This indicates that the treatment group formed a denser and more interconnected trabecular network.

The dynamic crosslinking network of OG and QCS gives the hydrogel excellent injectability and *in situ* adhesion. This allows the material to stay stably in the periodontal pocket and continuously release functional components. Such stability ensures that the material maintains full contact with the diseased tissue during the entire inflammation period. The contact killing ability of QCS breaks down bacterial membranes, reducing the bacterial load in the periodontal pocket in the early stage and weakening the cause of inflammation. This is shown *in vivo* by a significant decrease in the CEJ-ABC distance, proving that the periodontal infection was effectively controlled. Furthermore, adding MTA-Mg significantly improved the anti-inflammatory effect of the material. Finally, the low-temperature photothermal heat from MXene causes the biofilm matrix to loosen reversibly, speeding up bacterial removal and reducing the remaining inflammatory burden.

Chronic periodontitis compromises periodontal soft and hard tissues, including the gingiva, periodontal ligament, and alveolar bone, ultimately resulting in the loss of periodontal attachment [43]. To evaluate the protective efficacy of the GQM hydrogel on periodontal soft and hard tissues, H&E and Masson's trichrome staining were subsequently performed. Histological assessment revealed that the Periodontitis group exhibited extensive gingival epithelial hyperplasia, accompanied by substantial inflammatory cell infiltration beneath the basal layer of the epithelium. As depicted in Fig. 6(h), the number of infiltrating inflammatory cells in the GQM + NIR group was significantly lower than that in all other treatment groups. Compared to the Periodontitis group, the GQM + NIR group showed only a small amount of infiltrating inflammatory cells. The GQM + NIR group kept a complete gingival shape in the area between the first and second molars, with an intact and continuous surface epithelium. Additionally, the fibers around the GQM + NIR group were arranged regularly, which has a positive effect on the future recovery of periodontal tissues. The impact of the treatment on tissue structure was then evaluated by Masson's trichrome staining, which can visualize collagen fibers (Fig. 6(i)). In the Blank group, the gingival architecture exhibited densely arranged blue collagen fibers, which is characteristic of healthy connective tissue. Conversely, the disruption of the collagenous framework and disorganized fiber arrangement were evident in the Periodontitis group. Notably, in the GQM + NIR group, the morphology of the collagen fibers was highly comparable to that of the Blank control group, indicating that the GQM + NIR group effectively reduced collagen degradation caused by the inflammatory storm.

To investigate immunomodulation, we analyzed the expression of inflammatory mediators. In the GQM + NIR group, the levels of pro-inflammatory cytokines, specifically IL-1 β and IL-6, were significantly attenuated (Fig. 6(j) and Fig. S17(a) in the ESM). In parallel with the attenuation of pro-inflammatory responses, the levels of anti-inflammatory cytokines were markedly increased after treatment. Specifically, Arg-1 and IL-10 exhibited significant upregulation, indicating a shift toward a reparative immunological microenvironment (Fig. 6(k) and Fig. S17(b) in the ESM). These findings further substantiate that GQM + NIR treatment significantly reduces inflammatory cell infiltration and restores the structures of the basement membrane and connective tissue, demonstrating excellent therapeutic efficacy in reversing bone resorption in periodontitis.

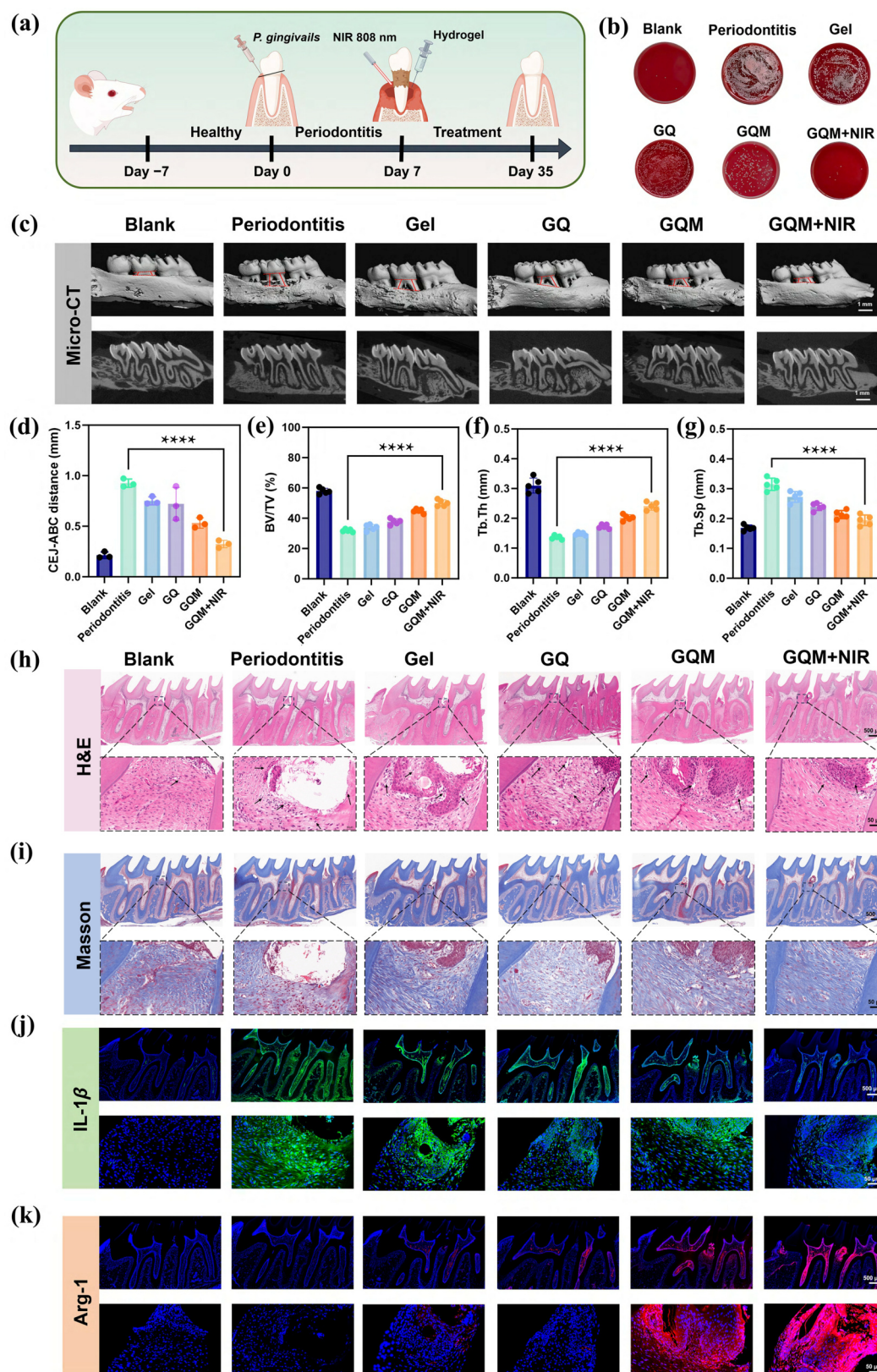


Figure 6 *In vivo* therapeutic effects of GQM hydrogels on periodontitis. (a) Schematic diagram of periodontitis induction by ligation. (b) Photographs of bacterial colonies collected from periodontal pockets. (c) 3D micro-CT reconstructions of alveolar bone in different groups (scale bars: 1.0 mm). (d) Quantitative analysis of the CEJ-ABC distance. Quantitative analysis of (e) BV/TV, (f) Tb.Th, and (g) Tb.Sp. (h) H&E staining images (scale bars: 500 μm; black box: bone and soft tissue area; scale bar: 50 μm). (i) Masson's trichrome staining images (scale bar: 500 μm; black box: bone and soft tissue area; scale bar: 50 μm). (j) Immunofluorescence images of IL-1β (green fluorescence represents IL-1β-positive cells, blue fluorescence represents cell nuclei). (k) Immunofluorescence images of Arg-1 (red fluorescence represents Arg-1-positive cells, blue fluorescence represents cell nuclei). Data were expressed as mean ± SD ($n = 3$ per group). Statistical significance was performed by one-way ANOVA with Tukey post hoc test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

In summary, the GQM composite hydrogel leverages its multiple properties—including stable retention, contact antibacterial activity, photothermal enhancement, and immunomodulation—to achieve systemic infection control, resolution of inflammation, and bone tissue repair *in vivo*. The functional modules are highly synergistic in terms of both timing and mechanism, ultimately transitioning the periodontal lesion from a state of continuous destruction to one of homeostasis reconstruction, thereby demonstrating significant clinical potential.

4 Conclusions

This study developed an injectable hydrogel (GQM) loaded with novel magnesium–tannic acid-modified MXene nanosheets for chronic periodontitis treatment. The GQM hydrogel, consisting of OG, QCS, and MTA-Mg, disrupts bacterial biofilms and reprograms immune cell metabolism to alleviate inflammatory bone resorption in periodontitis. The NIR laser activated MTA-Mg to achieve a mild photothermal effect to inhibit the proliferation of periodontal bacteria such as *P. gingivalis* and *F. nucleatum*, and then disrupt the biofilm. Furthermore, MTA-Mg can increase the levels of OXPHOS by promoting electron transfer and thereby reactivate the mitochondrial respiratory chain, which can reprogram immune cell metabolism in periodontitis. *In vivo* periodontitis models further confirmed that the GQM hydrogel markedly eliminates bacterial biofilms, alleviates periodontal tissue inflammation, and reduces alveolar bone resorption. The GQM hydrogels together with mild photothermal therapy provide a novel therapeutic strategy for chronic periodontitis treatment.

Electronic Supplementary Material: Supplementary material (preparation of oxidized gellan gum, rheological analysis, antibacterial experiments, RT-qPCR, flow cytometry, immunofluorescence staining, RNA sequencing, animal experiments, ROS scavenging ability, detection of mitochondrial membrane potential, detection of intracellular ROS levels, NAD⁺/NADH level detection, detection of MTA-Mg nanosheets entering cells, analysis methods, and Figs. S1–S17) is available in the online version of this article at <https://doi.org/10.26599/NR.2026.94908819>.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and the ESM. Additional data related to this paper may be requested from the corresponding author upon request.

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Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

X. T. Y. and J. J. Z. contributed equally to this work. X. T. Y.

conceived and conducted the experiments, performed the analyses, and wrote the manuscript. J. J. Z. conceived and conducted the experiments, performed the analyses, and wrote the manuscript. C. K. W., Y. K. G., and B. P. contributed to the study conception and experiments. Y. M. Z., B. Y., and Q. L. conceived and conducted the experiments, supervised the research and wrote the manuscript.

Informed consent

Not applicable.

Ethics statement

All experimental procedures were conducted in accordance with the relevant ethical guidelines and regulations approved by the Animal Ethics Committee of Changchun Sci-Tech University (Permit Number: CKARI202314).

Use of AI statement

During the preparation of this work, the authors used ChatGPT in order to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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