Dexamethasone-loaded zeolitic imidazolate frameworks nanocomposite hydrogel with antibacterial and anti-inflammatory effects for periodontitis treatment

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ABSTRACT
Periodontitis is a bacterial-induced, chronic inflammatory disease characterized by progressive destruction of tooth-supporting structures. Pathogenic bacteria residing in deep periodontal pockets after traditional manual debridement can still lead to local inflammatory microenvironment, which remains a challenging problem and an urgent need for better therapeutic strategies. Here, we integrated the advantages of metal-organic frameworks (MOFs) and hydrogels to prepare an injectable nanocomposite hydrogel by incorporating dexamethasone-loaded zeolitic imidazolate frameworks-8 (DZIF) nanoparticles into the photocrosslinking matrix of methacrylic polyphosphoester (PPEMA) and methacrylic gelatin (GelMA). The injectable hydrogel could be easily injected into deep periodontal pockets, achieving high local concentrations without leading to antibiotic resistance. The nanocomposite hydrogel had high antibacterial activity and constructs with stable microenvironments maintain cell viability, proliferation, spreading, as well as osteogenesis, and down-regulated inflammatory genes expression in vitro. When evaluated on an experimental periodontitis rat model, micro-computed tomography and histological analyses showed that the nanocomposite hydrogel effectively reduced periodontal inflammation and attenuated inflammation-induced bone loss in a rat model of periodontitis. These findings suggest that the nanocomposite hydrogel might be a promising therapeutic candidate for treating periodontal disease.

1. Introduction
Periodontitis is a chronic inflammatory disease of polymicrobial etiology characterized by progressive destruction of tooth-supporting structures including gingiva, attached periodontal ligament, and alveolar bone [1]. It ranks top among causes of tooth loss worldwide [2]. Its overall prevalence is 45%–50%, and 11.2% cases are of the most severe periodontitis form, with significant economic and medical consequences [3]. Previous studies on pathological mechanism suggested that changes in the plaque microorganisms could disrupt the homeostasis between subgingival bacteria and the host resulting in periodontal tissue damage [4]. After attack by pathogenic bacteria, appropriate immune cells traffic into the inflamed periodontal tissue to eliminate microorganisms. However, continuous and excessive influx of immune cells aggravate the inflammation [5]. Accumulating evidence has demonstrated that chronic inflammation lead to the decreased osteogenic differentiation and inhibit

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bone formation [6,7]. Therefore, in addition to solve the bacterial hazard, inhibition of the uncontrolled inflammation and immune responses is critical for treating periodontitis.

Although nonsurgical periodontal treatment-cleaning and scaling, combined with proper oral hygiene-toothbrush and dental floss, is current available therapies for periodontitis [8], complete eradication of pathogenic bacteria from deep periodontal pockets is difficult under manual debridement. Pathogenic bacteria residing in the deep periodontal pockets after traditional manual debridement still lead to local inflammatory microenvironment, which remains a challenging problem. Therefore, more effective strategies to treat severe periodontitis are necessary. The local application of antibacterial drugs can provide some additional benefit compared with debridement alone. However, it is a challenge to control plaque microorganism, due to its complex structure and numerous mechanisms of antibiotic resistance [9,10]. Therefore, the search for novel antibacterial agents continues. Currently, there are great hopes for nanotechnology as an innovative method for obtaining new structures of nanometric size and different properties such as inflammatory treatment [11] and antibacterial (anti-biofilm) therapy [12,13].

Porous metal-organic frameworks (MOFs) have been investigated as promising therapeutic nanoparticles for antibacterial applications, since they can act as a reservoir of metal ions and provide gradual release to exert bactericidal activities. Previous studies demonstrated the zeolitic imidazolate frameworks-8 (ZIF), a type of Zn-based MOF, exhibits sustained antibacterial activity [14–16] and presented acid-responsive drug release profile [17,18]. However, this nanomaterial lacks anti-inflammatory properties, which is important in periodontitis treatments. Recent researches have indicated that polydopamine-mediated liposomes containing dexamethasone (DEX) and minocycline as implant surface coating displayed dual functions of anti-inflammatory and antibacterial [19]. A titanium surface coating containing dexamethasone-loaded ZIF nanoparticles (DZIF) can promote cell proliferation and osteogenic differentiation [20,21]. However, there has been no report on the effect of DZIF on the antibacterial and anti-inflammation effects in periodontitis treatments.

Furthermore, it become a welcome strategy that nanoparticles were delivered effectively into periodontal pockets to perform their functions in periodontal special microenvironments. Previous studies indicated that acid microenvironment existed in plaque microorganism, which will stimulate the acid response of ZIF nanoparticles to benefit the antibacterial and destruction of biofilm [22,23]. Therefore, local responsive delivery systems based on unique periodontitis microenvironments have exhibited potential to activate drug release, improve targeting and reduce side effects in periodontitis.

Based on the above considerations, a novel DZIF-doped photocrosslinkable hydrogel was designed to fulfill the combined antibacterial and anti-inflammatory effects for periodontitis treatment. The preparation and application of current hydrogel are illustrated in Scheme 1. This study aims to determine (i) whether the nanocomposite hydrogel loaded with DZIF exhibits excellent inhibitory properties against oral microbial flora and good biocompatibility with live cells and (ii) whether this novel hydrogel would effectively alleviate periodontal inflammation and protect from inflammation-induced bone loss in vitro and in vivo.

Scheme 1. (a) Schematic illustration showing the synthesis processes for DZIF nanoparticles. (b) Schematic showing nanocomposite hydrogel preparation by photocrosslinking methacrylic polyphosphoester (PPEMA) (c) and methacrylic gelatin (GelMA) (d). (e) Schematic showing antibacterial and anti-inflammation application via injection into deep periodontal pockets.
2. Materials and methods

2.1. Materials

Geltain (Gel), methacrylic chloride (MA), 2-hydroxy-4′-(2-hydroxyethyl)-2-methylpropionophenone (Irgacure 2959), zinc nitrate was purchased from Sigma Chemical Co. (MO, USA). 2-Methylimidazolide (2-Melm) and dexamethasone were purchased from Macklin Biochemical Co. (Shanghai, China). Lipopolysaccharides (LPS) was provided from Solarbio Biotechnology Co. (Beijing, China). Dulbecco’s Modified Eagle Medium (DMEM) and fetal bovine serum (FBS) was commercially obtained from HyClone (UT, USA). Live/Dead bacterial viability kit was brought from BestBio Biotechnology Co. (Shanghai, China). Other chemicals were obtained from Aladdin Industrial Co. Ltd. (Shanghai, China).

2.2. Preparation of nanoparticles and nanocomposite hydrogel

Preparation of nanoparticles: DEX (15 mg) was dissolved in the mixture solution (3 mL) comprising a ratio of methanol and water 2:1, zinc nitrate hexahydrate (0.2 g) and 2-methylimidazolide (2 g) were dissolved separately into 1 mL and 10 mL deionized water. The DEX solution and zinc solution were mixed and stirred for 5 min (pH 8, adjusted by NaOH), then the 2-methylimidazolide solution was added to the above solution under vigorous stirring for 30 min. The resultant solution was separated by centrifugation at 9500 rpm for 15 min and the white precipitates were washed with methanol for three times and dried at 60 °C in air overnight. ZIF-8 nanoparticles were also prepared and used as control.

Preparation of GelMA and PPEMA: Methacrylic gelatin (GelMA) were synthesized according to previous described method [24]. Briefly, gelatin 2 g was dissolved in 20 mL Dulbecco’s phosphate-buffered saline (DPBS) by stirring at 60 °C using a magnetic stirrer. Methacrylic anhydride (MA) 1.6 mL was added dropwise to the gelatin solution under vigorous stirring for 3 h at 50 °C. Then, warm DPBS 100 mL was added to stop the reaction. The resulting solution was dialyzed by using a 12–14 kDa cut-off dialysis membrane at 40–50 °C in deionized water. The deionized water was refreshed twice a day for one week. Then, the solution was lyophilized for 1 week to obtain white porous foam.

Methacrylic Polyphosphoester (PPEMA) were provided by School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University. In brief, PPEMA were synthesized by ring opening polymerization (ROP) by using 1,5,7-triazacyclononane [4.4.0] dec-5-ene (TBD) as catalyst, 2-ethoxy-2-oxo-1,3,2-dioxaphospholane (EEP) as monomer and diethylene glycol as co-monomer. Precipitates were washed with methanol for three times and dried at 60 °C.

Preparation of nanoparticle and nanocomposite hydrogel

A sample of the nanoparticle suspension solution (1 mL) was placed in a dialysis bag (Mw: 3500) containing 1 mL PBS solution. The dialysis bag was submerged in 18 mL of PBS and placed in an orbital shaker at 100 rpm for in vitro release at 37 °C. 2 mL of the sample was withdrawn at predetermined timepoints and analyzed by UV spectrophotometry at 242 nm, then 2 mL of fresh medium was replenished. The drug release profile of the nanocomposite hydrogel was also analyzed in the same manner.

2.3. Characterization of nanoparticle and nanocomposite hydrogel

2 mg of DEX powder was dissolved in 2 mL of deionized water and diluted to gradient solution. 2 mL of the diluted solution was measured with a UV–visible spectrophotometer (UV2550, SHIMADZU, Japan) at the characteristic peak of 242 nm. A standard curve for DEX was performed by OD values.

A certain amount of DZIF and ZIF particle powder was dissolved in 5 mL of 0.1 M aqueous hydrochloric acid solution, and then 2 mL of the supernatant was taken for UV spectrum analysis. The drug loading amount was calculated using the DEX standard curve.

The prepared DZIF and ZIF samples were further characterized by dynamic light scattering (DLS; Malvern, UK), Fourier transformed infrared spectroscopy (FTIR; Nicolet 5700, USA), X-ray diffraction (XRD; Bruker, Germany), thermogravimetric analysis (TGA; PerkinElmer, USA), transmission electron microscopy (TEM), and scanning electron microscopy (SEM).

The hydrogels were subject to universal testing machine compressive testing under a 1 mm/min moving condition, and then were submerged in PBS solution to swell by absorbing water at 37 °C for 24 h. In addition, the characterization of hydrogel was analyzed by FTIR, TGA, SEM.

2.4. Profile of drug release

Bacterial culture and biofilm formation: Two periodontal pathogens, Streptococcus mutans and Porphyromonas gingivalis (S. mutans and P. gingivalis) obtained from the Laboratory of Oral Microbiota and Systemic Diseases, Shanghai Ninth hospital, were cultured as described previously [25]. The inoculum concentration of S. mutans and P. gingivalis was adjusted to 10⁶ and 10⁷ colony forming units (CFU)/mL for biofilm formation, based on the standard absorbance curve at 600 nm.

Antibacterial tests: S. mutans suspension (50 μL, 10⁶ CFU/mL) was spread on the surface of BHI agar plates using sterile cotton sticks. The pure hydrogel and filter paper without nanoparticles were prepared as control group. The sterilized disc-shaped hydrogel of 10 mm diameter and round filter paper of 6 mm were placed on the nutrient agar plates and incubated at 37 °C for 48 h under anaerobic condition. The diameters of the inhibitory zone surrounding the disks were measured.

P. gingivalis suspension (300 μL, 10⁷ CFU/mL) was added to each well of a 24-well plate containing the hydrogel and 1.2 mL brain heart infusion broth (BHI) containing hemin. The plate was then placed at 37 °C in a shaking bed. At a predetermined time of 1, 2, and 4 days, 100 μL of the bacterial suspension was transferred to a 96-well plate and measured at OD600, and then an equal volume of broth replenish each well. The experiments were performed three times.

Quantification of biofilm disruption: According to the previous protocols [26], biofilm disruption was quantified by the crystal violet method. Aseptic glass coverslips (diameter = 10 mm) were placed into wells of a 24-well plate. Next, 400 μL of bacterial suspension (~10⁹ CFU/mL) was added to each well. The plate was incubated at 37 °C under stationary conditions to let the bacteria form a biofilm on the coverslips. After 24 h, the medium was discarded and coverslips were washed with PBS. Then, ZIF@PGel and DZIF@PGel hydrogel were added to the wells containing coverslips and 1.6 mL of broth. The wells with only bacterial and broth as control group. The plate was incubated under stationary conditions for additional 24 h. Then, coverslips were washed with PBS and dried for 10 min. Next, 300 μL crystal violet solution (1.0% w/v) was added to each coverslip. After 20 min, the coverslips were carefully taken out and placed in a new 48-well plate. PBS was then used to wash the stained biofilms. After washing with PBS and drying for 20 min, ethanol (300 μL, 90%) was each coverslip to ensure complete dissolution of the
crystal violet dye in the biofilm. 100 μL of each solution was transferred to a 96-well plate. The contents (100 μL) of each well were transferred to a 96-well plate, and the absorbance was measured at 570 nm on a microplate reader. The experiment was performed in triplicate.

**Live/Dead bacteria analysis:** For live/dead bacteria analysis, biofilm was formed under stationary conditions for 1 d (S. mutans) or 2 d (P. gingivalis), the 24 wells plate with biofilm was treated with various hydrogels and additional inoculated 24 h. Each well was stained following the instructions of the Live/dead bacterial kit. Biofilms were imaged with fluorescence microscope. All experiments were repeated three times.

**Visualization of Biofilm formation:** The hydrogel and bacterial suspension were added to the wells containing coverslips. Then, the plate was incubated under stationary conditions for additional 24 h. After the coverslips were washed with PBS and dried for 10 min, the treated biofilms were fixed with 2.5% (w/v) glutaraldehyde solution in PBS at 4 °C for 4 h. The coverslips were washed with PBS three times, dehydrated by gradient ethanol, and dried at room temperature. Then, the images were acquired by SEM.

**2.6. Cytocompatibility assay for nanocomposite hydrogel**

**Cell viability assay:** Cell proliferation was assessed by Cell Counting Kit-8 (CCK-8, Dojindo, Japan). We evaluated the viability of human gingival fibroblasts (HGFs) and rat osteoblasts (OBs) treated with ZIF@PGel and DZIF@PGel hydrogel at various concentrations of nanoparticles (0, 10, 20, 30, 40, and 50 μg/mL) in 48-well plates. The cell culture protocol has been described in our previous studies [25,27] and all experiments were carried out within the third passage of cell culture. The plates were incubated for 2 days. At the prescribed time points, 20 μL of CCK-8 working solution was added to each well and incubated at 37 °C for 1 h. The number of proliferating cells was measured by absorbance measured at 450 nm using a microplate reader.

**Live/dead staining:** The live/dead cell analysis was evaluated using a Calcein-AM/Propidium iodide (PI) Double Stain kit (Yeason, Shanghai, China). ZIF@PGel and DZIF@PGel hydrogel with nanoparticles at concentration of 30 μg/mL (the concentration was chosen based on the appropriate balance of cell viability) were added to each well in a 48-well plate. At the prescribed time points (1, 3 days), after removing the medium, the wells were washed once with PBS and then incubated with 200 μL working solution at 37 °C for 30 min. Then the cells were observed by a fluorescence microscope.

**Immunofluorescence staining:** For immunofluorescence staining, fibroblast markers such as vimentin and type I collagen, and osteoblast marker, osterix, were detected using the following primary antibodies: anti-Vimentin (1:500 dilution, Abcam, Cambridge, UK) and anti-Collagen I (1:200 dilution, Abcam, Cambridge, UK) and anti-Osterix (1:100 dilution, Abcam, Cambridge, UK). The cells were then incubated with species-matched secondary antibodies (Abcam, Cambridge, UK). Cell cytoskeleton was stained in green with FITC-Phalloidin (Enzo Life Science, Exeter, UK), and cell nuclei were counterstained in blue with DAPI (Invitrogen, Carlsbad, CA, USA). Representative images were taken with a confocal laser scanning microscope (CLSM) (Leica, Wetzlar, Germany).

**2.7. Transmission electron microscopy (TEM)**

To observe the ultrastructure of the periodontal tissue with or without inflammatory status, periodontal ligament tissues were carefully collected from extracted tooth samples from healthy individuals and periodontitis patients and observed under an electron microscope. The protocol was reviewed and approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (KY2021-338) and all participants provided written informed consent prior to any study procedures. Following fixation with 2.5% glutaraldehyde for 2 days, the samples were postfixed in 1% osmium tetroxide and dehydrated using a gradient series of ethyl alcohol. Subsequently, samples were embedded in Embed 812 resin (EMS, TED PELLA, USA) for 2 days and propylene oxide solutions. The blocks were sectioned transversely at 70–90 nm using a diamond knife (EM UC7; Leica, Wetzlar, Germany) for lead citrate staining and photographed with a transmission electron microscope (H-7650; Hitachi, Tokyo, Japan).

2.8. In vitro anti-inflammatory effects of nanocomposite hydrogel

HGFs and rat bone mesenchymal stem cells (BMSCs) were used for the in vitro study of the inflammatory response. BMSCs were flushed from femurs and tibiae of 1-month-old SD female rats. The BMSCs culture protocol and surface marker identification has been described in our previous study [27]. Briefly, HGFs and BMSCs were seeded into a 6-well plate at a density of 10^6 cells per well, respectively, and cultured in the presence of ZIF@PGel and DZIF@PGel hydrogel, LPS (1 μg/mL), or placebo (PBS). After 24 h of culture, cells were collected, total RNAs were extracted by TRIZOL reagent (Invitrogen, Carlsbad, CA, USA). The pro-inflammatory cytokines (IL-17a, IL-6 and TNF-a) and osteogenic marker (Runx2) mRNAs were quantified by qRT-PCR using PrimeScript™ RT Master Mix (No. RR036A, Takara) and SYBR® Premix Ex Taq™ II (No. RR420A, Takara) with ABI 7500 Fluorescent Quantitative PCR system (Applied Biosystems Life Technologies, USA) were used for the qRT-PCR analysis. The primer sequences were listed in Supplemental Table 1.

2.9. In vivo assessment of nanocomposite hydrogel in a rat model of experimental periodontitis

This experiment was approved by the Ethics Committee for Animal Care and Use of the Research Center for experimental medicine of Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, and the Institutional Animal Care and Use Committee of Charles River Laboratories (P2000099). Thirty female Sprague–Dawley rats (200–250 g) were randomly divided into three groups (n = 10 per group): control group (sham-operated), periodontitis group and treatment group (DZIF loaded hydrogel). The rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (5 mg/100 g body weight). To induce ligature-induced periodontitis, a ligature wire (0.2 mm diameter) was tied around the maxillary second molar bilaterally. The sham surgical procedure was the same but without ligature placement, as previously described [25]. The ligatures remained in place in the periodontitis group during the entire process. After 4 weeks, ligature wires in treatment group were removed, and the hydrogel injected into the periodontal pockets were polymerized under UV light after scaling and root planning (SRP) to simulate periodontal treatment. Meanwhile, the fluorescent labeling was used to evaluate new-bone formation, as we previously reported [27]. Alizarin Red S (30 mg/kg, Sigma-Aldrich, USA) was administered intraperitoneally, followed by calcein (20 mg/kg, Sigma-Aldrich, USA) in the same way 1 week later.

Another 4 weeks, the gingival index (GI) was evaluated and classified according to the scoring criteria of gingival inflammation (0 = healthy, 1 = slight, 2 = moderate, and 3 = severe), and then rats were sacrificed. For bone analysis, the maxillary samples were scanned using a micro-computed tomography (CT) scanner (Scanco Medical AG, Bassersdorf, Switzerland) at a pixel size of 14.8 μm with 55 kV tube voltage and 330 ms exposure time. After 3D reconstruction of CT images, the vertical distance between the alveolar bone crest (ABC) and the cemento–enamel junction (CEJ) in maxillary second molar was evaluated for bone loss. Three anatomical sites (mesial, middle, and distal) were recorded with the average value calculated for buccal and palatal surface. After micro-CT scanning, histomorphometric samples were processed as non-decalcified hard tissue or decalcified sections. For hard-tissue sections, the samples were embedded in methyl methacrylate and cut into 30 μm thickness. Double-labeled surfaces were observed under a confocal laser scanning microscope (LSM 800, Carl Zeiss, Jena, Germany). For paraffin
sections, the samples were decalcified, embedded in paraffin, and sectioned at 5 μm thickness. Histological analysis was performed including staining with hematoxylin-eosin (H&E), Masson’s trichrome (Morphisto, Frankfurt, Germany) and tartrate-resistant acid phosphatase (TRAP) (Sigma Aldrich, St Louis, MO, USA) following the manufacturer’s protocol. The number of osteoclasts was counted using the ImageJ software (v 4.0). To determine changes in the inflammatory infiltration status, the slices were incubated overnight with primary antibodies against matrix metalloproteinase (MMP) 9 (1:50, Proteintech, USA) and TNF-α (1:100, Proteintech, USA) after antigen retrieval. The immunofluorescence signal was visualized using specific fluorescent secondary antibodies (Proteintech) and DAPI nuclear counterstain.

2.10. Statistical analysis

All data are expressed as mean ± standard deviation (SD). Differences between various treatments were evaluated by one-way ANOVA followed by Tukey’s multiple comparison tests at three significance levels (*p < 0.05, **p < 0.01, and ***p < 0.001). Graphs were plotted using GraphPad Prism 6 and Origin software 8.0.

3. Results and discussion

3.1. Characterization of nanoparticle

The dispersions of ZIF and DZIF nanoparticles appeared milky white (Fig. 1a). Representative SEM and TEM images of ZIF and DZIF
nanoparticles (Fig. 1b) showed that ZIF and DZIF nanoparticles had a relatively uniform rhombic dodecahedron morphology. The geometry of DZIF nanoparticles was well maintained compared with that of the original ZIF, and DZIF showed a larger diameter. UV–visible spectroscopy was used to quantify the loading of DEX. As shown in Fig. 1c, the acid-treated ZIF solution did not show an absorption peak, while the acid-treated DZIF solution exhibited a clear absorption peak at a wavelength of 242 nm, suggesting that the DEX molecules were successfully encapsulated in ZIF particles. Calculated from the prepared DEX standard curve $y = 38.557x-0.0166$ ($R^2 = 0.9998$) (Fig. 1d), the DEX drug loading was determined to be 19.2%.

DLS (Fig. 1e) showed that DEX-loaded nanoparticles have a larger particle size and distribution (from 250 ± 80 to 400 ± 175 nm) than ZIF nanoparticles. Both nanoparticles could be dispersed stably in water.

The structural characteristics of ZIF and DZIF were studied by XRD analysis (Fig. 1f). The diffraction peaks at 7.3° and 12.7° at 2θ confirm the successful growth of ZIF particles. The crystal structure of DZIF was not affected by the presence of DEX molecules compared with ZIF.

As shown in Fig. 1g, the peaks of ZIF at 422 cm$^{-1}$ and 1100-1400 cm$^{-1}$ regions were attributed to the Zn–N and C–N stretching vibration peaks, respectively, confirming the successful growth of ZIF-8 particles. Besides, it was found that the main absorption peak of DZIF is a combination of DEX and ZIF with ZIF and DEX drug peaks, while the absorption peaks of DEX crystals were at 1665 cm$^{-1}$ and 890 cm$^{-1}$. Thus, it was demonstrated that the prepared DZIF particles contained DEX molecules.

Previous literature has shown that the hydroxyl and carboxyl groups of drugs can strongly interact with each other by coordination with Zn$^{2+}$ in ZIF [28]. TGA (Fig. 1h) showed that the weight of DEX decreased rapidly from 99.8% (260°C) to 7.9% (460°C) but did not show a further rapid decline with continuous heating. Considering the thermal stability of ZIF below 570°C, the slight weight loss of DZIF at 200°C was attributed to the DEX decomposition, and the larger weight loss was considered as the decomposition of the DEX and ZIF coordination.

3.2. Characterization of nanocomposite hydrogel

The schematic diagram (Fig. 2a) shows how the nanocomposite hydrogel was formed via photocrosslinking the pre-prepared solution. The pictures of PGeI and DZIF@PGeI hydrogels was presented in Fig. 2b and Fig. S1, in addition, the microstructures of hydrogels were observed by SEM. The PGeI hydrogel after lyophilization is heterogeneous and consists of a mixture of dispersed material matrix and voids. The microstructure of the hydrogel after incorporation of nanoparticles was basically the same as that of PGeI, and the pore size of the hydrogel was 200–400 μm. Both PGeI and DZIF@PGeI hydrogels had a 3D porous structure and can be used for tissue engineering.

The compressive stress-strain curve of the hydrogel (Fig. 2c) showed a positive correlation between the Gel and PPE ratio. The compressive modulus ranged from <5 kPa (1:2) to ~40 kPa (2:1). A higher proportion of Gel increased the crosslinking density of the hydrogel, while the hydrogel showed a flexible state as the proportion of PPE increased. Considering the spatial characteristics of periodontum, gelatin with a certain flexibility for irregular and narrow space structures are more suitable for implants to maintain stability under the movement of the oral cavity and periodontal tissue. Therefore, we chose the ratio of 1:1 served as a carrier for the nanoparticles.

The degree of swelling of a hydrogel is related to the number of pores and hydrophilic groups, which ultimately affects the mechanical strength of the material. As shown in Fig. 2d, the swelling degree of the PGeI hydrogel containing PPE component (142.9% ± 13.6) was lower than that of the Gel hydrogel (489.0% ± 9.5) at 2 h. The pores reduction may be attributed to the formation of an interpenetrating network between polyphosphate and gelatin. In addition, when the hydrogel was immersed in the PBS for 2 h, the swelling degree of the hydrogel remained basically unaltered, indicating that the hydration effect of the hydrogel occurs within the first 2 h.

The FTIR analysis of lyophilized hydrogel are shown in Fig. 2e. According to reports in the previous literature [25,29], the characteristic peak at 1654 cm$^{-1}$ can be attributed to the tensile vibration of C=O, and the characteristic peak at 1548 cm$^{-1}$ can be attributed to the tensile vibration of the N–H band. Absorption peaks at 1267 cm$^{-1}$ and 1165 cm$^{-1}$ could be attributed to the antisymmetric and symmetrical bending vibration of P=O, respectively, while the strong absorption peak at 983 cm$^{-1}$ could be attributed to the P–O–C stretching vibration absorption. The characteristic peak at 535 cm$^{-1}$ could be attributed to the vibration of the imidazole ring. These results confirmed the successful preparation of nanocomposite hydrogel.

In order to evaluate the thermal stability of nanocomposite hydrogel, the TGA analysis results are shown in Fig. 2f. The weight loss percentage of DZIF@PGeI gel was the highest (68.8%), while the weight loss percentage of pure PGeI was the lowest (49.3%). Considering the weight loss values, it was clear that the thermal stability of ZIF@PGeI and DZIF@PGeI were not significantly different (60.1% and 68.8%, respectively). Interestingly, the thermal stability of PGeI was slightly higher than that of nanocomposite hydrogel, which may be attributed to the strong network generated by the intermolecular hydrogen bonding and electrostatic interaction between the functional groups of the two gela-

3.3. Drug release profile

By monitoring the intensity of the UV absorption peak of the same amount of DZIF sample at 242 nm and using the concentration of the original ZIF sample as a reference to eliminate interference of MOF itself, the final released DEX concentration was determined using the standard curve of the known free DEX concentration. As shown in Fig. 2g, the drug release from DZIF in the PBS buffer solution mainly occurred on the first day, and the cumulative release reached 80% at pH 5.8 in comparison with 60% at pH 7.4. It is worth noting that the release rate become slower after 1 day and reach a steady state after about 2 days, indicating that the DEX release rate depends on the dissolution of the particles. Furthermore, DZIF nanoparticles exhibited initial acid-responsive release. ZIF nanoparticles can rapidly decompose when immersed in PBS, and the decomposition of the crystalline network leads to the formation of zinc phosphate insoluble particles [30]. Moreover, ZIF has a certain degree of stability in biologically relevant solutions maintaining its crystal structure at pH 7.4 and degrading at pH 5.0 which is suitable as potential carrier for pH-triggered drug release [31].

The initial release of DEX from the nanocomposite hydrogel is crucial for controlling periodontal inflammation. In the investigation of drug release from DZIF nanoparticle, the DEX release profile of DZIF@PGeI hydrogel was further evaluated. To explore the influence of the polyphosphate component on the drug release in the nanocomposite hydrogel, a single component GelMA mixed with DZIF nanoparticles was used as control (Gel group). As shown in Fig. 2h, the release curve of the hydrogel in PBS with different pH values showed sustained release in all groups. It could be found that less amount of DEX from hydrogel was released from PGeI group compared to Gel group in the same pH conditions, which might be attribute to the better packed and connected network in PGeI hydrogel.

3.4. Antibacterial properties

Bacterial colonization is regarded as the initiating factor of periodontitis, this microbial community could also mediate inflammation pathological (Fig. 3a). S. mutans was widely recognized as one of the key microorganism strains of dental plaque, and plaque accumulation is a major factor in periodontitis and dental implant failure [32,33]. P. gingivalis is an important oral pathogen associated with severe
periodontitis in adults, and it exerts growth-enhancing effects on the oral microbiota, leading to inflammatory periodontal bone loss [34,35]. Assay of the antibacterial activities of ZIF and DZIF nanoparticles against S. mutans (Fig. 3b) showed that the zones of inhibition of ZIF and DZIF were 2.7 ± 0.3 mm and 2.1 ± 0.2 mm, respectively, after 2 days of incubation, showing significant differences compared with the control group. The antibacterial activity of ZIF was significant than that of DZIF due to the antibacterial action mainly produced by zinc ions, which may be attributed to the relatively reduced release of zinc ions from DEX-loaded DZIF nanoparticles (Fig. S2).

MOFs are considered to exhibit an antibacterial effect due to metal cations released from the MOFs by hydrolysis in the solution state [36]. ZIF is a Zn-based MOF, consisting of coordination of zinc ion and 2-methylimidazole [37]. Zinc is an essential trace element in the human body with superior antibacterial effects [38]. The antibacterial effects of zinc nanoparticles can be attributed to the generation of reactive oxygen species on the nanoparticle surface and the electrostatic attractive forces accumulating on the bacterial cell membrane [39,40].

Further research on antibacterial properties of nanocomposite hydrogel are shown in Fig. 3c. The zones of inhibition in two nanocomposite hydrogels groups were 2.1 ± 0.2 mm (ZIF@PGel) and 1.8 ± 0.2 mm, respectively. Hydrogels loaded with nanoparticles exhibited better antibacterial activity than single PGel hydrogel. S. mutans, an aciduric gram-positive bacterium [41], may have stimulated the acid-olysis of nanoparticles, which leads to antibacterial property. In addition, P. gingivalis (a gram-negative anaerobe implicated in periodontitis) suspension were cultured for antibacterial counting experiment with nanocomposite hydrogel. Fig. 3f shows that absorbance value of hydrogel group was lower than that of control group within 4 days (p < 0.05). The antibacterial effects in the two groups were the most significant on day 2.
Therefore, two groups of hydrogels had a certain inhibitory effect on the growth of *P. gingivalis*, which may be related to the swelling properties of the hydrogel and the dissociation characteristics of the nanoparticles. The formation and destruction of bacterial biofilm are crucial for the pathogenesis of periodontal disease [42,43]. Biofilm destruction was determined by crystal violet staining, and the amount of residual bacteria was assessed by measuring the absorbance at 570 nm. Absorbance values of bacterial biofilm were significantly different between the two groups (*p* < 0.01, Fig. 3d and f). The results of CFU counts (Fig. S3) also indicated the biofilm-disrupting effect of nanocomposite hydrogel after the formation of bacterial biofilm. Fig. 3h shows representative live/dead staining of biofilm (1 d for *S. mutans*, 2 d for *P. gingivalis*), live bacteria were stained green, and dead bacteria were stained red. For both species, the control groups were nearly fully covered by live bacteria. In contrast, the two hydrogel groups had mainly red staining with compromised bacteria. Meanwhile, the effect of nanocomposite hydrogel against the bacterial biofilm formation was investigated through SEM scanning. In 3.5. Biological analysis in vitro

Recent studies showed that the toxicity of ZIF was closely related to the higher concentration of zinc ion [44], as ZIF nanoparticles gradually degraded into Zn$^{2+}$ and methylimidazole in the cell culture medium and in vivo environment. Moreover, the cytotoxicity of MOF nanoparticles may be related to their constitutive organic linker [45]. In this study, the viability of HGFs and OBs at different concentrations of nanoparticle hydrogel were investigated using the CCK-8 assay. As shown in Fig. 4a,
cell activity decreases gradually with an increase in the concentration of nanoparticles. The toxicity of the two hydrogels was evident when the ZIF concentration in ZIF@PGel was higher than 30 μg/mL and the DZIF concentration in DZIF@PGel was higher than 40 μg/mL. In contrast, the cell viability was determined to be greater than 90% at a concentration of 30 mg/mL or lower. Therefore, hydrogels loaded with a concentration of 30 μg/mL nanoparticles were selected for use in subsequent experiments.

After HGFs and OBs cells were cultured with hydrogel for 1 and 3 days, respectively. The viability of cells was assayed by live (green)/dead (Red) staining. Fig. 4b and d shows that HGF (b) and OB (d) have abundant living cells at 2 time points in each group, the density of cells in each group increased significantly on the third day compared with that on the first day, and almost no cells died in each group. The cell proliferation of the DZIF group and gel group was similar by counting the number of cells, while the cell proliferation rate of OB in the DZIF group was faster compared with gel group (Fig. S4). The results demonstrated the nanocomposite hydrogel had good compatibility with the two different types of cells. Furthermore, vimentin and collagen I, as fibroblast markers, were investigated by CLSM after 2 days incubation (Fig. 4c), meanwhile, expression of osterix in OBs were shown in Fig. 4e. The proteins expression in HGFs and OBs of all three groups exhibits a similar tendency on day 2. There was no significant effect on cellular function.

Cell adhesion performance on the surface of the hydrogel is a manifestation of biocompatibility, and it also affects cell proliferation and function. GelMA or PPE for cell culture shows good biocompatibility and cell adhesion ability. The morphological analysis of cells grown on the surface of all three groups of hydrogels for 1 day, by observing under an inverted fluorescence microscope revealed green cytoskeletons stretched on the surface of all three groups of hydrogels with clearly visible blue nuclei (Fig. S5). In contrast, the cell adhesion morphology of DZIF group was similar to that of single PGel hydrogel. Therefore, hydrogels either single
or doped with nanoparticles exhibit good biocompatibility.

3.6. Anti-inflammatory properties

It has been demonstrated that the development of periodontitis is modulated by biofilm colonizers on teeth, eliciting an inflammatory host reaction [5]. As shown in Fig. 4f, biologically active substances within bacterial plaques induce a local inflammatory response in the gingival soft tissues and periodontium, resulting in the recruitment of inflammatory cells produces a host of cytokines [46]. The imbalance expression of inflammatory mediators can greatly increase in host immune activity, resulting in the destruction of the supporting tissue and alveolar bone [47,48]. However, the ultrastructure evidence of periodontal tissue under inflammatory microenvironment is limited. TEM images (Fig. 4g) show that the normal periodontal membrane contains many non-activated fibroblasts in collagen fibers, whereas abundant fibroblasts, lymphocytes, plasma cells, and scattered mast cells are present in the collagen fibers of inflamed periodontal ligament. Therefore, the ability to regulate inflammation is a desirable property of biomaterials used in the treatment of periodontitis.

In the present study, nanocomposite biomaterial with controlled release of anti-inflammatory and immunomodulatory drugs such as DEX for the host response modulation might an effective strategy. ZIF nanoparticles loaded with DEX had several merits: (1) DEX, as an effective steroidal anti-inflammatory and immunosuppressive agent, is widely used in the design of many biomaterials to reduce immune response [49,

Fig. 5. The nanocomposite hydrogels effectively attenuated inflammation-induced bone loss in vivo. (a) Schematic diagram and photographs showing treatment and harvest timepoints in an experimental periodontitis rat model; (b, c) Representative three-dimensional (3D) reconstructions and (d) 2D slices of maxillae in all groups using micro-CT. (e) Sequential fluorescence labeling of bone formation in non-decalcified bone sections (red, Alizarin Red S label; green, calcein label); (f) Statistical analysis of gingival index (GI) evaluated according to the scoring criteria; (g, h) The vertical distance between alveolar bone crest (ABC) and cemento-enamel junction (CEJ) at three predetermined sites each on buccal and palatal surfaces (n = 5 per group, Error bar represents mean ± SD, *p < 0.05, **p < 0.01, ***p < 0.001.). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
(2) DEX is reported to promote the differentiation of bone marrow-derived stromal cells and mesenchymal stem cells \([51,52]\). Moreover, DEX could promote the proliferation of periodontal membrane stem cells \([53]\). Runx2 is the main transcriptional regulator of osteoblast differentiation \([54]\). Fig. 4h shows schematic illustration of inflammatory environment effect on osteogenesis. DEX-loaded nanoparticles in the DZIF hydrogel group significantly increased the expression of Runx2 in BMSCs compared with the ZIF hydrogel group under the inflammatory environment (Fig. 4j), indicating that DZIF hydrogels can reduce the inflammatory factors production of cells and protect BMSCs from the inflammatory microenvironment.

Previous research confirmed that LPS could activate the NF-κB signal pathway to increase the expression of inflammatory factors such as TNF-α, IL-1β and IL-6 \([26,55]\). Among them, TNF-α, IL-6 and IL-17 are called strong pro-inflammatory molecules, if not properly controlled, they can cause tissue destruction \([56]\). In the present study, HGFs from human primary culture were used to establish a model of LPS-induced inflammation via the NF-κB signaling pathway leading to expression of TNF-α, IL-17α, and IL-6 \([57]\). Fig. 4i–k and Figure 4l shows the relative gene expression of three inflammatory factors at 24 h. LPS-stimulated HGFs exhibited higher TNF-α, IL-17α and IL-6 expression at the indicated time points compared with the blank control group. In contrast, slowly released DEX from the DZIF hydrogel group effectively downregulated the expression of pro-inflammatory mediators in HGFs \((p < 0.05)\). Meanwhile, compared with the LPS control group, the mRNA Levels TNF-α, IL-17α and IL-6 were similar in the ZIF group, which may be attributed to the toxicity of nanoparticles or the minor cell damage caused by the excessive reactive oxygen species generated by Zn\(^2+\). The results implied that DZIF hydrogel effectively inhibited the expression of LPS-induced inflammatory mediators such as TNF-α, IL-17α and IL-6 and DZIF as a functional component in the hydrogel can protect cells by releasing DEX.

### 3.7. In vivo evaluation

A rat model of periodontal inflammation was established by wire ligation and LPS stimulation (Fig. 5a). The model establishment was evaluated by measuring the ABC-CEJ distances at six anatomical sites of two maxillary molars in the reconstructed 3D images, including three points at the buccal and palatal side each. As shown in Fig. 5b-e and 5g-h, the ABC-CEJ distances in the periodontitis model rats were 1550 ± 164.3 and 1333 ± 163.3 μm on the buccal and palatal sides, respectively. Additionally, the GI of the periodontitis group was 2.5 ± 0.5 (Fig. 5f). In terms of the symptoms of bleeding on probing and alveolar bone loss, the rat periodontal inflammation model was successfully established. The GI and ABC-CEJ distances of the periodontitis group were higher than those

![Histological staining of periodontal tissue. (a) Histological H&E-stained sections of maxillae from each group are shown. The vertical line extends from the CEJ to the ABC. (b) Masson’s trichrome-stained sections of maxillae from each group are shown. (c) TRAP staining and immunofluorescence staining of MMP9 and TNF-α from each group; (d) Statistical analysis of ABC-CEJ distance as determined by H&E staining in each group. (e) The number of osteoclasts as determined by TRAP staining in each group. (Error bar represents mean ± SD, *p < 0.05, **p < 0.01, ***p < 0.001).](image-url)
in the control group (P < 0.01). After 4 weeks of treatment, ABC-CEJ distances in the hydrogel group were 783.3 ± 231.7 and 766.7 ± 250.3 µm on the buccal and palatal sides, respectively, which were significantly lower compared to the periodontitis group (P < 0.01). This indicates that the nanocomposite hydrogel can partly repair the bone mass in periodontitis.

H&E and Masson’s trichome staining evaluated the infiltration of inflammatory cells and repair of damaged periodontal tissue in periodontitis between the maxillary and second molars (Fig. 6a and b, 6d). TRAP staining analysis revealed fewer osteoclasts in the periodontal tissues of DZIF hydrogel than in those of untreated periodontitis group (Fig. 6c and e). Meanwhile, Fig. 6c shows that immunofluorescence staining of MMP9 and TNF-α was conducted to further detect the expression of inflammatory cytokines. Since MMP9 is mainly expressed by infiltrating leukocytes and TNF-α are produced by macrophages and lymphocytes, increased cytokines may indicate intense inflammatory activity [58,59]. The DZIF hydrogel exhibits only scattered inflammatory cells in the periodontal tissue compared with the periodontitis group (Fig. 6c).

Some studies have shown inflammatory microenvironment negatively affects the process of bone regeneration. The sustained release of inflammatory cytokines leads to gingival recession and alveolar bone loss [60]. Therefore, timely relief of the inflammatory microenvironment can help alveolar bone regeneration. DEX released from nanocomposite hydrogel can modulate inflammatory response to improve the inflammatory microenvironment. Similarly, it was reported that GelMA and PPE can slightly promote the repair of alveolar bone defects [61,62]. In the current study, more alveolar bone was observed in the hydrogel group than the periodontitis group. Furthermore, inflammatory immune reactions in response to periodontal microorganisms must be curbed by reducing the bacterial load to achieve relief [5]. Previous studies showed the microbial recolonization can occur very fast after SRP, if proper oral hygiene is not maintained. It only takes 3 days to accumulate a complex and organized mature microbial community [63]. In vivo results show that less abundant CFU of the two hydrogel groups than the control group were present on the plates of 48 h incubation (Fig. S6). The continuous release of Zn²⁺ could prevent bacterial colonization and biofilm formation, contributing to relief from inflammatory reaction and achieving periodontal tissue repair. Taken together, the animal experiment provides evidence on the favorable effect of hydrogel on periodontal healing.

4. Conclusion

The present study developed a novel multifunctional nanocomposite hydrogel by doping DZIF (30%) into pGel. TEM, SEM, XRD, and TGA analyses confirmed the good physical and chemical properties of DZIF nanoparticles and nanocomposite hydrogels. The acid environment in vitro can aids drug release and improves drug targeting. The good antibacterial activity and biocompatibility of the hydrogel were verified in vitro. In vitro and in vivo models if inflammation showed that the nano-composite hydrogels effectively reduce the expression of related inflammatory factors and favor the periodontal healing. Therefore, the nanocomposite hydrogels, due to their dual antibacterial and anti-inflammatory effects, are expected to provide a reference for treating complex periodontal diseases.

Author statement

Ning Li: Methodology, Formal analysis, Investigation, Writing - original draft. Liangyan Xie: Methodology, Formal analysis. Yicheng Wu: Formal analysis. YONGJIA LIU: Investigation. YAN WU: Investigation. Jie Yang: Methodology, Validation. YIMING GAO: Conceptualization. XIUYIN ZHANG: Supervision. LITING JIANG: Methodology, Validation, Writing-editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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