molecules

MDPI

Review

GelMA-Based Biomaterial Platforms for Alveolar Bone Regeneration: A Critical Narrative Review of Design Strategies and Translational Perspectives

Jingjun Yang [1], Qiyin Liu [2], Yilin Guo [2], Yuqing Wei [1], Jiali Chen [2], Ying Liu [2,*] and Yan Gao [1,*]

[1] Department of Oral Implantology, Stomatological Hospital, School of Stomatology, Southern Medical University, Guangzhou 510220, China; yangjingjun1019@163.com (J.Y.); 19192878202@163.com (Y.W.)

[2] Department of Endodontics, Stomatological Hospital, School of Stomatology, Southern Medical University, Guangzhou 510220, China; liuqiyin671@163.com (Q.L.); yilinguo83@gmail.com (Y.G.); cherrychanis@163.com (J.C.)

* Correspondence: yingliu0504@126.com (Y.L.); gyly20130709@126.com (Y.G.)

Abstract

Alveolar bone defects resulting from tooth extraction, periodontitis, and other pathological conditions can compromise dental implant placement and long-term treatment outcomes. Conventional approaches, including autogenous and allogeneic bone grafts and barrier membranes, have limitations related to donor-site morbidity, material availability, and defect-specific regenerative requirements. Gelatin methacryloyl (GelMA) hydrogels have been investigated as scaffolds for bone tissue engineering because of their cell-responsive properties, tunable mechanical characteristics, biodegradability, and compatibility with biofabrication techniques. This critical narrative review examines recent developments in GelMA-based biomaterial platforms for alveolar bone repair, focusing on composite design strategies, osteogenesis-related biological mechanisms, and preclinical applications in oral bone defects. A complementary descriptive bibliometric analysis provides context on research activity and thematic trends. Particular attention is given to the anatomical relevance of experimental models and the distinction between cellular responses, bone formation in non-alveolar models, and regeneration demonstrated in periodontal or alveolar defects. We also discuss the limitations that currently restrict clinical translation, including material processing, degradation control, long-term biosafety, and the limited availability of clinical evidence. By evaluating both the reported findings and the remaining uncertainties, this review identifies considerations for the further development and assessment of GelMA-based biomaterials in alveolar bone regeneration.

Keywords: GelMA; composite hydrogels; alveolar bone defects; bone regeneration; biomaterials

Academic Editors: Giuseppe Cirillo and Artur J. M. Valente

Received: 16 September 2026
Revised: 28 October 2026
Accepted: 19 November 2026
Published: 28 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

1.1. Research Background

The alveolar bone, the projecting portion of the maxilla and mandible that houses and supports tooth roots, is highly active in systemic metabolism and bone remodeling [1]. Under physiological conditions, it maintains its morphological and structural stability through a dynamic equilibrium between osteoblasts (mediating bone formation) and osteoclasts (mediating bone resorption) [2–4]. However, tooth loss—predominantly caused by severe periodontitis, dental caries, or trauma—severely disrupts this dynamic

balance [5–7]. Following tooth extraction, the sudden loss of periodontal ligament (PDL)-mediated mechanical stimulation initiates rapid and irreversible three-dimensional ridge resorption [8–10]. Such defects not only severely impair the patient's masticatory and phonetic functions as well as facial aesthetics but also pose a significant challenge in implant dentistry. Adequate bone volume is a prerequisite for achieving primary implant stability and ensuring long-term osseointegration [11]. This underscores an urgent clinical need for therapeutic interventions and exogenous biomaterials to reconstruct the severely resorbed implant site [12–14].

Alveolar bone has anatomical, mechanical, and biological characteristics that distinguish its regenerative environment from that of other skeletal sites. Anatomically, the buccal bone plate of the alveolar ridge is inherently thin (frequently <1 mm) and occasionally presents with natural fenestrations or dehiscences, making the buccal aspect predominantly susceptible to severe resorption following tooth loss. The local mechanical environment depends on defect location, scaffold function and membrane or flap coverage. Implanted constructs may experience compressive and shear deformation, while exposed materials also encounter oral fluids. Mechanical support and retention should therefore be evaluated for the intended application rather than inferred directly from bite-force measurements [15].

Microbial exposure varies with the defect and surgical configuration; infected periodontal sites and exposed biomaterials face different challenges from defects protected by primary wound closure. In pathological conditions such as periodontitis, keystone pathogens (e.g., *Porphyromonas gingivalis*) and their virulence factors trigger sustained inflammatory cascades. This chronic immune-inflammatory microenvironment severely disrupts local homeostasis, leading to the overactivation of osteoclasts and the profound suppression of endogenous osteogenesis [16]. Crucially, from the perspective of tissue regeneration dynamics, a severe temporal mismatch exists between soft and hard tissue healing. The proliferation and apical migration of gingival epithelial cells and fibroblasts occur at a substantially faster rate than the recruitment and differentiation of osteoblasts. This rapid "epithelial downgrowth" allows soft connective tissues to aggressively invade and occupy the bone defect space, competitively impeding true osseous regeneration [17].

Established regenerative options include autogenous grafts, allografts, synthetic bone substitutes, and barrier-assisted procedures [18]. Graft–membrane combinations have also been evaluated in human alveolar ridge preservation trials [19]. Selection should consider donor-site requirements, remodeling, structural support, membrane behavior, and surgical handling [20].

Hydrogels are three-dimensional polymer networks capable of retaining substantial amounts of water, providing a hydrated environment that can resemble certain features of the extracellular matrix [21,22]. Their physicochemical properties and degradation behavior can be adjusted for applications in bone tissue engineering [23,24]. Gelatin methacryloyl (GelMA), a photocrosslinkable gelatin derivative, has received considerable attention because it combines cell-responsive characteristics with tunable mechanical properties and the capacity to incorporate bioactive agents [25–27]. Nevertheless, unmodified GelMA has limitations in mechanical strength, degradation control, and infection resistance, particularly when used in the complex oral environment. Composite formulations have therefore been investigated to improve scaffold stability and introduce additional biological functions [28]. This review examines GelMA-based strategies for alveolar bone repair, with an emphasis on material design, osteogenesis-related mechanisms, experimental evidence, and barriers to clinical translation.

1.2. Review Approach and Complementary Bibliometric Analysis

This article is a critical narrative review complemented by a descriptive bibliometric analysis.

To characterize the research landscape and evolving scientific interests in GelMA-based bone regeneration, a descriptive bibliometric analysis was conducted using the Web of Science Core Collection (WoSCC), covering the Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI). The bibliometric search was performed on 9 March 2026, and the analyzed dataset covered publication years 2011–2025. The search strategy combined GelMA-related terminology with terms associated with alveolar and periodontal bone defects, osteogenesis, bone regeneration, and bone tissue engineering. English-language articles and reviews were retrieved using the database filtering functions. No additional manual screening of titles or abstracts was performed for the bibliometric dataset. The bibliometric data were analyzed using the Bibliometrix R package **(version 5.5.0; R version 4.5.0)** to investigate annual publication trends, international collaboration, citation patterns, keyword co-occurrence, and temporal changes in research topics. Detailed information regarding the search strategy, record management, and analytical procedures is provided in Supplementary Methods S1, with the corresponding findings presented in Table S1 and Figures S1–S5.

The bibliometric analysis and the narrative synthesis were assembled for different purposes. The former describes research activity, whereas biological interpretations in the main review are based on individual studies. Experimental studies discussed in the narrative synthesis were identified through manual searches of PubMed. Publications were read and selected for discussion according to their relevance to the material systems, biological mechanisms, and regenerative applications addressed in this review. Their findings were incorporated into the corresponding thematic sections, with consideration of the experimental models and outcomes reported. The exact DOI-level overlap between the experimental studies discussed in the narrative synthesis and the bibliometric dataset has not been verified.

1.3. Scope of Experimental Evidence and Model-Specific Interpretation

In this review, evidence derived from experimental alveolar bone defects and extraction socket models is distinguished from findings obtained in periodontitis and peri-implantitis models. The former can directly assess bone repair within alveolar structures, whereas the latter primarily investigate disease-associated inflammatory bone loss, local microenvironmental regulation, and, where specifically demonstrated, periodontal or peri-implant bone regeneration. Importantly, prevention of further bone resorption should not be considered equivalent to regeneration of previously lost bone.

Studies involving calvarial defects, non-alveolar defects, or other skeletal sites provide valuable information regarding osteogenic potential, scaffold integration, and bone repair but do not fully reproduce the anatomical architecture, mechanical loading, microbial exposure, or tissue interfaces characteristic of alveolar defects. Subcutaneous implantation used to assess biocompatibility, host responses, or degradation is distinguished from ectopic implantation demonstrating mineralized tissue formation. Neither type directly establishes regeneration within an orthotopic periodontal or alveolar defect. In vitro studies involving mesenchymal stem cells, periodontal ligament stem cells, or osteoblasts provide complementary mechanistic evidence but cannot independently demonstrate functional tissue regeneration in vivo.

Evidence is interpreted according to both the experimental setting and the outcome demonstrated, distinguishing in vitro osteogenic activity, ectopic mineralized tissue formation, non-alveolar bone repair, alveolar bone repair, and periodontal or peri-implant tissue reconstruction. Attenuation of inflammatory bone loss is identified separately

from new tissue formation. Cell proliferation and viability are assessed separately from osteogenic differentiation. Early differentiation readouts, such as alkaline phosphatase (ALP) activity, and later outcomes, such as mineralized matrix deposition in vitro, support cellular osteogenic responses but do not independently demonstrate restoration of functional bone.

Evidence of bone formation is evaluated using microcomputed tomography (micro-CT), including bone volume fraction (BV/TV), bone mineral density (BMD), and trabecular measurements were reported, together with histological identification and histomorphometric quantification of new bone. Vascularization, tissue maturation, and integration with native bone, periodontal tissues, or implant surfaces are considered separately. Periodontal attachment and peri-implant re-osseointegration are evaluated using evidence of cementum–ligament organization and bone–implant contact, respectively.

2. Core Physicochemical and Biological Properties of GelMA Hydrogels

2.1. Molecular Architecture and Synthetic Strategies of GelMA Hydrogels

Gelatin, a product of the partial hydrolysis of collagen, is a natural macromolecular hydrocolloid. Gelatin methacryloyl (GelMA) is a prominent derivative synthesized through the chemical modification of gelatin, wherein the amino groups on its side chains are substituted with methacryloyl groups from methacrylic anhydride (MA) [25]. A primary biological advantage of GelMA lies in its preservation of the arginine-glycine-aspartic acid (RGD) cell adhesion sequences and matrix metalloproteinase (MMP)-degradable motifs inherent in the natural gelatin backbone [26,29]. This characteristic endows GelMA with favorable cell-responsive properties, facilitating cell adhesion and proliferation while allowing enzymatically mediated degradation through cell-secreted MMPs, thereby providing a dynamic microenvironment conducive to tissue remodeling.

The introduction of methacryloyl groups enables GelMA to undergo rapid free-radical polymerization under photoirradiation to form a crosslinked three-dimensional polymer network [30]. By adjusting the degree of substitution (DS, or degree of methacryloylation) and crosslinking conditions, researchers can adjust the stiffness, swelling behavior, and degradation kinetics of the hydrogel [31].

Since van den Bulcke et al. [32] first reported the preparation of GelMA via the reaction of gelatin with MA in 2000, this synthetic approach has remained one of the most widely adopted strategies due to its high reaction efficiency and controllable degree of substitution. In recent years, to further broaden its biomedical applications, researchers have introduced alternative synthesis and modification methods. For instance, Li et al. [33] utilized glycidyl methacrylate (GMA) for the secondary modification of GelMA, resulting in a modified GelMA-based hydrogel (GelMAGMA) with an enhanced storage modulus and improved enzymatic resistance. Furthermore, Abdollahi's team [34] developed a microwave-assisted green synthesis approach that reduced energy consumption and processing time while improving the physicochemical properties of GelMA hydrogels (Figure 1).

Despite these advances, optimization of GelMA synthesis and modification remains a balance between improving material performance and preserving biological functionality. Although enhanced crosslinking strategies can effectively improve mechanical stability and degradation resistance, excessively high crosslinking densities may restrict cell proliferation, reduce nutrient diffusion, and hinder extracellular matrix deposition. Moreover, additional chemical modifications require comprehensive evaluation regarding their long-term biosafety and biological compatibility.

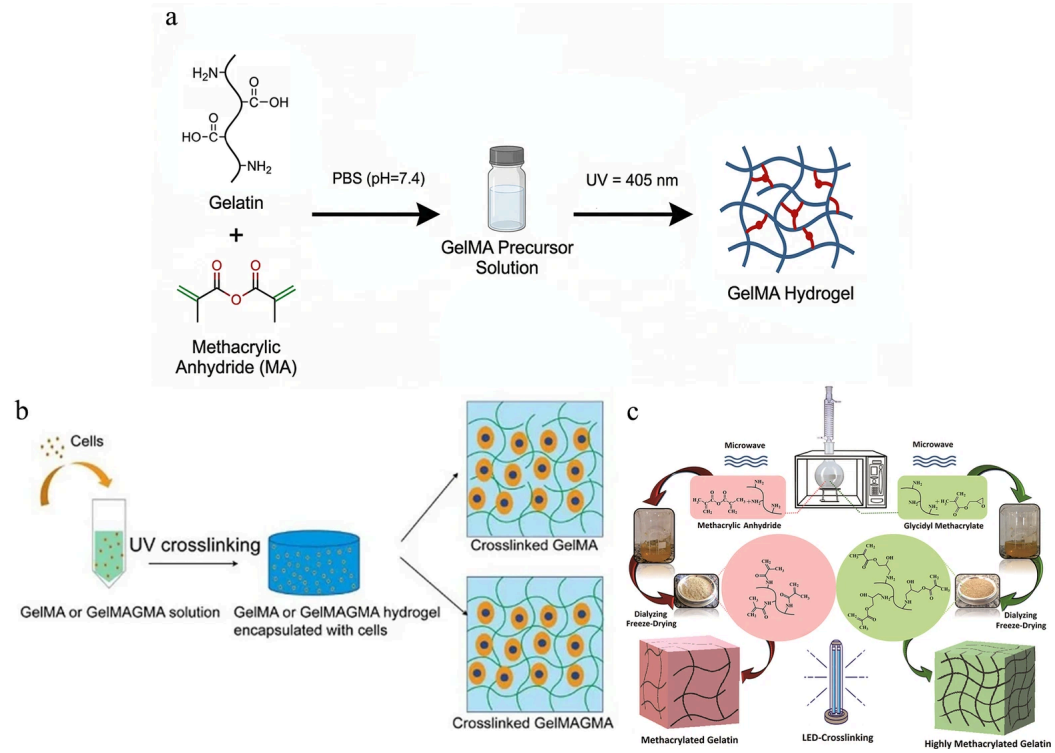

Figure 1. (**a**) Schematic illustration of GelMA hydrogel synthesis. (**b**) Cell encapsulation in GelMA and GelMAGMA networks. Reproduced with permission from Xiaomeng Li et al., Polymers; published by MDPI, 2017 [33]. (**c**) Microwave-assisted functionalization using glycidyl methacrylate or methacrylic anhydride, followed by purification and LED curing. Adapted reprinted with permission from Ref. [34].

2.2. Optimization of Crosslinking Strategies for Enhanced Biological Performance

Although GelMA hydrogels possess excellent biocompatibility, tunable mechanical properties, and favorable cell-responsive characteristics, the crosslinking process represents a critical determinant of their biological performance in tissue regeneration. In the context of alveolar bone repair, particularly in defects associated with tooth extraction, periodontitis, or peri-implant inflammation, implanted biomaterials are required not only to provide structural support but also to establish a favorable microenvironment for cell survival, migration, and osteogenic differentiation. Therefore, optimizing GelMA crosslinking strategies is essential for balancing mechanical stability, degradation behavior, and biological functionality.

Conventional ultraviolet (UV) photocrosslinking may adversely affect cell viability through photoinitiator-derived radical formation and light-associated cellular damage, particularly under prolonged irradiation or at elevated photoinitiator concentrations [35,36]. Visible-light-activated systems have therefore been investigated to reduce these limitations [37]. However, their cytocompatibility remains dependent on the photoinitiator formulation, irradiation conditions, and cellular environment, necessitating optimization for the intended biological application.

For instance, Goto et al. [38] utilized riboflavin as an alternative to the traditional photoinitiator (Irgacure 2959) and employed visible light instead of a UV source for photocrosslinking. This strategy not only endowed the hydrogel with mechanical strength comparable to those crosslinked conventionally but also substantially reduced cytotoxicity, improving osteoblast compatibility under the conditions examined.

Wang et al. [39] used freeze-ultraviolet crosslinking to prepare porous GelMA hydrogels and examined p38 mitogen-activated protein kinase (MAPK) involvement using

SB203580. The inhibitor attenuated the reported osteogenic and angiogenic responses in vitro and in vivo, providing functional pharmacological support for a contribution of p38 signaling under the tested conditions. The animal experiments included mandibular defects and subcutaneous implantation, which provide different types of evidence for bone repair and vascular responses. These findings support p38 involvement in the evaluated systems but do not establish an exclusive mechanism or a causal interaction between angiogenesis and osteogenesis.

2.3. Matrix Mechanosensing and Osteogenic Signal Transduction

The mechanical requirements of a GelMA construct depend on defect containment, scaffold geometry, and its role as a filler, cell carrier, or barrier [40–42]. Matrix stiffness influences stem-cell behavior within this material and geometrical context [43,44].

Wu et al. [45] examined human periodontal ligament stem cells (hPDLSCs) encapsulated in three-dimensional GelMA hydrogels. Lower-stiffness formulations were associated with greater cell spreading, osteogenic marker expression, and Yes-associated protein (YAP) nuclear localization; cell-laden constructs also improved bone formation in rat alveolar defects. These findings associate matrix properties with YAP localization and osteogenic responses. However, nuclear localization alone does not establish that YAP is required for osteogenic differentiation or mediates the in vivo repair effect (Figure 2).

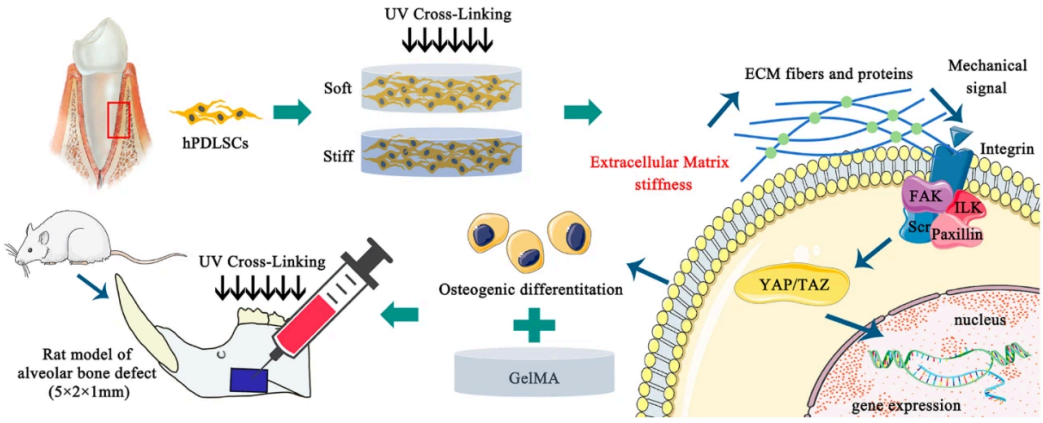

Figure 2. Matrix-stiffness study of hPDLSC-laden GelMA hydrogels. The experimental workflow links formulation-dependent stiffness to cellular osteogenic readouts, YAP localization and repair assessment in rat alveolar defects. The accompanying signaling scheme provides a proposed mechanotransduction context; the study does not establish that the complete integrin–FAK/Src–YAP/TAZ cascade is required for bone repair. Adapted reprinted with permission from Ref. [45].

Fu et al. [46] provided functional evidence in a two-dimensional GelMA substrate model: inhibition of the MAPK kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway with U0126 reduced YAP nuclear localization and osteogenic marker expression. In a separate rat experiment, local verteporfin treatment reduced YAP nuclear localization and alveolar bone mass. These results support a contribution of ERK/YAP-associated mechanotransduction to PDLSC responses and periodontal bone homeostasis. The animal intervention did not test whether YAP mediates the regenerative effects of an implanted GelMA scaffold.

The different stiffness responses in these studies should be interpreted in the context of three-dimensional encapsulation versus two-dimensional surface culture. Neither study establishes a universal stiffness–osteogenesis relationship. In addition, evidence concerning YAP should not be extended to transcriptional coactivator with PDZ-binding

motif (TAZ) without direct assessment of that coactivator.

2.4. From a Pristine Hydrogel to a Multifunctional Composite Pro-Regenerative Platform

Taken together, its adjustable photocrosslinking characteristics and cell-adhesive properties make GelMA a three-dimensional matrix for the adhesion, proliferation and osteogenic differentiation of various stem cells, including bone marrow mesenchymal stem cells (BMSCs) [24,47–49]. Furthermore, it can be readily integrated with bioactive materials (e.g., hydroxyapatite and bioactive glass) to further augment its mechanical properties and osteogenic capacities [30].

3. Development and Distinct Characteristics of GelMA Hydrogel Composites

Polymer-network modification, inorganic additives, and bioactive cargo have been incorporated into GelMA to alter structural stability, release behavior, and cellular responses [50]. The following sections examine these approaches in relation to their formulation characteristics and experimental outcomes (Figure 3).

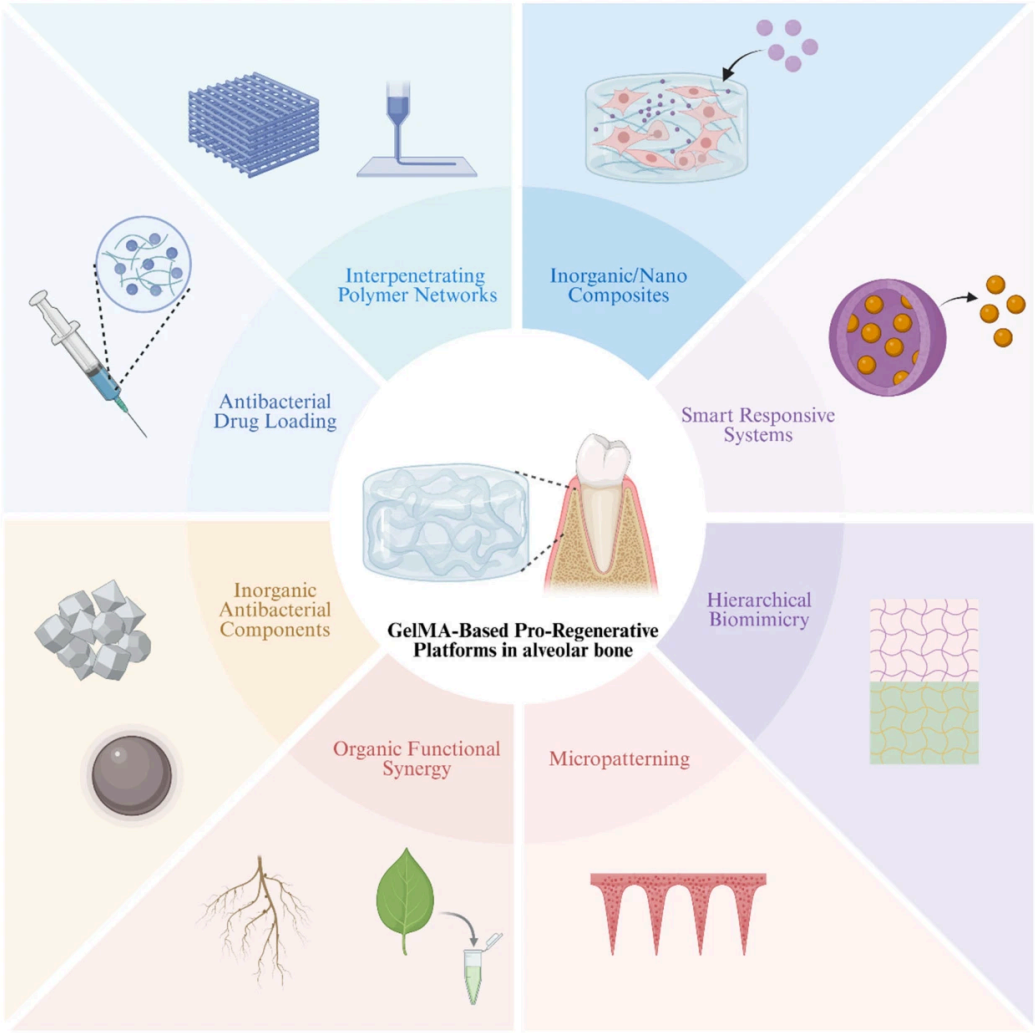

Figure 3. Design routes used in GelMA-based composite platforms, including polymer-network modification, inorganic additives, controlled delivery and spatial fabrication. The categories describe material-design approaches; they do not represent equivalent levels of regenerative evidence. Created in BioRender. Yang, J. (2026) https://www.biorender.com/(accessed on 8 October 2026).

3.1. Interpenetrating Polymer Networks and Mechanical Enhancement

Combining GelMA with additional polymers or fibrous networks allows the architecture and mechanical behavior of the resulting construct to be modified [51–58]. These changes can also alter water uptake, transport, and enzymatic remodelability, linking reinforcement to the matrix environment experienced by encapsulated cells.

For instance, Ma et al. [59] developed bioprinted GelMA/poly(ethylene glycol) dimethacrylate(PEGDA) hydrogels and investigated the effects of polymer composition on scaffold properties and periodontal ligament stem cell (PDLSC) behavior. Increasing the PEGDA fraction raised the compressive modulus from 4.5 ± 2.3 kPa for GelMA alone to 23.5 ± 2.6 kPa at a GelMA/PEGDA volume ratio of 1:4, while reducing swelling and slowing enzymatic degradation. However, PEGDA-rich formulations were less favorable for PDLSC spreading and osteogenic differentiation. The 4:1 formulation, despite having a lower compressive modulus (13.8 ± 1.7 kPa), supported stronger osteogenic responses and was selected for subsequent in vivo evaluation. Implantation of the PDLSC-laden hydrogel enhanced new bone formation in a rat alveolar bone defect model. PEGDA enrichment changed GelMA content, swelling behavior, and enzymatic degradation together with stiffness. The osteogenic responses therefore reflect differences in the complete network formulation, including the relative abundance of cell-interactive GelMA and its remodeling characteristics.

Electrospun fibers have also been incorporated into GelMA-based scaffolds to improve their structural organization and mechanical properties. Electrospun fibers can form porous supporting networks within GelMA-based constructs. A recent study [60] fabricated a GelMA/polycaprolactone (PCL) blended electrospun scaffold loaded with cerium oxide (CeO_2) nanoparticles. The resulting scaffolds exhibited improved physicochemical characteristics and supported cellular responses associated with osteogenic differentiation under in vitro conditions. These findings demonstrate the feasibility of combining fibrous reinforcement with bioactive nanoparticle incorporation for periodontal tissue engineering. Nevertheless, because the study did not establish regenerative efficacy in an orthotopic periodontal or alveolar bone defect model, its findings should be interpreted as preliminary material-development and cellular evidence rather than direct proof of periodontal tissue regeneration (Figure 4).

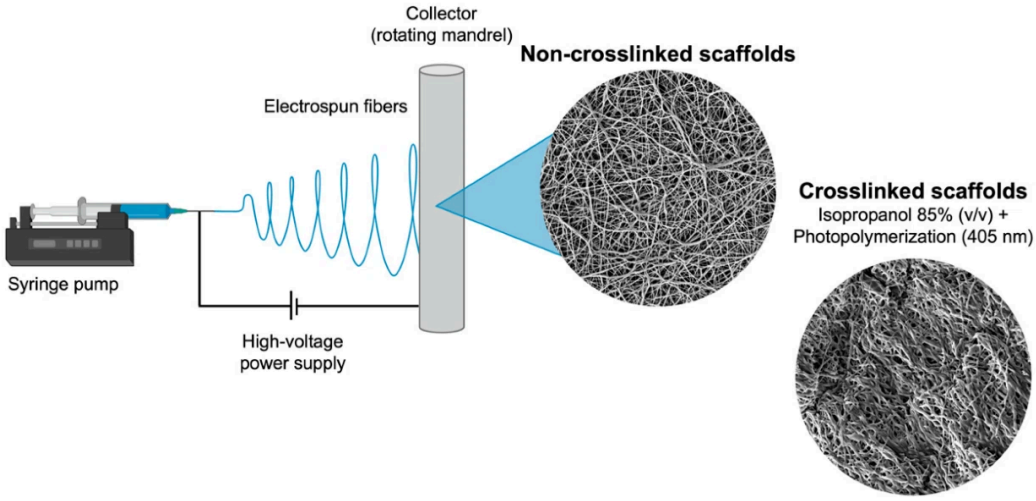

Figure 4. Schematic representation of the electrospinning technique used for the fabrication of the designed scaffolds. Reproduced with permission from Sahar Aminmansour et al., Materials; published by MDPI, 2024 [60].

3.2. Composite Empowerment via Inorganic and Nanoscale Materials

The uniform dispersion of inorganic materials possessing unique physicochemical properties (e.g., hydroxyapatite, bioactive glasses) or nanoscale particles (e.g., metal oxides, metal–organic frameworks [MOFs]) into the GelMA matrix represents an effective approach for elevating the comprehensive performance of scaffolds [61,62]. Inorganic components may improve scaffold stiffness and provide mineral-associated surface cues for cell attachment and differentiation. Depending on their composition and dissolution behavior, these materials can also release calcium, phosphate, or soluble silicate species that influence osteogenesis-related cellular responses.

For instance, Chen et al. [63] fabricated GelMA/nano-hydroxyapatite (nHA) microgel arrays encapsulating human periodontal ligament stem cells (hPDLSCs). The composite microgels promoted cellular proliferation and osteogenic differentiation in vitro. In vivo, enhanced mineralized tissue formation and vascularization were observed following ectopic subcutaneous implantation in nude mice. Although these findings support the osteogenic potential of the composite microgels, the ectopic implantation model does not directly demonstrate periodontal or alveolar bone regeneration.

Similarly, Ai et al. [64] developed a bioactive glass/BMSC-loaded GelMA (BG/BMSCs@GelMA) composite hydrogel and evaluated its bone-regenerative performance in a rat calvarial defect model. The reported findings suggested favorable effects on osteogenesis, angiogenesis, and immune regulation. However, because calvarial defects differ from alveolar bone defects in their anatomical and local physiological characteristics, these findings should be interpreted as supportive evidence for general bone regeneration rather than direct validation of alveolar bone repair.

Building upon the foundation of compositional compounding, structural optimization constitutes another critical direction for enhancing scaffold performance. Mei et al. [65] incorporated mesoporous bioactive glass (MBG) nanoparticles into GelMA and utilized 3D printing technology to fabricate a macroporous scaffold. The composite scaffolds supported the attachment and proliferation of human periodontal ligament cells and enhanced their osteogenic and cementogenic differentiation under in vitro conditions. These findings suggest that combining inorganic bioactive components with controlled scaffold architecture may provide favorable cellular cues for periodontal tissue engineering. However, the study did not directly establish periodontal ligament–cementum–alveolar bone regeneration in an orthotopic defect model, and its regenerative potential therefore requires further in vivo validation.

Dubey et al. [66] combined melt-electrowritten PCL meshes with AMP-containing GelMA to produce fiber-reinforced membranes. Mechanical reinforcement depended on membrane thickness, whereas AMP incorporation did not consistently increase stiffness. The constructs supported osteogenic responses of human mesenchymal stem cells in vitro and bone formation in rat calvarial defects.

The effects of inorganic reinforcement are strongly dependent on filler concentration and scaffold architecture. In the BG/GelMA system studied by Ai et al. [64], increasing BG content improved compressive properties and resistance to enzymatic degradation, whereas the highest BG concentration examined (2.0%) was less favorable for cell viability. Mei et al. [65] reported differences in compressive stress among BG/GelMA formulations containing 0–10% BG, but these differences were not statistically significant. A further example was provided by Dubey et al. [66], who found that the reinforcing effect of PCL meshes depended on membrane thickness and that AMP incorporation did not consistently increase stiffness. These observations suggest that inorganic loading should be optimized in relation to scaffold geometry, cellular compatibility, and the intended biological function rather than mechanical properties alone.

The incorporation of controlled-release systems provides an additional strategy for

enhancing the biological functionality of GelMA-based composites. Zhou et al. [67] developed a microsphere-composite hydrogel consisting of GelMA, methacrylated heparin (HepMA), and nano-hydroxyapatite (nHAP) microspheres loaded with platelet-derived growth factor-BB (PDGF-BB), which were further incorporated into a simvastatin-containing GelMA matrix. The composite system enabled sustained release of the incorporated bioactive agents and enhanced the migration and osteogenic differentiation of rabbit bone marrow-derived mesenchymal stem cells in vitro. These findings support its potential as a bioactive delivery platform for bone tissue engineering. However, its efficacy in alveolar bone repair remains to be established through direct evaluation in anatomically relevant defect models.

However, when confronting complex diseases such as periodontitis—which are characterized by a confluence of infection, inflammation, and tissue destruction—single-function therapeutic systems are inadequate; thus, multifunctional synergistic composite systems have emerged as a prominent research hotspot. Luo et al. [68] developed a GelMA–phenylboronic acid/hydroxyadamantane composite microgel carrying antimicrobial peptide and CeO_2 microspheres. The study reported antibacterial and reactive oxygen species (ROS)-scavenging activity in vitro and improved bone-related measures in infected alveolar defects after four weeks. These observations support formulation-specific preclinical assessment, while restoration of the periodontal attachment apparatus and the necessity of the implicated signaling pathways remain unestablished.

Li et al. [69] evaluated MXene/Ag-HA/GelMA hydrogels using MC3T3-E1 cells and a rat calvarial defect model. RNA sequencing identified Wnt- and MAPK-related enrichment, while qPCR and tissue immunostaining showed increased Dmp1/DMP1 and decreased Dusp1/DUSP1 expression. These findings identify signaling associations and candidate regulators, but do not independently demonstrate activation of canonical Wnt/β-catenin signaling or establish that DMP1, DUSP1, or either pathway is required for the observed osteogenic effects (Figure 5).

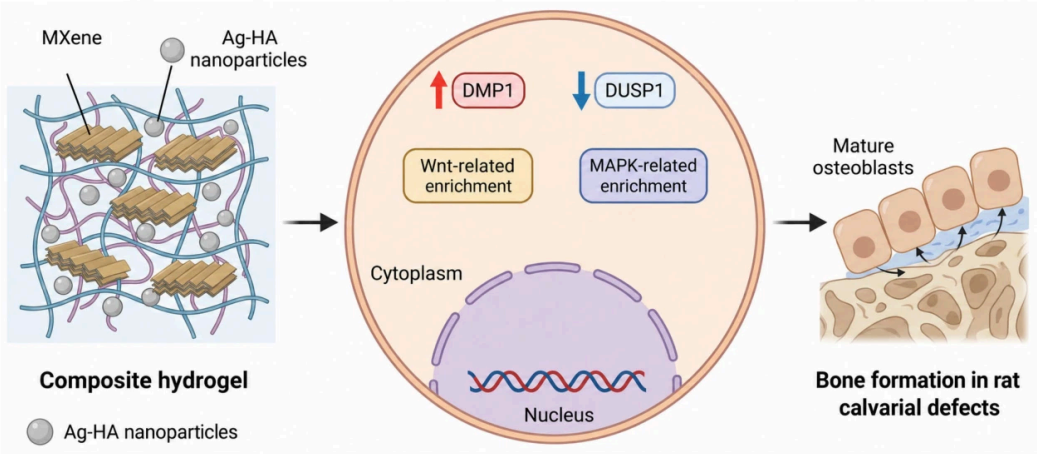

Figure 5. Molecular observations and bone-repair outcomes reported for MXene/Ag-HA/GelMA hydrogels. Increased Dmp1/DMP1 and decreased Dusp1/DUSP1 expression accompanied Wnt- and MAPK-related enrichment. Bone formation was evaluated in rat calvarial defects. Schematic illustration based on the findings of Ref. [69].

Xia et al. [70] found that molybdenum (Mo) increased phosphorylation of signal transducer and activator of transcription 3 (STAT3) and enhanced osteogenic responses in human PDLSCs. Stattic attenuated Mo-associated osteogenic marker expression, ALP activity, and mineralization, providing pharmacological evidence for a functional contribution of STAT3 in vitro. Separately, GelMA–PDLSC constructs cultured with Mo before

implantation improved bone formation in rat calvarial defects. STAT3 inhibition was not evaluated in the defect model, so the cellular intervention does not establish STAT3 dependence of the in vivo repair effect. The reported experiments also do not independently demonstrate a requirement for upstream Janus kinase (JAK) signaling.

3.3. Development of Smart Responsive Systems

GelMA can be combined with stimuli-responsive components to develop hydrogels whose properties or release behavior change in response to local conditions [71,72]. Piezoelectric fillers, pH-sensitive carriers, and responsive polymer networks have been investigated for regulating antibacterial activity, drug release, and cellular responses. The performance of these systems depends on the magnitude and duration of the relevant stimulus, as well as the composition of the surrounding tissue environment [73–75].

For example, Roldan et al. [76] developed an injectable piezoelectric hydrogel (PiezoGEL) using GelMA and barium titanate (BTO) piezoelectric fillers. Antibacterial activity was accompanied by downregulation of porP and fimA and upregulation of oxyR. These transcriptional changes suggest altered adhesion- and oxidative stress-associated responses, but do not establish that the individual genes mediate bacterial inhibition. PiezoGEL enhanced BMSC osteogenic responses in vitro. In a mouse periodontitis model, treatment reduced periodontal inflammation and improved alveolar bone-related outcomes. These findings provide disease-relevant preclinical evidence supporting the potential of PiezoGEL for periodontal treatment, although further studies are required to determine the extent of functional periodontal attachment regeneration.

During osteoclast differentiation and the bone resorption process, elevated levels of lactic acid are generated within the local microenvironment. Osteoclasts also release protons and enzymes, leading to the acidification of the resorption lacunae. To address this pathological challenge, Gong et al. [77] developed a pH-sensitive drug delivery system utilizing chitosan-coated mesoporous silica nanoparticles loaded with naringin (CS@MSNs-naringin). To achieve the in-situ release of the nanoparticles within bone defects, they incorporated these nanoparticles into a GelMA composite hydrogel. This system functions optimally in acidic microenvironments, facilitating the sustained release of naringin to modulate local osteoclast activity. Reduced osteoclast formation and resorptive activity were accompanied by lower phosphorylation of MAPK and nuclear factor kappa B (NF-κB) pathway components, reduced c-Fos/NFATc1 expression, and diminished NFATc1 nuclear localization. Changes in Bax, cleaved caspase-3, and Bcl-2 were assessed separately as apoptosis-related responses. These findings suggest pathway involvement but do not demonstrate that MAPK/NF-κB inhibition is required for the anti-osteoclastic effects. Separately, GelMA-mediated delivery of the nanoparticles enhanced bone formation in rat calvarial defects. This outcome does not establish the proposed signaling mechanism in vivo or demonstrate efficacy in alveolar defects.

3.4. Advanced Manufacturing and Structural Design

GelMA-based fabrication methods, including bioprinting, microfluidics and electrospinning, permit control of scaffold geometry, pore connectivity, surface features and component distribution [78,79]. These features may support the design of periodontal interfaces and heterogeneous oral defects [80–83]. Structural fidelity in vitro should nevertheless be evaluated separately from tissue regeneration in anatomically relevant models.

3.4.1. Multi-Hierarchical Structural Biomimicry

Designing gradient structures (e.g., pore size gradients, compositional gradients) or

multi-layered architectures can simultaneously meet the distinct regenerative demands of cortical and cancellous bone, offering novel insights for repairing complex bone defects [84,85]. The microenvironment of oral tissues is highly specialized, characterized by the presence of multiple tissue interfaces such as the periodontal ligament–alveolar bone and epithelium-bone interfaces. These distinct tissues exhibit significant differences in composition, mechanical strength, and growth rates, thereby imposing stringent requirements on the interfacial adaptability and functional specificity of biomaterials.

Vurat et al. [80] developed a multicellular 3D-bioprinted microtissue model mimicking the human periodontal ligament–alveolar bone interface. The construct incorporated periodontal ligament fibroblasts and osteoblasts within spatially organized GelMA-based bioinks, providing a platform for investigating tissue-specific cellular interactions and potential drug responses. In addition, subcutaneous implantation of acellular constructs in Wistar rats was performed to evaluate histocompatibility and degradation behavior. Importantly, this model was designed primarily for periodontal tissue-interface simulation and preliminary biomaterial assessment, rather than direct reconstruction of an orthotopic alveolar bone or periodontal defect. Therefore, its significance lies in supporting the feasibility of multicellular structural biomimicry, while further validation in periodontal defect models is required to establish regenerative efficacy.

Wei et al. [86] developed a modularized biphasic scaffold consisting of a non-stoichiometric calcium silicate (nCSi) bioceramic component and a GelMA/silanized hydroxypropyl methylcellulose (Si-HPMC) hydrogel membrane. The hierarchical architecture was designed to provide complementary functions for mineralized tissue formation and soft tissue exclusion. Its periodontal regenerative performance was evaluated in a canine periodontal intrabony defect model, with histological findings supporting the potential of the scaffold for periodontal tissue repair. This study therefore provides more anatomically and indication-relevant preclinical evidence than ectopic implantation or isolated cell-culture investigations. Nevertheless, further studies are needed to establish long-term functional periodontal attachment stability and clinical applicability (Figure 6).

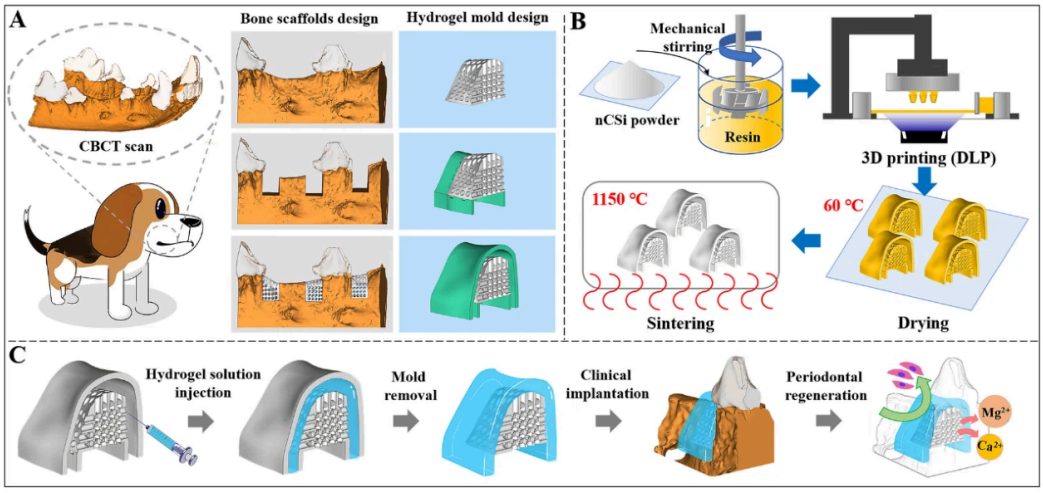

Figure 6. Design and fabrication of an nCSi scaffold integrated with a GelMA/Si-HPMC membrane for canine periodontal defects [86]. (**A**) CBCT-based defect reconstruction and digital design. (**B**) DLP printing and sintering of the nCSi scaffold. (**C**) Membrane assembly by mold injection and photocrosslinking, followed by implantation into surgically created canine one-wall periodontal defects. Reproduced with permission from Yingming Wei et al., Biomaterials Research; published by AAAS, 2022 [86].

Multilayer GelMA-based constructs allow different structural and biological func-

tions to be incorporated into separate regions of a scaffold, an approach that may be useful for reproducing aspects of the periodontal tissue interface.

3.4.2. Microscale Fabrication and Local Delivery

Zhang et al. [87] developed a patch combining a rapidly dissolving, tetracycline-loaded gelatin backing with biodegradable GelMA microneedles containing tetracycline-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles and cytokine-loaded silica microparticles. This design enabled local delivery of antibacterial and immunomodulatory agents. In a ligature-induced rat periodontitis model, the therapeutic patch reduced inflammatory mediators and improved alveolar bone-related micro-CT outcomes, including bone crest measurements and estimated bone recovery. These results provide disease-relevant preclinical evidence for periodontal tissue protection and repair. However, radiographic improvement alone does not establish complete regeneration of the periodontal ligament–cementum–alveolar bone complex.

Yi et al. [88] used droplet microfluidics to produce GelMA microspheres containing injectable platelet-rich fibrin (i-PRF) and nHA. Growth factor release continued for up to 28 days, and encapsulated hPDLSCs showed enhanced proliferation, spreading and osteogenic differentiation in vitro. These findings support a cellular delivery strategy; efficacy in periodontal or alveolar defects remains untested.

3.5. Antibacterial and Anti-Inflammatory Functions Synergizing with Osteogenesis

Alveolar bone defects, particularly those induced by chronic inflammation such as periodontitis, are frequently accompanied by infection and an inflammatory microenvironment. Therefore, these systems should be evaluated for infection control, host inflammatory responses and bone-related outcomes as distinct endpoints.

3.5.1. Functional Synergy of Organic Materials

Natural bioactive compounds, including flavonoids, have been incorporated into GelMA to combine local delivery with anti-inflammatory and osteogenesis-related cellular effects. Their activity and host–cell compatibility depend on the compound, concentration, release profile and experimental model. Naringenin (NA), a typical flavonoid, demonstrates remarkable potential in enhancing bone regeneration and modulating inflammation. Cardoso et al. [89] developed NA-loaded GelMA-based nanofibers via electrospinning. Their research verified that this material possesses both osteogenic and anti-inflammatory properties, serving as a dual-functional scaffold material for bone tissue engineering. The reported findings support the potential of these constructs for modulating cellular responses associated with inflammation and bone formation, but do not directly demonstrate periodontal or alveolar bone regeneration in vivo.

Li et al. [90] incorporated kaempferol into GelMA to achieve sustained local delivery in experimental rat periodontitis. Treatment reduced periodontal inflammation and alveolar bone loss. Changes in oral and intestinal microbial composition accompanied these periodontal responses.

Zhang et al. [91] incorporated psoralen (Pso) into GelMA hydrogels exhibiting flowability, cohesiveness, self-healing behavior, and sustained release. The formulation showed antibacterial activity and promoted osteogenic responses in vitro.

Guo et al. [92] combined GelMA with Radix Dipsaci (RD) and silicate nanosheets. The composite showed antibacterial, anti-inflammatory and osteogenesis-related activity, with improved inflammatory and alveolar bone-related outcomes in a periodontitis model. Sun et al. [93] reported that GelMA-delivered ginsenoside Rb3 reduced inflammatory responses and alveolar bone loss in experimental periodontitis. In LPS-stimu-

lated PDLSCs, treatment decreased p38/ERK phosphorylation and increased PI3K/AKT phosphorylation. Network pharmacology and protein analyses identified these signaling responses, but pathway-specific perturbations were not used to establish a causal requirement for either pathway. The findings therefore indicate treatment-associated signaling changes rather than demonstrate that MAPK suppression or PI3K/AKT activation mediates bone regeneration. Although these studies support the therapeutic potential of bioactive GelMA composites in periodontal disease models, the findings should be interpreted according to the specific endpoints evaluated rather than as evidence of complete periodontal tissue regeneration.

3.5.2. Utilization of Inorganic Antibacterial Components

Silver-containing particles and zinc-based frameworks have been incorporated into GelMA to provide local antibacterial activity, but antibacterial activity should be assessed alongside host–cell responses under defined concentration and exposure conditions. Wang et al. [62] tested Ag-HA/GelMA against Escherichia coli and Staphylococcus aureus, with MC3T3-E1 cell assessments over 1–5 days. These experiments support activity against the tested organisms and short-term cytocompatibility, but do not establish efficacy against periodontal multispecies biofilms or long-term oral safety.

Periodontal disease is a prevalent oral condition. The alveolar bone defects it induces frequently encounter multiple practical challenges during pharmacological treatment. Not only is it difficult to achieve adequate local drug concentrations and maintain therapeutic duration, but the efficacy is also often compromised by the emergence of drug resistance in pathogenic bacteria, creating a critical bottleneck in clinical management. Silver-, zinc- and copper-containing components have been investigated for local antibacterial delivery from GelMA. Resistance-related claims require repeated-exposure susceptibility testing and cannot be inferred from initial antibacterial activity. Liu et al. [94] incorporated zeolitic imidazolate framework-8 at 0.05%, 0.1% and 0.2% (*w*/*v*) into GelMA. The formulations released Zn^{2+} over 14 days, and rBMSC assays at days 1, 3 and 7 showed no significant differences in cell viability among the tested groups. The hydrogel inhibited P. gingivalis in vitro. The rat experiments comprised a short ligature/LPS-associated periodontal-inflammation arm and a longer ligature-induced alveolar bone-loss arm. In the latter, treatment followed ligature removal and debridement, and CEJ–ABC distance and BV/TV were assessed after four weeks. These results do not establish a general safety threshold, local tissue exposure or complete periodontal attachment regeneration.

Ma et al. [95] reported antimicrobial activity against P. gingivalis and cytocompatibility with periodontal ligament stem cells for bismuth-containing GelMA fibers in vitro. These findings support the tested local delivery approach, but do not establish preservation of oral commensals or long-term periodontal safety. Bone protection and regeneration require evaluation in relevant in vivo models.

A low risk of resistance cannot be inferred from initial growth inhibition or biofilm reduction. Claims of reduced resistance should be supported by repeated-exposure experiments that track changes in susceptibility and, where relevant, resistance-associated traits. This requirement applies to inorganic antimicrobials as well as antibiotic-loaded systems.

3.5.3. Loading Antibacterial Drugs

By loading conventional periodontal antibiotics such as minocycline and metronidazole into GelMA hydrogels, their sustained release capabilities can be harnessed to achieve sustained local antibiotic delivery, potentially reducing the need for systemic ex-

posure. Molecularly imprinted polymers (MIPs) provide binding sites complementary to template molecules in shape and chemical functionality and can be used to regulate drug loading and release. Utilizing this theory, Khademi et al. [96] prepared surface-imprinted chitosan-modified bioactive glass (MIP) particles to achieve the controlled release of doxycycline (DOX), and further constructed a composite hydrogel using GelMA as the matrix. This composite hydrogel was verified to possess both in vitro osteogenic activity and highly efficient hemostatic functions, alongside antioxidant and antibacterial properties. It effectively promoted the proliferation, spreading, and osteogenic differentiation of human dental pulp stem cells (hDPSCs). These findings support the feasibility of integrating localized antibiotic delivery with osteogenesis-related cellular stimulation. Nevertheless, the study did not directly demonstrate alveolar bone or periodontal tissue regeneration in vivo, and additional disease-specific investigations are required.

Although strategies based on the controlled release of antibiotics can achieve broad-spectrum antibacterial and multifunctional repair, the obligate anaerobic nature of core periodontal pathogens (such as *Porphyromonas gingivalis*) and the hypoxic state of the inflammatory microenvironment continue to pose targeted challenges for precision therapy. There is an urgent need to develop differentiated antibacterial regimens targeting the microenvironment.

Porphyromonas gingivalis is an obligate anaerobe and a keystone pathogen in periodontal dysbiosis [16]. Simultaneously, within the chronic inflammatory microenvironment, hypoxia exacerbates the inflammatory response, further delaying the clearance of pathogens. Therefore, developing a novel strategy with antibacterial properties is crucial for eradicating residual biofilms and preventing the rapid proliferation of pathogens. Zou et al. [97] utilized a calcium peroxide-loaded GelMA hydrogel injected into periodontal pockets to modulate the local oxygen concentration. The reported findings demonstrated oxygen-mediated antibacterial activity and suppression of periodontal biofilms, suggesting the potential of local oxygen delivery as an adjunctive approach for managing periodontal infection. However, successful biofilm inhibition should not be interpreted as direct evidence of alveolar bone regeneration, and further studies are necessary to determine whether this strategy provides sustained periodontal tissue protection and regenerative benefits in vivo.

To summarize the diverse design strategies discussed in Section 3 and Table 1 provides an overview of GelMA-based composite systems, including their experimental models, principal findings, and relevance to alveolar bone regeneration.

Table 1. Overview of GelMA-Based Composite Systems: Experimental Models, Principal Findings, and Relevance to Alveolar Bone Regeneration. Evidence scope is defined by the experimental model and demonstrated outcome. Subcutaneous implantation used only for compatibility or degradation assessment is not classified as ectopic osteogenesis. Reduced inflammatory bone loss is distinguished from new tissue formation. Intended applications describe research aims rather than validated clinical indications.

GelMA-Based System	Principal Findings	Intended Application	Experimental Model and Evidence Scope
GelMA/PEGDA hydrogels [59]	Formulation-dependent PDLSC osteogenic responses; the 4:1 formulation was selected for evaluation in rat alveolar defects.	Alveolar bone regeneration; Periodontitis	Alveolar bone repair: new bone formation in rat alveolar defects.
C GelMA/PCL-5% CeO [60]	Improves mechanical properties and promotes	Periodontal regeneration	In vitro: osteogenic cellular responses.

GelMA-Based System	Principal Findings	Intended Application	Experimental Model and Evidence Scope
	mineralized nodule deposition.		
GelMA/nHA microgels [63]	Promotes osteogenic differentiation of stem cells.	Periodontal regeneration	Ectopic mineralized tissue formation following subcutaneous implantation in mice.
BG/BMSCs@GelMA hydrogel [64]	Vascular-associated responses accompanied improved bone repair in rat calvarial defects.	Bone regeneration	Non-alveolar bone repair: rat calvarial defects.
BG/GelMA [65]	Facilitates cell attachment and osteogenic/cementogenic differentiation.	Periodontal regeneration	In vitro: osteogenic and cementogenic differentiation of periodontal ligament cells.
GPA membranes [66]	Osteogenic hMSC responses in vitro and bone formation in rat calvarial defects.	Periodontal regeneration	Non-alveolar bone repair: rat calvarial defects.
GHnH-P@GS hydrogel [67]	Enhanced stem-cell migration and osteogenic differentiation in vitro.	Alveolar bone regeneration	In vitro: stem-cell migration and osteogenic differentiation.
GelMA-PBA@CeO2@AMP [68]	Antibacterial and ROS-scavenging activity, immunomodulatory responses, and improved bone-related outcomes in infected alveolar defects.	Alveolar bone regeneration; Periodontitis	Alveolar bone repair: infected alveolar defect model.
MXene/Ag-HA/GelMA [69]	Increased Dmp1 and decreased Dusp1 expression accompanied osteogenic responses; pathway necessity was not established.	Alveolar bone regeneration	Non-alveolar bone repair: rat calvarial defects
GelMA+PDLSC+Mo [70]	Enhanced PDLSC osteogenic responses with in vitro support for STAT3 involvement; bone repair was evaluated separately in rat calvarial defects.	Bone regeneration	In vitro PDLSC osteogenic responses; non-alveolar bone repair in rat calvarial defects.
PiezoGEL [76]	Antibacterial and BMSC osteogenic responses in vitro; improved inflammatory and bone-related outcomes in mouse periodontitis.	Periodontitis	In vitro cellular assays and mouse periodontitis; inflammatory and alveolar bone-related outcomes.
GelMA+CS@MSNs-Naringin [77]	Inhibits osteoclastogenesis and bone resorption via pH-responsive release.	Bone regeneration	Non-alveolar bone repair: rat calvarial defects.
Gel-MA and Gel-MA/HAp-MNP bioinks [80]	Bioprinted periodontal interface modeling in vitro; acellular subcutaneous implants were evaluated for	Periodontal regeneration	In vitro periodontal interface model; subcutaneous compatibility and degradation assessment.

GelMA-Based System	Principal Findings	Intended Application	Experimental Model and Evidence Scope
	compatibility and degradation.		
nCSi scaffold/GelMA/Si-HPMC membrane [86]	Supported bone and periodontal ligament formation in canine periodontal defects using a combined scaffold–membrane construct.	Periodontal regeneration	Periodontal tissue reconstruction: bone and periodontal ligament formation in canine defects.
GelMA MNs patches [87]	Delivers targeted antibacterial and immunomodulatory effects via microneedles.	Periodontitis	Rat periodontitis: inflammatory responses and micro-CT bone outcomes.
GelMA+NA5%[89]	Provides anti-inflammatory cues while maintaining cellular functions.	Periodontitis	In vitro: osteogenic and anti-inflammatory activity.
Gel_Ka [90]	Reduced periodontal inflammation and alveolar bone loss in rats.	Periodontitis	Inflammatory bone-loss attenuation: rat periodontitis.
PSO-GelMA [91]	Promotes BMSC osteogenic differentiation in vitro while inhibiting S. aureus and F. nucleatum.	Periodontitis	In vitro: antibacterial activity and BMSC osteogenic differentiation.
GelMA-SN-RD [92]	Integrates mechanical support with osteogenic and anti-inflammatory functions.	Periodontitis	Rat periodontitis: inflammatory and alveolar bone-repair outcomes.
GelMA@G-Rb3 [93]	Reduces alveolar bone loss and mitigates endotoxin-induced inflammation.	Periodontitis	Inflammatory bone-loss attenuation: rat periodontitis.
GelMA-Z [94]	Reduces bacterial load and relieves inflammation via sustained Zn^{2+} release.	Periodontitis	Rat periodontitis: inflammatory and alveolar bone-related outcomes.
FB92 and FB95 [95]	Antimicrobial activity against P. gingivalis and PDLSC cytocompatibility in vitro.	Periodontitis	In vitro: antibacterial activity and PDLSC cytocompatibility.
GelMA/MIP [96]	Supported hDPSC osteogenic differentiation in vitro; antibacterial, antioxidant, and hemostatic activities were also evaluated.	Periodontitis	In vitro: hDPSC osteogenic differentiation and antibacterial activity.

4. Mechanisms of GelMA-Functionalized Hydrogels in Alveolar Bone Osteogenesis and Repair

4.1. Scaffold Biomimetics and Osteoconduction Mechanisms

GelMA composites provide an ECM-like environment for cell encapsulation and bioactive-factor delivery [98]. Composition, architecture and degradation should be assessed together. Cellular viability, proliferation and differentiation are surrogate outcomes; osteoconduction and bone regeneration require tissue-level evidence of new bone formation within or around the construct.

GelMA retains RGD adhesion motifs and MMP-sensitive sequences, providing a basis for cell-interactive scaffolds. Pan et al. [99] demonstrated that GelMA-encapsulated hPDLSCs supported bone repair in a rat alveolar bone defect model, providing direct preclinical evidence of regenerative potential. However, the contribution of specific RGD-mediated adhesion or MMP-dependent remodeling pathways to the observed regeneration was not independently established in that study. Aksel et al. [100] compared ECM-containing colloidal microgels with bulk GelMA in a regenerative endodontic model. Bulk GelMA supported higher DPSC viability, ALP activity, and calcium deposition, whereas endothelial tubule-like structures formed in the colloidal matrices but not in bulk GelMA. Furthermore, Wang et al. [101] demonstrated that EphrinB2-overexpressing dental pulp stem cells embedded in 3D-bioprinted GelMA constructs exhibited enhanced osteogenic marker expression and mineralization in vitro.

Beyond individual cell responses, spatial organization and interactions between different cell populations may contribute to tissue regeneration. Tang et al. [102] combined Hertwig's epithelial root sheath cells and dental papilla cells within 3D-bioprinted GelMA constructs and evaluated their effects following transplantation into rat alveolar sockets. The findings supported the contribution of epithelial–mesenchymal interactions to mineralized tissue formation and alveolar bone repair in this experimental setting. Yang et al. [103] developed a 3D-bioprinted decellularized extracellular matrix (dECM)/GelMA module containing dental follicle cells and evaluated it in canine periodontal defects. At 3 months, micro-CT showed increased BV/TV and trabecular thickness, while histomorphometry showed greater bone regeneration height than with GelMA alone. Histology identified fibers inserting into newly formed bone, more mature periodontal ligament collagen, and larger Haversian systems. These findings support structural periodontal tissue repair and maturation (Figure 7).

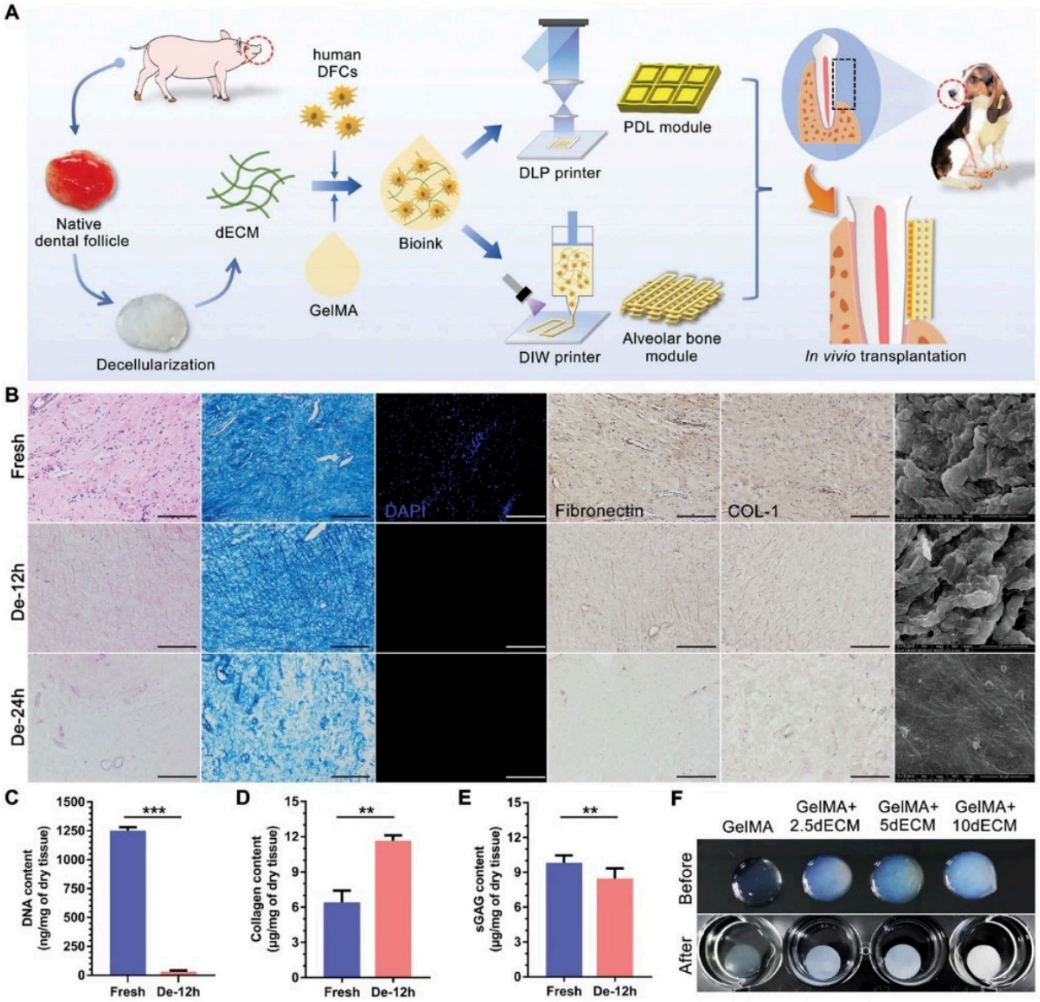

Figure 7. Preparation and characterization of a dental follicle dECM/GelMA bioink. (**A**) Design of cell-laden modules for canine periodontal repair. (**B**) Native and decellularized porcine dental follicle tissue examined by histological, protein-staining and electron-microscopy methods. (**C**–**E**) DNA, collagen and sulfated glycosaminoglycan (sGAG) content, respectively. (**F**) Bioinks before and after photocrosslinking. Scale bars in (**B**): 100 μm. Data are shown as mean ± SD; $n = 4$ for (**C**) and n = 3 for (**D**,**E**). $^{**}p < 0.01$; $^{***}p < 0.001$. Reproduced from Yang et al. [103] under CC BY 4.0.

4.2. Delivery and Osteoinduction Mechanisms: Active Regulation of Biological Signals

GelMA-based delivery systems retain growth factors and extracellular vesicles locally, with biological responses determined by cargo identity, release behavior, and interactions with recipient cells. Miao et al. [104] bioprinted GelMA/sodium alginate (SA)/bioactive glass microsphere (BGM) constructs containing mouse bone marrow mesenchymal stem cells (mBMSCs), bone morphogenetic protein-2 (BMP-2), and platelet-derived growth factor (PDGF). In beagle periodontal defects at 8 weeks, the cell- and growth factor-loaded constructs increased micro-CT BV/TV, trabecular number, and regenerated bone height relative to original defect height compared with untreated defects. Histomorphometry also showed increased new bone height and area relative to defect dimensions. These findings support local bone repair; they do not establish complete functional periodontal restoration or identify a causal intracellular signaling pathway.

Beyond routine defect repair, bone regeneration under complex pathological microenvironments—such as diabetes—is often accompanied by severe metabolic disturbances and chronic inflammation, necessitating delivery systems capable of targeted im-

munomodulation. The cytokine interleukin-10 (IL-10) plays a pivotal role in inducing the polarization of pro-inflammatory (M1) macrophages toward a pro-repair (M2) phenotype. Accordingly, Hu et al. [105] developed an IL-10-loaded, heparin-modified GelMA sustained-release system for alveolar ridge defects in diabetic rats. The study demonstrated that heparin modification on GelMA chains significantly optimized biological functionality and drug release kinetics. IL-10 delivery was associated with increased M2-associated macrophage responses and improved bone formation under diabetic conditions. These findings provide anatomically relevant preclinical evidence supporting the potential contribution of macrophage-associated immunomodulation to bone repair under diabetic conditions. Nevertheless, the observed association between macrophage polarization and improved bone formation does not independently establish that M2 polarization is the sole or indispensable mechanism underlying the regenerative effect.

Small extracellular vesicles (sEVs), including exosomes, have emerged as promising carriers of bioactive molecules capable of influencing intercellular communication and cellular behavior. Their incorporation into GelMA-based scaffolds offers a potential strategy for providing localized biological cues within tissue-engineered constructs. Han et al. [106] used 3D bioprinting to incorporate small extracellular vesicles (sEVs) from human periodontal ligament cells or human gingival fibroblasts into GelMA. The results confirmed that this system efficiently mediates intercellular communication and significantly enhances the adhesion and osteogenic differentiation of human buccal fat pad-derived mesenchymal stromal cells (hBFP-MSCs) in vitro. These findings support the feasibility of using periodontal cell-derived sEVs to modulate cellular responses within GelMA-based constructs. Nevertheless, the study primarily demonstrated functional cellular outcomes and did not establish a specific causal molecular pathway or directly validate alveolar bone regeneration in vivo.

To address more severe pathological environments, such as intense inflammation, the composite modification of hydrogel matrices coupled with exosome synergy has become key to enhancing therapeutic efficacy. Liu et al. [107] developed a nano-hydroxyapatite-methacrylated gelatin/methacrylated alginate (nHAP-GelMA/algMA, or NGA) composite system loaded with human umbilical cord blood-derived exosomes (UCB-Exos; NGA@UCB-Exos). MiR-182-5p mimics and inhibitors altered MYD88 expression, while wild-type/mutant MYD88 3′-UTR reporter assays supported direct targeting. In BMSCs, miR-182-5p inhibition reversed exosome-associated reductions in MYD88 expression and p65 phosphorylation and attenuated the osteogenic response. These interventions provide functional evidence for a contribution of exosomal miR-182-5p in vitro, although they do not establish the complete downstream pathway as necessary for regeneration. At 4 weeks after treatment in a rat peri-implantitis model, the exosome-loaded hydrogel increased peri-implant BV/TV, BMD, trabecular thickness, and trabecular number relative to the control and unloaded-hydrogel groups. H&E and Masson's trichrome staining provided complementary evidence of bone formation and reduced inflammatory infiltration. Nevertheless, although the study provides both functional cellular evidence and disease-relevant in vivo regenerative evidence, the causal requirement for this signaling pathway in the animal model was not independently established through pathway-specific intervention in vivo.

4.3. Immunomodulation-Promoted Osteogenesis

The interactions between the immune and skeletal systems play important roles in periodontal tissue homeostasis and bone regeneration. Under pathological conditions such as periodontitis, persistent microbial stimulation and dysregulated inflammatory

responses can promote osteoclast activity and impair osteogenic cellular functions, contributing to progressive alveolar bone loss. Consequently, the modulation of local immune responses has emerged as a promising strategy for developing GelMA-based regenerative platforms. Nevertheless, the immunomodulatory mechanisms reported in existing studies have been investigated using different cellular systems and animal models, and their causal contributions to bone regeneration should be interpreted according to the available experimental evidence.

Deng et al. [108] immobilized biotinylated MSC-derived exosomes within biotin-modified GelMA using streptavidin. The construct supported exosome retention and was associated with reduced M1-associated markers, increased M2-associated responses, and improved repair of artificial periodontal multitissue defects.

To further strengthen the synergy between anti-infection and anti-inflammation, researchers have begun targeting the regulation of immune cell programmed death pathways. Zhuo et al. [109] integrated GelMA with a peptide (CP05), an antimicrobial peptide (MP196), and neutrophil exosomes to prepare a multi-effect composite hydrogel. While continuously releasing active components for potent antibacterial effects, the system upregulates genes and proteins associated with neutrophil apoptosis. Neutrophil apoptosis, efferocytosis and M2-associated macrophage responses increased after treatment. In vivo rat models confirmed that this strategy effectively alleviates periodontal inflammation and significantly reduces alveolar bone loss. These results suggest that regulation of neutrophil responses and macrophage-associated immune activity may contribute to the observed periodontal protection. Nevertheless, the relative contributions of antibacterial activity, neutrophil apoptosis, and macrophage immunomodulation to the in vivo bone-protective effects remain to be fully established.

Beyond immune cell phenotypic regulation, specific inflammatory signaling pathways have been investigated as potential therapeutic targets. Addressing this mechanism, Liu et al. [110] developed a modified GelMA composite hydrogel (pGM/cPL@NI) loaded with a specific NLRP3 inhibitor (MCC950). Delivery of MCC950 reduced NLRP3 inflammasome-associated inflammatory readouts and was accompanied by improved osteogenic responses. These findings provide experimental support for the contribution of NLRP3 inhibition to the immunomodulatory activity of the system. In a rat periodontitis model, the hydrogel reduced inflammatory bone loss, with outcomes assessed using CEJ–ABC distance, BV/TV, and histology. The periodontal bone-protective effects may also involve the antibacterial and antioxidant properties of the multifunctional hydrogel and should not be attributed exclusively to NLRP3 inhibition. Similarly, in the context of complex diabetes-associated periodontitis, Ge et al. [111] co-encapsulated self-assembled nanoparticles containing chlorhexidine and epigallocatechin gallate within a GelMA and oxidized hyaluronic acid (OHA) hydrogel (GOE1 hydrogel). The system demonstrated antibacterial, antioxidant, and anti-inflammatory activities, while in vivo treatment reduced periodontal inflammatory infiltration and alveolar bone loss. Transcriptomic and molecular analyses implicated interleukin-17 (IL-17)-associated inflammatory regulation and macrophage-related immune responses in the observed therapeutic effects. These findings suggest that modulation of IL-17-related signaling may contribute to the biological activity of the composite hydrogel. Nevertheless, the specific requirement for the IL-17/Act1 axis in mediating alveolar bone protection remains to be established through targeted functional intervention experiments.

Cui et al. [112] incorporated melatonin-loaded M2 macrophage-derived exosomes (Mel@M2-exos) into GelMA hydrogels. In LPS-stimulated human periodontal ligament cells (hPDLCs), treatment reduced endoplasmic reticulum (ER) stress- and unfolded protein response (UPR)-associated markers and improved osteogenic differentiation. In

a rat ligature-induced periodontitis model, treatment reduced inflammatory bone loss. These findings associate cellular stress responses with osteogenic recovery and periodontal protection, but do not establish that ER-stress modulation is necessary for either the cellular or in vivo effect (Figure 8).

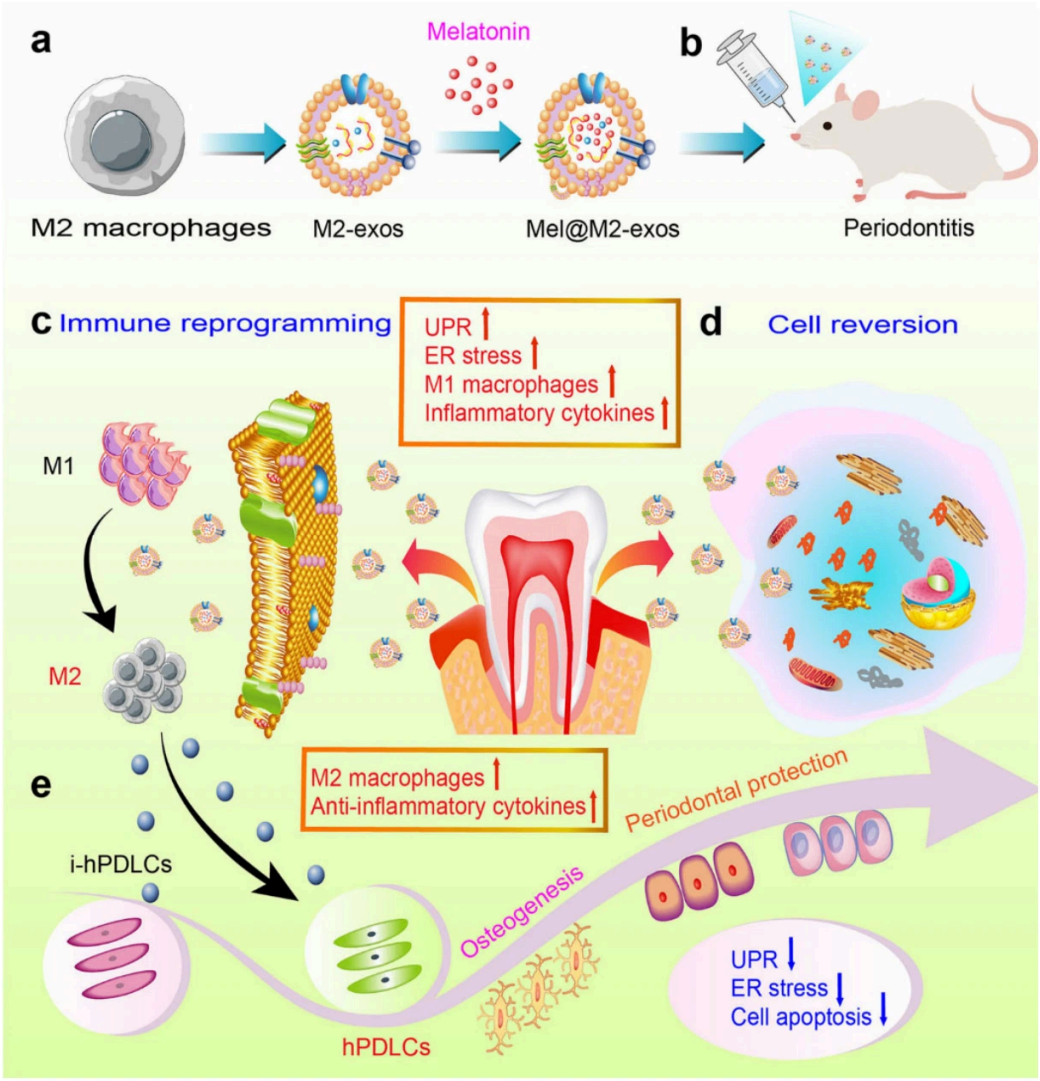

Figure 8. Schematic illustration of engineered M2 macrophage-derived exosomes for the treatment of inflammatory bone loss in periodontitis via modulation of endoplasmic reticulum (ER) stress and immune reprogramming. (a) Preparation of melatonin-engineered exosomes derived from M2 macrophages.(b) Potential therapeutic application ofMel@M2-exosin rats with ligation-induced periodontitis.(c) Immune reprogramming and macrophage repolarization induced byMel@M2-exos. (d) Modulation of ER stress and reversal of cellular states byMel@M2-exos.(e) Restoration of impaired hPDLC function under inflammatory conditions byMel@M2-exos.Reproduced with permission from Ya Cui et al., Advanced Science; published by Wiley, 2023 [112].

Xiu et al. [113] integrated iron-curcumin nanoparticles (Fe-Cur NPs), polydopamine, and minocycline hydrochloride into GelMA microspheres fabricated via microfluidic technology. The composite microspheres exhibited photothermal antibacterial, antioxidant, and anti-inflammatory activities and reduced alveolar bone loss in a rat periodontitis model. Molecular analyses revealed increased expression of nuclear factor erythroid 2-related factor 2 (NRF2)-associated antioxidant mediators, including heme oxygenase 1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), together with re-

duced expression of NLRP3 inflammasome-associated markers. These results are consistent with the involvement of NRF2-related antioxidant responses and NLRP3-associated inflammatory regulation. Nevertheless, because the proposed mechanism was primarily supported by molecular expression analyses, additional pathway-specific inhibition or genetic intervention experiments are required to establish whether NRF2 activation is indispensable for the therapeutic effects.

The immunomodulatory studies differ in model relevance and mechanistic strength. Candidate immunomodulatory systems should also be assessed for preserved bacterial control and host–cell function. Lower cytokine levels or increased M2-associated markers cannot by themselves exclude impaired antimicrobial defense, residual infection, or material-associated inflammation. In multifunctional formulations, reduced inflammation may follow bacterial suppression, direct immune modulation, or both. Evaluation should therefore follow microbial clearance, immune-cell recruitment, tissue integration, and persistent local or foreign-body responses over a period matched to material residence (Figure 9).

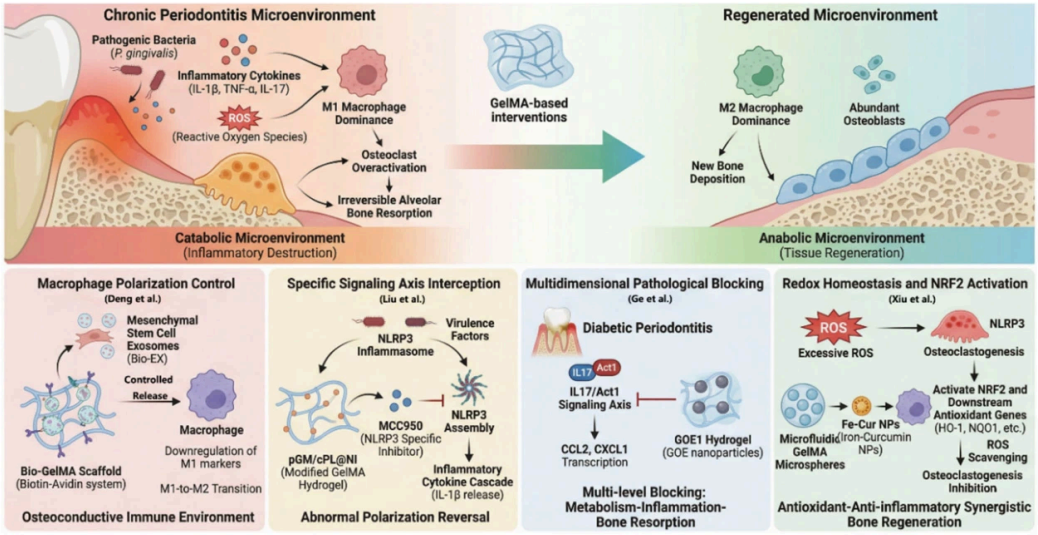

Figure 9. Conceptual overview of immunomodulatory strategies investigated with selected GelMA-based systems. The panels summarize exosome-associated macrophage responses [108], delivery of the NLRP3 inhibitor MCC950 [110], antimicrobial and inflammatory responses in diabetic periodontitis [111], and NRF2- and NLRP3-associated molecular findings for Fe–Cur-containing microspheres [113]. Arrows summarize proposed relationships across separate studies; they do not demonstrate a shared causal pathway or establish that macrophage polarization, IL-17/Act1 signaling, or NRF2 activation is necessary for functional periodontal regeneration. The depicted regenerated tissue is a conceptual therapeutic objective, not evidence of complete periodontal reconstruction.

4.4. Vascular and Osteogenic Responses

GelMA-based composites have been investigated for their effects on both vascular and osteogenic responses. These endpoints should be assessed independently before inferring angiogenesis–osteogenesis coupling. Endothelial marker expression and vessel-like structures indicate vascular responses, but do not establish perfusion or vessel maturity. Likewise, osteogenic differentiation in culture should be distinguished from bone formation demonstrated by imaging and histology. Coexisting vascular and bone-related findings do not by themselves establish a causal interaction or restoration of functional vascularized bone.

Mahmoud et al. [114] fabricated electrospun β-tricalcium phosphate (β-TCP)-con-

taining GelMA/PCL membranes. Increased mineralization and osteogenic gene expression in alveolar bone-derived mesenchymal stem cells (aBMSCs) in vitro were accompanied by greater bone volume and BV/TV in rat critical-size calvarial defects at 6 weeks. H&E and Masson's trichrome staining provided tissue-level evidence of new bone, while CD31 and vWF immunolabeling indicated vascular-associated responses. These findings support bone formation in a calvarial model, but do not directly establish perfused vascular networks, causal angiogenesis–osteogenesis coupling, or functional alveolar bone restoration.

However, compared to conventional healthy bone defects, the microenvironment of infectious bone lesions, such as those in periodontitis, is significantly more complex, requiring a multifaceted synergy of antibacterial, anti-inflammatory, and regenerative effects. To address this clinical challenge, Chen et al. [115] developed antimicrobial peptide-grafted GelMA microspheres (GelMA-AMP) to encapsulate and controllably release hypoxia-inducible factor-1α (HIF-1α), while co-incorporating stem cells from human exfoliated deciduous teeth (SHEDs). The system supported SHED osteogenic responses and changes in inflammation- and angiogenesis-related readouts. These concurrent findings do not independently establish that vascular changes mediate the osteogenic effect. In the periodontitis model, the microspheres reduced inflammation and were associated with vascular and bone-related tissue responses. These findings should be distinguished from direct evidence of perfusion, mature bone architecture, or restored periodontal function.

4.5. Mitochondrial Dynamics-Mediated Osteogenesis Mechanism

Mitochondria serve not only as the primary energy hub of the cell but also as central mediators in various intracellular signaling transduction pathways. Their metabolic activity is a decisive factor in determining stem cell fate, playing a crucial regulatory role particularly during the differentiation of bone marrow mesenchymal stem cells (BMSCs).

An et al. [116] compared two types of graphene oxide quantum dots (GOQDs) and found that Y-GOQDs elicited stronger osteogenic responses in hPDLSCs. Mitofusin 2 (MFN2) silencing disrupted the mitochondrial network and attenuated Y-GOQD-associated increases in osteogenic markers and ALP activity, providing functional genetic support for MFN2-associated regulation in vitro. GelMA-encapsulated Y-GOQD-treated cell-sheet fragments also improved repair of rat mandibular periodontal bone defects. However, MFN2 silencing was not tested in the defect model, so the cellular intervention does not establish that MFN2 is required for the in vivo repair effect (Figure 10).

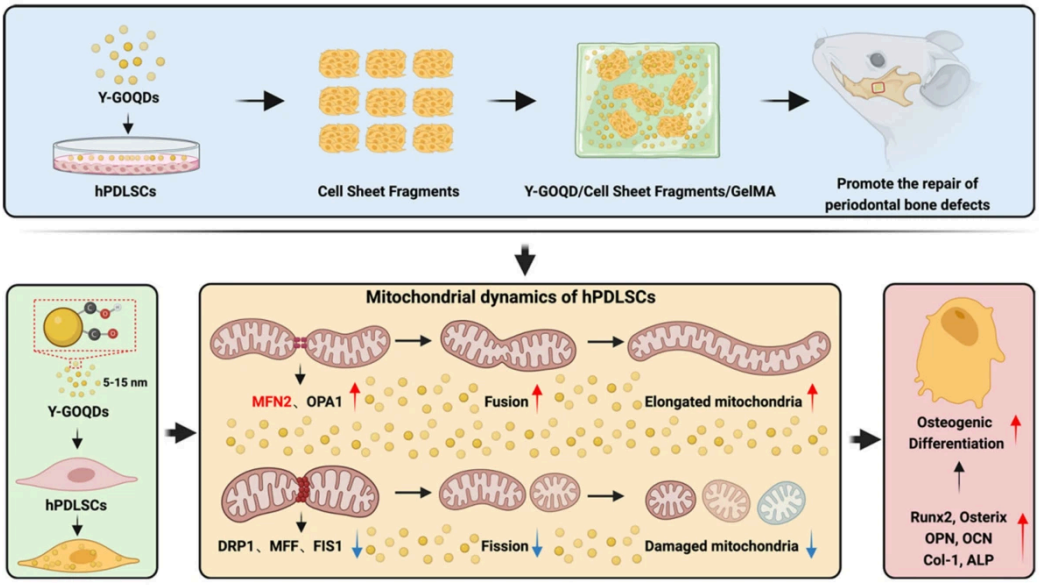

Figure 10. Y–GOQD–associated mitochondrial responses in hPDLSCs and their separate evaluation in a rat periodontal defect model. MFN2 knockdown attenuated mitochondrial–network and osteogenic responses in vitro, supporting a cellular contribution of mitochondrial dynamics. Implantation of GelMA–encapsulated cell–sheet fragments improved defect repair, but MFN2 dependence was not tested in vivo. Other marker–linked connections are shown as associations. Schematic illustration based on the findings of Ref. [116].

Table 2 summarizes the mechanisms of GelMA-functionalized hydrogels in alveolar bone osteogenesis and repair, distinguishing among cellular, tissue, and mechanistic findings.

Table 2. Mechanisms of GelMA-Functionalized Hydrogels in Alveolar Bone Osteogenesis and Repair. Cellular, tissue and mechanistic findings are distinguished. Expression, enrichment, localization, release, and marker changes alone establish neither pathway necessity nor sufficiency.

Functionalized GelMA System	Target Cell/Component	Reported Mechanistic Observations and Evidence	Cellular Effect	Reported Outcome/Evidence Scope
GelMA	hPDLSCs	Cell-supportive GelMA matrix retaining RGD motifs and MMP-sensitive sequences.	Supported hPDLSC viability and osteogenic responses.	Rat alveolar defects: micro-CT and histological new bone at 4/8 weeks
GelMA	DPSCs	ECM-dependent responses in colloidal microgels; bulk GelMA was a comparator	DPSC viability, ALP and calcium deposition; odontogenic/angiogenic responses depended on matrix and ECM source.	In vitro dental-pulp model; no alveolar-defect outcome
GelMA	HERS/Dental papilla cells	Epithelial–mesenchymal interaction (EMI)	Promotes cell–cell interaction	Rat alveolar-socket constructs at 8 weeks: histological new bone and mineralization-associated staining

Functionalized GelMA System	Target Cell/Component	Reported Mechanistic Observations and Evidence	Cellular Effect	Reported Outcome/Evidence Scope
dECM/GelMA	Dental follicle cells (DFCs)	ECM-associated structural cues; specific causal molecular mediators not established	Promotes cell migration and differentiation	Canine periodontal repair at 3 months; reconstructed bone–ligament interface.
GelMA/SA/BGM	mBMSCs	Co-delivery of BMP-2 and PDGF with mBMSCs	Growth-factor-associated osteogenic and soft-tissue-related cellular readouts	Beagle periodontal defects at 8 weeks; histomorphometric new bone height and area.
GelMA/i-PRF/nHA	hPDLSCs	Sustained release of multiple growth factors (GFs) from i-PRF	Promotes cell proliferation, spreading, and osteogenic differentiation	Enhanced hPDLSC osteogenic differentiation in vitro; in vivo regeneration not established.
Heparin-modified GelMA	Macrophages	Sustained release of IL-10	Induces M1-to-M2 macrophage polarization	Diabetic-rat alveolar-ridge defects at 1/4 weeks; new bone formation assessed by micro-CT and histology, with Bio-Oss Collagen, unloaded GelMA–heparin and blank controls.
GelMA@SEV	hBFP-MSCs	Delivery of sEVs from hPDLCs or human gingival fibroblasts	Enhances cell adhesion and osteogenic differentiation	Enhanced hBFP-MSC adhesion and osteogenic differentiation in vitro.
NGA@UCB-Exos	Immune/Bone cells	Reporter assays and miR-182-5p perturbation support MYD88 targeting at the cellular level	Modulates inflammation and promotes osteogenesis	Improved peri-implant BV/TV, BMD, Tb.Th, and Tb.N at 4 weeks in rats, with histological support.
Bio-GelMA@Bio-EX	Macrophages	Streptavidin-mediated immobilization of biotinylated exosomes	Reduced M1-associated markers and increased M2-associated responses.	Artificial periodontal multitissue defects; tissue repair accompanied by macrophage-marker changes, without an active periodontitis model.
GelMA-CP05-MP196@NEs	Neutrophils/Macrophages	Upregulates neutrophil apoptosis-related genes and proteins	Promotes neutrophil apoptosis and M2 macrophage polarization	Reduced inflammation-associated alveolar bone loss in rats
pGM/cPL@NI	Macrophages	Delivery of the NLRP3	Reduced	Rat periodontitis;

Functionalized GelMA System	Target Cell/Component	Reported Mechanistic Observations and Evidence	Cellular Effect	Reported Outcome/Evidence Scope
(MCC950)		inhibitor MCC950	inflammasome/cytokine-related readouts under the tested conditions	reduced inflammatory bone loss assessed using CEJ–ABC distance, BV/TV and histology.
GOE1 Hydrogel	Immune/Bone cells	IL-17-associated macrophage responses reported in transcriptomic analysis	Antimicrobial, redox and inflammatory cellular readouts	Reduced periodontal inflammation and alveolar bone-loss measures in diabetic periodontitis
GelMA@Mel@M2-exos	hPDLCs	ER-stress/UPR marker changes in inflamed hPDLCs; pathway necessity not demonstrated in vivo	Scavenges free radicals; promotes osteogenic differentiation	Attenuation of inflammatory bone loss in rat ligature periodontitis
GM@Fe-Cur/PDA/MH	Macrophages	Increased Nrf2/HO-1 and reduced NLRP3-related expression; associative evidence	ROS and macrophage phenotype-associated changes	Reduced inflammatory and bone-loss measures in rat periodontitis; Nrf2 necessity not established
GelMA/PCL-TCP	aBMSCs; rat calvarial tissue	CD31/vWF immunolabeling; causal coupling not established	aBMSC osteogenic differentiation in vitro	Increased BV/TV and histological new bone in rat calvarial defects at 6 weeks.
HIF-1α@GelMA-AMP@SHED	SHEDs	HIF-1α delivery with osteogenic and angiogenesis-related responses; causal coupling not established	Stimulates osteogenic differentiation; regulates anti-inflammatory genes	In vivo periodontitis; reduced inflammation with vascular- and bone-related tissue responses. Functional periodontal restoration was not established.
Y-GOQD/Cell/GelMA	hPDLSCs (Mitochondria)	MFN2 knockdown attenuated mitochondrial and osteogenic responses in vitro	Promotes mitochondrial fusion; inhibits fission	Improved repair of rat periodontal defects; MFN2 dependence not tested in vivo

5. Preclinical Evidence and Potential Clinical Applications of GelMA-Based Hydrogels in Alveolar Bone Regeneration

GelMA-based systems have been investigated for post-extraction socket healing, periodontitis-associated bone loss, peri-implantitis and selected maxillofacial defects. These indications differ in defect geometry, inflammatory conditions and requirements for tissue reconstruction. The studies summarized below provide preclinical evidence of varying anatomical relevance and should not be interpreted as established clinical efficacy (Figure 11).



Figure 11. Schematic overview of potential oral applications of GelMA-based biomaterial platforms. The illustration depicts four clinically relevant indications: (1) post-extraction alveolar ridge preservation, (2) periodontal bone regeneration, (3) peri-implantitis-associated bone defect management, and (4) reconstruction of complex maxillofacial bone defects. These applications are supported by preclinical studies of varying anatomical and disease-specific relevance and should not be interpreted as established clinical indications.

5.1. Alveolar Defect Reconstruction and Post-Extraction Socket Repair

Post-extraction remodeling can reduce ridge dimensions and complicate subsequent rehabilitation. GelMA-based approaches have therefore been investigated as conformable fillers and carriers of bioactive agents, with outcomes assessed separately for socket bone healing and ridge dimensional preservation.

Xu et al. [117] developed a ceramic-craft-inspired osteogenic (CIO) hydrogel composed of GelMA, nanoclay, and bone graft components. This injectable and rapidly photocurable material exhibited favorable moldability and structural adaptability for irregular bone defects. The study included non-alveolar skeletal evaluation and, importantly, demonstrated its potential for alveolar bone defect reconstruction in a cynomolgus monkey model. The latter provides more anatomically relevant preclinical evidence than calvarial defect studies alone. Nevertheless, alveolar bone defect reconstruction and post-extraction socket preservation represent distinct experimental indications. Therefore, the findings support the potential utility of the CIO hydrogel for alveolar bone reconstruction but should not be interpreted as direct evidence of efficacy in extraction socket

preservation without corresponding socket-specific evaluation.

Beyond scaffold adaptability and osteogenic activity, the incorporation of additional bioactive components may help address the inflammatory and vascular requirements of extraction socket healing. Yang et al. [118] constructed a highly injectable and mechanically robust hydrogel using GelMA and oxidized dextran (ODex). They loaded this matrix with a metal–organic framework (MOF)—composed of magnesium ions and gallic acid (GA)—alongside an osteogenic growth peptide (OGP). The study examined antioxidant and vascular-associated responses alongside osteogenic differentiation in vitro, followed by evaluation in rat extraction sockets. These cellular findings and the in vivo bone outcomes are considered separately below (Figure 12). They also demonstrated that the formulation of a dual-network hydrogel requires a balance between gelation kinetics and mechanical performance. Increasing the ODex concentration from 1% to 8% reduced the initial gelation time from approximately 127 to 0.9 min. However, the G15OD5 formulation achieved a higher compressive modulus than G15OD8 (502 ± 40 versus 467 ± 35 kPa) and a lower equilibrium swelling ratio (8.2 ± 1.26% versus 14 ± 2.1%). The intermediate ODex concentration therefore provided a more favorable combination of injectability, mechanical stability, and swelling control under the conditions examined.

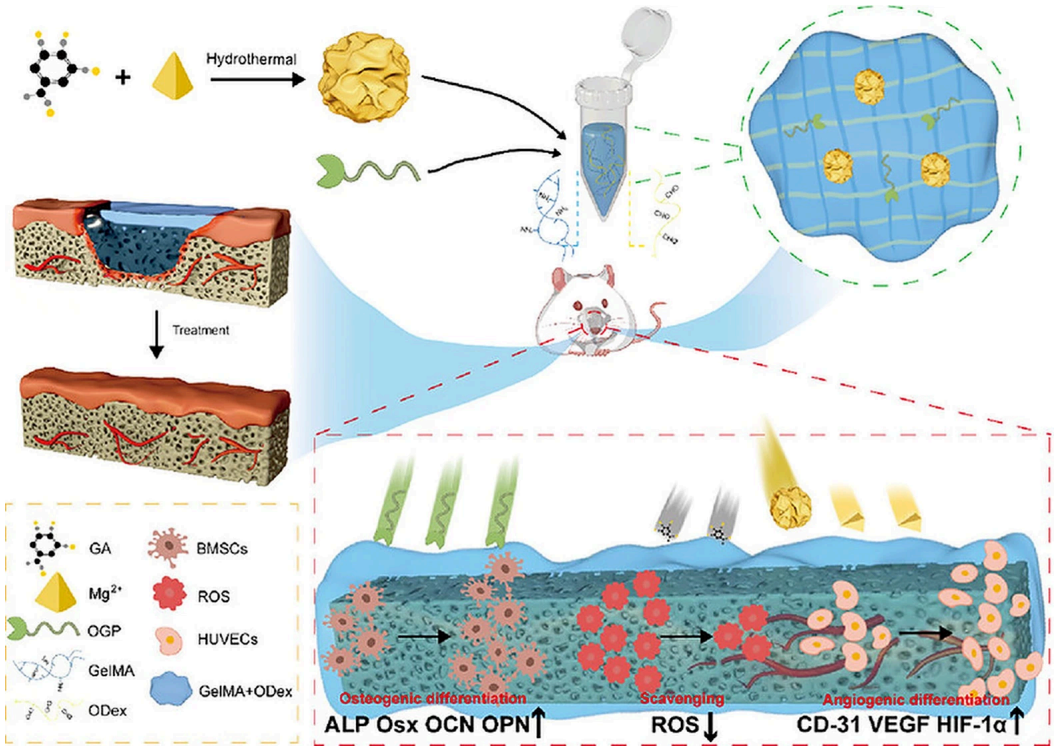

Figure 12. Formulation and application of the MOF/OGP-loaded GelMA/ODex composite hydrogel for tooth extraction socket healing. The schematic depicts the integration of Mg-GA MOFs and OGP into an injectable dual-network hydrogel. The schematic illustrates the proposed antioxidant, osteogenic, and angiogenic actions of the composite, including changes in ROS and the indicated molecular markers. Adapted reprinted with permission from Ref. [118].

In rat maxillary incisor extraction sockets, the MOF/OGP-loaded hydrogel increased micro-CT BV/TV at 14 and 28 days relative to the blank and hydrogel-only controls. The study separately quantified new bone area from sagittal micro-CT images. H&E and Masson's trichrome staining at 28 days provided complementary evidence of new bone. These results support short-term socket bone repair, but do not establish long-term ridge

dimensional preservation, bone maturation, or suitability for subsequent implant loading.

5.2. GelMA-Based Strategies for Periodontitis-Associated Bone Loss and Defect Repair

Local GelMA-based delivery systems have been investigated as adjuncts to periodontal debridement. Tissue adhesion and sustained release are intended to improve local retention and prolong exposure to bioactive components in the oral environment. Addressing this clinical need, Qi et al. [119] utilized α-lipoic acid (LA), an endogenous mitochondrial coenzyme known for its robust anti-inflammatory, antioxidant, and pro-osteogenic properties. GelMA stabilized the PolyLA-based network, with sustained release of LA-derived species evaluated in artificial saliva. Evaluated in a moist environment, the resulting PolyLA-GelMA composite patch exhibited excellent tissue adhesion alongside potent antioxidant and antibacterial activity. In a rat periodontitis model, the patch reduced alveolar bone resorption and inflammatory changes. These findings support inflammatory control and bone preservation under the tested conditions.

Beyond small-molecule coenzymes, bioactive lipid mediators integrated with GelMA offer another avenue for the precise modulation of the periodontal microenvironment and subsequent tissue repair. Resolvins (RvDs), which are downstream metabolites of docosahexaenoic acid (DHA), exhibit potent anti-inflammatory properties by actively attenuating pro-inflammatory mediator signaling. Xing et al. [120] incorporated resolvin D1 (RvD1) into a GelMA hydrogel to construct a sustained-release delivery system. This formulation significantly enhanced the proliferation and viability of periodontal ligament cells (PDLCs) in vitro. In a rat ligature-induced periodontitis model, treatment reduced inflammatory infiltration and osteoclast-related outcomes, while micro-CT and histology supported alveolar bone repair. These findings do not establish complete functional periodontal attachment regeneration.

Li et al. [121] incorporated dexamethasone-loaded ZIF-8 nanoparticles into a poly(phosphoester) methacrylate (PPEMA)/GelMA hydrogel (DZIF@PGel). Their two-day concentration screen showed declining viability of human gingival fibroblasts and rat osteoblasts as nanoparticle loading increased, illustrating the need to define cytocompatibility for each formulation. The selected hydrogel inhibited S. mutans and P. gingivalis in culture and single-species biofilm assays and attenuated inflammation-associated alveolar bone loss in rats. These findings support antibacterial and bone-protective effects under the tested conditions; they do not establish a general safety threshold for zinc-based frameworks or efficacy against complex multispecies oral biofilms. Preservation of commensal communities and compatibility during prolonged degradation require further evaluation (Figure 13).

Deng et al. [108] used biotin–streptavidin binding to retain MSC-derived exosomes within GelMA, improving repair in an artificial periodontal multitissue defect. This model supports periodontal reconstruction but does not reproduce active periodontitis with persistent infection. The delivery design and macrophage-associated findings are discussed in Section 4.3.

Liu et al. [122] evaluated progranulin (PGRN)/GelMA as an adjunct to scaling and root planing (SRP) in dogs with Class II furcation involvement. At 8 weeks, SRP + PGRN/GelMA showed greater new bone volume and new cementum length than SRP alone or SRP + GelMA. This comparison supports an adjunctive effect of the loaded formulation in this canine model. Human clinical effectiveness and comparative efficacy against regenerative surgery or graft–membrane treatment remain to be established.

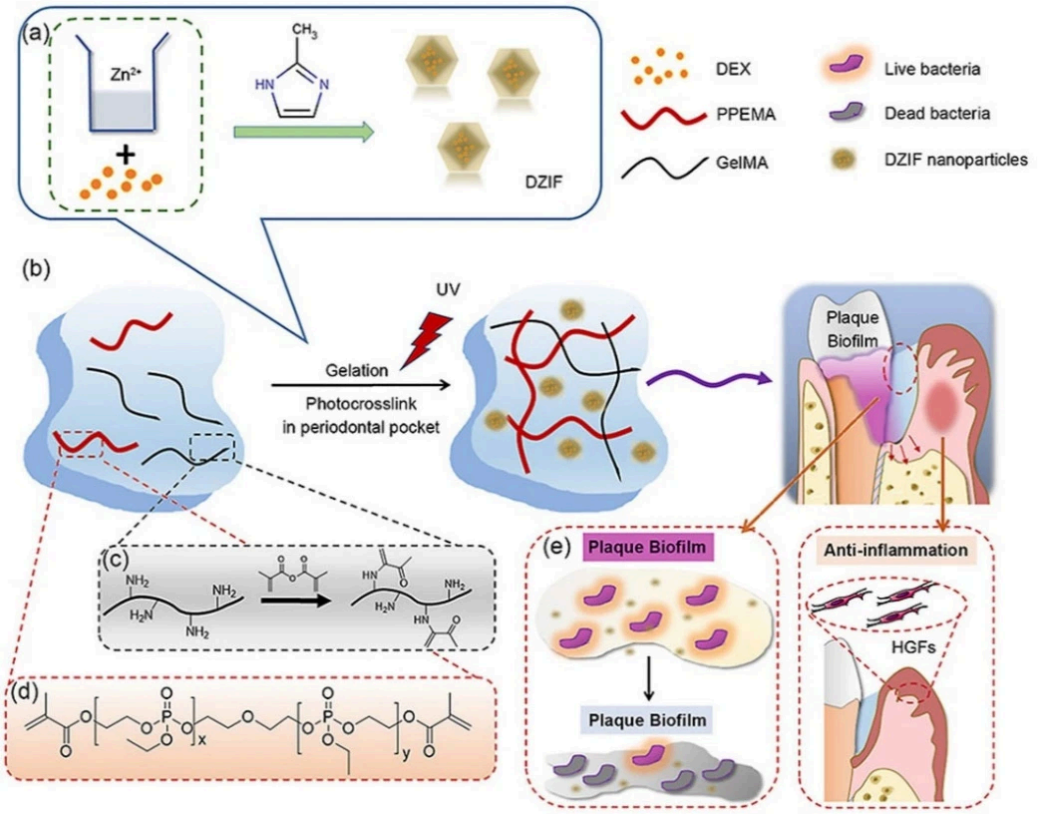

Figure 13. Design and application of the injectable DZIF/PPEMA/GelMA nanocomposite hydrogel. (**a**) Preparation of DZIF nanoparticles. (**b**–**d**) Composition and in situ UV photocrosslinking of the composite hydrogel upon injection into the periodontal pocket. (**e**) Schematic illustration of proposed antibacterial and anti-inflammatory actions within the periodontal pocket. Reproduced with permission from Ning Li et al., Materials Today Bio; published by Elsevier, 2022 [121].

5.3. Preclinical Strategies for Peri-Implantitis Management

Peri-implantitis is an important biological complication of dental implant treatment and may lead to progressive peri-implant bone loss and eventual implant failure. Its pathological progression is characterized by a vicious cycle of chronic inflammation within the peri-implant tissues and progressive alveolar bone resorption. Consequently, the development of composite biomaterials with synergistic therapeutic functions has become a focal point in preclinical biomaterials research targeting peri-implantitis.

Hu et al. [123] developed an ultrasound-responsive GelMA composite containing hematoporphyrin monomethyl ether-loaded ZIF-8 nanoparticles, BMP-2-loaded PLGA nanospheres, and metformin. Under ultrasound irradiation, the composite showed antibacterial activity in vitro. In a bacteria-induced peri-implantitis model in rats, treatment reduced peri-implant inflammation and bone loss. These findings support disease control and bone preservation; new bone formation and re-osseointegration were not established. Exosome-loaded composites provide another approach to local delivery in peri-implantitis. Liu et al. [107] evaluated NGA@UCB-Exos in a rat peri-implantitis model. At 4 weeks, treatment increased peri-implant BV/TV, BMD, trabecular thickness and trabecular number, with histological evidence of bone formation. These findings support preclinical peri-implant bone repair; quantitative bone–implant contact, durable stability and performance under sustained loading require separate evaluation.

5.4. Potential Applications in Complex Oral and Maxillofacial Bone Defects

Complex oral and maxillofacial bone defects arise from different pathological condi-

tions, including infection, congenital abnormalities, and medication-related osteonecrosis. These defects differ in their anatomical characteristics, local biological environment, and requirements for tissue reconstruction. Infected defects require control of microbial activity alongside bone repair, whereas alveolar clefts present structural challenges related to the continuity and morphology of the maxillary alveolar ridge. Medication-related osteonecrosis of the jaw (MRONJ) involves impaired bone remodeling and soft tissue healing, creating additional difficulties for regenerative treatment. GelMA-based composites have been investigated for these indications through the incorporation of structural reinforcements, antimicrobial components, and bioactive agents. However, the available evidence remains largely preclinical, and the suitability of individual formulations depends on the specific defect model and therapeutic objective.

Nie et al. [124] developed a 3D-printed multifunctional hydrogel scaffold composed of GelMA, β-tricalcium phosphate, sodium alginate, and MXene nanosheets (GTAM). The composite scaffold combined photothermal antibacterial activity with osteogenic properties and was evaluated in a Staphylococcus aureus-infected mandibular bone defect model in rats. The results demonstrated favorable infection control and bone repair within the mandibular defect environment. Although this model provides relevant evidence for infected jawbone reconstruction, the investigated defect should not be assumed to reproduce the specific anatomical and periodontal characteristics of alveolar bone defects. Further studies in infection-associated alveolar defects are therefore necessary to establish its application-specific regenerative efficacy.

Luo et al. [125] developed a 3D-printed GelMA/β-tricalcium phosphate (β-TCP) composite scaffold incorporating bone marrow mesenchymal stem cells (BMSCs), with the aim of developing a biomaterial platform for alveolar cleft reconstruction. The study evaluated scaffold morphology, mechanical properties, biocompatibility, and the osteogenic behavior of BMSCs in vitro. The results supported the feasibility of combining GelMA/β-TCP scaffolds with stem cells for bone tissue engineering. However, the study did not establish regenerative efficacy in an in vivo alveolar cleft defect model. Therefore, its relevance to alveolar cleft reconstruction should be interpreted as preliminary material-development and cellular evidence, requiring subsequent validation in anatomically appropriate defect models.

Medication-related osteonecrosis of the jaw (MRONJ) is associated with impaired jawbone remodeling and mucosal healing, creating a distinct environment for regenerative treatment. Furthermore, invasive dental procedures, such as tooth extractions, significantly elevate the risk of disease onset. To develop biomaterials capable of mitigating MRONJ incidence, Tu et al. [126] combined GelMA/polydopamine with PTH and miR-218-transfected alveolar mucosa-derived stem cells in a rat model involving zoledronic acid, dexamethasone, and surgically created wounds on healed maxillary alveolar ridges. At 21 days, the PTH- and cell-loaded formulation showed higher BV/TV than unfilled wounds (38.46 ± 10.02% versus 21.81 ± 6.18%). This analysis was restricted to specimens without sequestra. Improved mucosal coverage and changes in bone-remodeling markers were also reported.

The preclinical evidence for GelMA-based biomaterials across different oral bone-related indications and experimental models is summarized in Table 3.

Table 3. Preclinical Evidence for GelMA-Based Biomaterials across Oral Bone-Related Indications and Experimental Models. Bone repair, attenuation of inflammatory bone loss, periodontal tissue reconstruction, and re-osseointegration are distinct outcomes. Increased bone volume or reduced defect-associated bone loss alone does not establish complete functional periodontal or peri-implant regeneration.

Intended Indication	Material Format	Composite System	Experimental Model and Evidence Scope	Observed Outcome	Ref.
Alveolar defect reconstruction	Injectable hydrogel	CIO hydrogel	Non-alveolar and alveolar bone repair: rabbit calvarial and cynomolgus monkey alveolar defects.	Alveolar defect repair with CIO plus Bio-Gide; regenerated tissue compared with native bone, not a transplanted autograft.	[117]
Extraction-socket bone repair	Injectable hydrogel	GelMA-ODex	Rat maxillary incisor extraction sockets; short-term socket bone repair.	Increased micro-CT BV/TV at 14/28 days; new bone supported by H&E/Masson staining at 28 days.	[118]
Periodontal defect repair	Hydrogel	Bio-GelMA@Bio-EX	Artificial periodontal multitissue defect; not an active periodontitis model	Improved repair of artificial periodontal multitissue defects; exosome retention and macrophage responses were also evaluated.	[108]
Periodontitis	Tissue patch	PolyLA-GelMA	Rat periodontitis; inflammatory control and attenuation of alveolar bone resorption.	Wet adhesion, antibacterial and antioxidant activity, and reduced alveolar bone resorption in rat periodontitis.	[119]
Periodontitis	Hydrogel	GelMA/RvD1	Rat ligature-induced periodontitis; inflammatory control and alveolar bone repair.	Improved PDLC viability in vitro; reduced inflammation and osteoclast-related outcomes, with micro-CT and histological evidence supporting alveolar bone repair in rats.	[120]
Periodontitis	Nanocomposite hydrogel	DZIF@PGel	Rat periodontitis; attenuation of inflammation-associated alveolar bone loss.	Reduced inflammation-associated alveolar bone loss in a rat periodontitis	[121]

Intended Indication	Material Format	Composite System	Experimental Model and Evidence Scope	Observed Outcome	Ref.
				model.	
Periodontitis	Injectable hydrogel	PGRN/GelMA	Canine Class II furcation involvement; new bone and cementum formation.	Greater new bone volume and new cementum length at 8 weeks than with SRP alone or SRP + GelMA.	[122]
Peri-implantitis	Ultrasound-responsive hydrogel	HMME@ZIF-8/Met/BMP-2@PLGA/GelMA	Bacteria-induced peri-implantitis in rats; inflammatory control and bone-loss attenuation.	Reduced peri-implant inflammation and bone loss; new bone formation and re-osseointegration were not established.	[123]
Peri-implantitis	Composite hydrogel	nHAP-GelMA/algMA	Rat peri-implantitis; peri-implant bone repair, with re-osseointegration not established.	Improved peri-implant BV/TV, BMD, Tb.Th, and Tb.N at 4 weeks in rats, with histological evidence of bone formation.	[107]
Infectious Bone Defect	3D printed scaffold	GTAM (GelMA/β-TCP/SA/MXene)	S. aureus-infected rat mandibular defects; infected jawbone repair.	Improved infection control and bone repair in infected mandibular defects.	[124]
Congenital Defect (Alveolar Cleft)	3D printed scaffold	GelMA/β-TCP	In vitro BMSC/scaffold assays; no in vivo alveolar cleft model	Supported BMSC adhesion, proliferation and osteogenic differentiation in vitro.	[125]
Drug-induced Defect (MRONJ)	Adhesive scaffold	GelMA/PD	Rat MRONJ-associated maxillary alveolar ridge wounds; disease-specific mucosal and bone repair.	Improved mucosal coverage and bone repair; osteoblast–osteoclast coupling was assessed by tissue-level markers.	[126]

6. Advantages, Challenges, and Future Perspectives

6.1. Functional Attributes and Comparative Evidence

GelMA retains the Arg-Gly-Asp (RGD) cell adhesion motifs and matrix metallopro-

teinase (MMP)-responsive degradation sites of gelatin. Polymer concentration, degree of methacryloyl substitution, and photocrosslinking conditions can be adjusted to alter its material properties. These attributes provide scope for material design, but their biological consequences depend on the complete formulation and processing conditions. Improved tissue integration, adequate defect support, and reduced host immune responses cannot be inferred from these attributes alone.

Extraction sockets and defects with loss of supporting bone walls impose different requirements on a filler. Conformability and retention are relevant to both, whereas poorly contained defects require particular attention to space maintenance. Injectability alone does not establish resistance to collapse. The CIO and GelMA-ODex studies should therefore be interpreted within their respective defect configurations, rather than used to rank the two formulations [117,118].

Separating a compartment for bone formation from a barrier compartment is relevant to periodontal defects that require both tissue ingrowth and exclusion of unwanted soft tissue [86]. Whether this architecture improves durable periodontal attachment beyond early tissue formation remains unresolved.

For inflamed periodontal or peri-implant sites, immunomodulatory delivery should be evaluated as an adjunct to infection control. The relevant regenerative outcomes include new bone and, where appropriate, periodontal attachment or bone–implant integration [107,122]. A reduction in inflammatory markers alone does not identify the most suitable carrier. Table 4 summarizes the material strategies and remaining limitations.

Table 4. Comparative assessment of representative GelMA-based strategies for bone and periodontal tissue regeneration. The listed models represent separate evaluations across the cited studies and do not imply that every formulation achieved the same tissue or functional outcomes.

Material Strategy	Principal Biological Function	Representative Experimental Models	Major Limitation	Ref.
Polymer-network reinforcement and fibrous composites	Improved mechanical stability, structural support, and osteogenic cell responses	Rat alveolar bone defects; rat calvarial defects; in vitro cellular models	Mechanical reinforcement may compromise cell infiltration or degradation kinetics; validation under physiological oral loading remains limited	[59,60,66]
Inorganic and nanoparticle incorporation	Osteoconductive stimulation, mineralization, and modulation of angiogenic or inflammatory responses	In vitro osteogenic responses; ectopic mineralized tissue formation; rat calvarial repair; infected alveolar defect repair.	Variability in particle distribution and release; limited long-term safety data	[63–70]
Stimuli-	Localized	Mouse	Therapeutic	[76,77]

Material Strategy	Principal Biological Function	Representative Experimental Models	Major Limitation	Ref.
responsive delivery systems	antibacterial activity, regulated drug release, and osteoclast modulation	periodontitis; rat calvarial defects	responses depend on local stimuli; performance under fluctuating oral conditions remains insufficiently established	
Advanced biofabrication and hierarchical scaffold design	Spatial organization of cells and bioactive components, tissue-interface reconstruction, and localized delivery	In vitro interface and cellular models; subcutaneous compatibility and degradation assessment; canine periodontal tissue repair; rat periodontitis-related bone outcomes.	Manufacturing complexity and reproducibility; limited demonstration of long-term functional integration across periodontal tissues	[80,86–88]
Antibacterial and immunomodulatory composites	Suppression of microbial activity, inflammatory regulation, and attenuation of periodontal bone destruction	In vitro antibacterial and cellular assays; rat periodontitis; experimental periodontal defects	Limited validation against complex multispecies biofilms; inflammatory bone protection does not necessarily indicate complete periodontal regeneration	[90–97,108–113]
Cell-, growth factor-, and extracellular vesicle-loaded systems	Enhanced osteogenic differentiation, local bioactive-factor delivery, and modulation of the regenerative microenvironment	In vitro cell models; canine periodontal defects; diabetic rat alveolar defects; rat peri-implantitis and periodontal defects	Variability in biological cargo, loading and release; limited long-term safety data and incomplete in vivo validation of proposed molecular mechanisms	[104–107,116]

Table 4 compares GelMA-based strategies and does not establish their ranking against conventional treatments. The controls in the underlying studies are critical to this distinction. The fiber-reinforced GelMA/AMP membrane was tested against empty defects and component formulations in rat calvarial defects [66]. In canine one-wall periodontal defects, adding a GelMA/Si-HPMC membrane to nCSi scaffolds improved bone and periodontal ligament formation relative to the scaffold alone; a conventional graft–collagen membrane procedure was not included [86]. In the cynomolgus monkey alveolar defect experiment, CIO was covered with Bio-Gide, and regenerated bone was compared with native bone rather than a transplanted autograft [117]. The PGRN/GelMA study provides an adjunctive comparison against SRP-based controls [122]. These findings support specific material functions and adjunctive applications, but do not establish superiority over conventional graft–membrane treatment.

Comparative assessment should address the intended function of the complete regenerative construct. Space maintenance requires evaluation of retained augmented volume during degradation, beyond initial stiffness. Biological integration should be assessed through vascularized bone formation, material replacement, and relevant tissue interfaces. Handling benefits require comparison of placement time, retention, curing reliability, and fixation needs. Infection control should be compared under the same debridement and antimicrobial care, using relevant biofilm and host-tissue outcomes. Predictability requires reproducible defect repair and sustained function over indication-appropriate follow-up. Where matched comparisons are unavailable, these remain priorities for research rather than demonstrated therapeutic advantages.

The available quantitative data indicate that changes in GelMA formulation do not necessarily produce parallel improvements in mechanical and biological properties. In the GelMA/PEGDA system, the formulation with the highest compressive modulus was not the one selected for subsequent cell-mediated bone repair [59]. Similarly, increasing the oxidized dextran content in GelMA-based dual-network hydrogels accelerated gelation but did not consistently improve compressive properties or swelling control [118]. In BG-containing GelMA scaffolds, numerical differences in compressive properties were observed without statistically significant differences between formulations [65]. These findings underscore the importance of evaluating mechanical performance alongside cellular responses and degradation behavior. A detailed comparison of reported formulation parameters, crosslinking conditions, physicochemical properties, and biological outcomes is provided in Supplementary Table S2.

Reinforcement should be evaluated against more than initial stiffness. Additional networks, inorganic loading, and denser crosslinking can change swelling, enzymatic remodelability, and the cellular environment alongside mechanical properties. Their biological effects cannot therefore be assigned to stiffness alone. Short-term cell survival should be assessed separately from spreading, migration, nutrient transport, and tissue integration; satisfactory viability does not establish that these functions are preserved.

Cell exclusion also has different implications across a regenerative construct. Limiting soft-tissue ingress is appropriate for a GBR barrier, whereas tissue ingrowth is required in the bone-forming compartment. Reinforcement should therefore be matched to the spatial function of the material and its intended persistence, with mechanical retention assessed alongside cellular remodeling and replacement by new tissue.

6.2. Challenges

Despite encouraging preclinical findings, several challenges must be addressed before GelMA-based biomaterials can be considered for routine use in alveolar bone regeneration. Beyond their regenerative performance, clinical translation requires reliable ster-

ilization, safe photocrosslinking, reproducible manufacturing, controlled degradation, and comprehensive assessment of long-term biological responses. These considerations are particularly relevant to intraoral applications, where the materials may be exposed to oral microorganisms, inflammatory conditions, and mechanical loading.

Sterilization represents an important consideration because GelMA is a protein-derived polymer whose physicochemical properties may be altered during processing. Rizwan et al. [127] compared autoclaving, ethylene oxide treatment, and gamma irradiation and found that these methods affected hydrogel stiffness, degradation behavior, cell viability, and printability differently. Autoclaving and ethylene oxide treatment reduced compressive stiffness, whereas gamma irradiation of crosslinked hydrogels increased stiffness and delayed enzymatic degradation. Gamma irradiation of the GelMA precursor also impaired its subsequent gelation and printability. These findings indicate that sterilization procedures cannot be selected solely on the basis of antimicrobial efficacy. Their effects on the precursor, crosslinked network, and biological performance must also be evaluated. For cell-laden constructs, which are generally incompatible with terminal sterilization after cell incorporation, aseptic preparation using appropriately sterilized components requires separate validation of sterility and contamination control.

Photocrosslinking raises additional safety concerns when GelMA is intended for direct application to oral tissues. Although light-activated gelation permits minimally invasive placement and adaptation to irregular defects, the biological response depends on the photoinitiator, its concentration, irradiation wavelength and intensity, exposure duration, and degree of polymer conversion. Monteiro et al. [128] demonstrated that GelMA could be polymerized using a dental curing light while maintaining favorable viability of encapsulated odontoblast-like cells under selected conditions. However, cell viability declined with changes in irradiation time or photoinitiator concentration. Nguyen et al. [129] further reported cytotoxic effects following the combined exposure of mammalian cells to lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) and 405 nm light under specific experimental conditions. Visible-light curing therefore should not be regarded as inherently non-cytotoxic. For intraoral use, curing protocols must achieve adequate polymerization without excessive exposure of gingival, periodontal, or other adjacent tissues. Potential cytotoxicity associated with unreacted photoinitiators, residual reactive groups, and soluble reaction products also warrants evaluation.

Manufacturing reproducibility is another obstacle to the translation of GelMA-based composites. Because GelMA is synthesized from gelatin, variations in the source and properties of the starting material may influence methacryloyl functionalization and the characteristics of the final hydrogel. Grijalva Garces et al. [130] demonstrated that gelatin source, Bloom strength, and raw-material batch variability affected GelMA functionalization and hydrogel properties. Conversely, Zhu et al. [131] showed that controlled synthesis conditions could produce GelMA with consistent substitution levels and physicochemical properties across multiple batches. These findings emphasize the importance of defining reproducible manufacturing procedures and material specifications. Relevant quality attributes include the degree of methacryloyl substitution, polymer composition, precursor viscosity, photocuring behavior, mechanical properties, swelling, and degradation profile. For composite systems containing nanoparticles, growth factors, or extracellular vesicles, the consistency of component loading, distribution, and release behavior must also be established. Scale-up should establish whether increased batch volume alters mixing, temperature control, particle dispersion, or photocuring uniformity. Batch acceptance criteria should link these processing variables to composition, gelation, mechanical behavior, and the activity of incorporated biological cargo. Mechanical comparisons require consistent definitions and test conditions. Ma et

al. [59] determined compressive modulus from 0–10% strain at a crosshead speed of 1 mm/min, whereas Mei et al. [65] used approximately 5–20% strain and also reported stress at 90% deformation. These quantities describe different aspects of the response and should not be treated as interchangeable. Specimen geometry, scaffold architecture, hydration, temperature, and loading rate further affect the measured behavior. Crosshead speed should also be distinguished from strain rate, which depends on specimen height. Apparent differences between formulations may therefore reflect testing conditions as well as composition.

Monotonic compression characterizes the initial response under the selected protocol, but does not establish resistance to repeated deformation, creep, or crack growth. Small-amplitude oscillatory rheology describes viscoelasticity within its test range; precursor shear-thinning primarily informs processing and does not demonstrate shear resistance of the cured implant. Adhesion tests also depend on the interface: the lap-shear measurements of Sharifi et al. [132] used functionalized glass, which does not reproduce adhesion to wet oral tissues. These measurements alone cannot establish long-term retention in an oral defect.

Application-specific evaluation should combine relevant cyclic compression, shear, or tensile testing with assessment after fluid exposure and enzymatic aging. Loading amplitude, frequency, cycle number, hysteresis, residual deformation, and retained mechanical properties should be reported. Where exposure is expected, oral fluids and relevant pH conditions should be considered, together with stability at physiological temperature. The test configuration should reflect whether the material serves as a protected filler, a cell carrier, or a barrier membrane. Mechanical retention should also be followed alongside degradation and tissue integration, rather than inferred from the initial modulus or separate mass-loss measurements.

The degradation behavior of GelMA must also be matched to the regenerative requirements of the targeted defect. Its susceptibility to enzymatic cleavage facilitates cellular remodeling, but premature degradation may compromise space maintenance and mechanical support before sufficient new bone has formed. Conversely, excessive crosslinking may prolong material persistence and restrict cellular infiltration and matrix deposition. Degradation kinetics are influenced by GelMA concentration, degree of methacryloyl substitution, crosslinking conditions, and the composition of incorporated materials. Mei et al. [65] reported approximately 50% mass loss after 28 days in PBS, whereas the 0%, 1%, and 5% BG formulations approached complete mass loss within 60 min in 1 mg/mL collagenase II. These results illustrate the dependence of apparent degradation kinetics on the test medium. Sharifi et al. [132] demonstrated that changes in visible-light crosslinking conditions affected the mechanical properties, enzymatic degradation, and cell compatibility of GelMA hydrogels. For alveolar bone applications, degradation should therefore be assessed under conditions that account for the inflammatory and enzymatic characteristics of the intended defect, rather than relying exclusively on degradation measurements in simplified buffer systems. Longitudinal evaluation of scaffold retention, structural integrity, and new bone formation is needed to establish whether degradation and tissue replacement occur at compatible rates.

Long-term biosafety remains insufficiently characterized for many multifunctional GelMA composites. A favorable short-term viability result applies to the tested cell type, concentration, and exposure period; it does not establish compatibility throughout scaffold degradation. Evaluation should include residual synthesis reagents and photoinitiators, released metal ions, and particle-associated effects in the complete formulation. Yang et al. [103] reported circulating immunoglobulin and complement measurements within the stated reference ranges and no apparent major-organ lesions after implanta-

tion of the dECM/GelMA construct in beagles. These measurements provide initial systemic compatibility data for a formulation containing tissue-derived matrix and cells.

Loss of hydrogel mass should be distinguished from clearance of inorganic fillers. For zinc-based MOFs, monitoring should include both metal-containing species and released organic ligands [121]. Residual particles and released constituents should be followed alongside local inflammatory and foreign-body responses, tissue integration, and systemic distribution where relevant. Such assessments should determine whether antimicrobial exposure remains compatible with gingival, periodontal ligament, and bone-forming cells as the material changes.

Antibacterial results should be interpreted according to whether the assay measures planktonic growth, established single-species biofilms, or multispecies communities. Growth inhibition and biofilm biomass reduction are distinct endpoints, and neither alone establishes eradication. More representative testing should address mature biofilms, salivary conditioning, repeated exposure, and bacterial regrowth after treatment.

The effects on beneficial oral microorganisms also require direct assessment. Broad antibacterial activity does not establish preferential suppression of pathogens, and a reduction in total bacterial burden does not demonstrate restoration of a health-associated community. Studies should measure pathogen and commensal abundance, community recovery, and relevant microbial functions alongside host–cell responses.

Quantitative bone outcomes should be reported with the anatomical site, defect dimensions, follow-up period, region of interest, control group, sample size, and variability. BV/TV, calibrated BMD, and trabecular measurements obtained using different regions, segmentation thresholds, or time points should not be used to rank formulations directly. In mineral-containing composites, imaging should distinguish residual material from newly formed bone and be corroborated histologically.

Histological new bone height or area should also be distinguished from dynamic bone formation rates. Endothelial immunostaining alone does not establish vascular perfusion, and greater bone volume does not establish mature lamellar architecture or functional integration. Assessment should therefore include bone maturation and remodeling, integration with native bone, and indication-specific periodontal attachment or bone–implant contact. Functional stability under relevant loading and longer follow-up are needed to determine whether structural repair persists.

Surgical evaluation should address working time, injection or scaffold placement, retention in bleeding defects, and reproducible curing under the available intraoral illumination geometry. For use with guided bone regeneration, the intended role as a defect filler, cell carrier, or barrier should be defined. Compatibility with particulate grafts, membrane coverage, fixation, and flap closure should be assessed. Replacement studies should use the corresponding conventional treatment as an active control, whereas adjunctive studies should compare the same conventional procedure with and without the GelMA formulation.

Regulatory planning should specify the intended use, tissue contact, composition, delivery method, and target jurisdiction. Constructs containing cells, drugs, or growth factors may also raise combination-product considerations. The applicable pathway should therefore be established for the specific product rather than inferred from the GelMA matrix alone.

6.3. Future Perspectives

At the level of material design, there is an urgent need to develop stimuli-responsive crosslinked networks (by introducing pH-, enzyme-, or mechanosensitive bonds).

For example, MMP-sensitive networks could be investigated to determine whether local enzymatic activity supports material remodeling at a rate compatible with tissue formation. Simultaneously, it is imperative to optimize the surface modification technologies of inorganic nanophases, elucidate their in vivo metabolic kinetics, and support long-term safety assessment.

Regarding functional synergy, to combat complex infections, composite strategies combining broad-spectrum bacteriostatic action with targeted bactericidal agents (e.g., antimicrobial peptides combined with bacteriophages) should be explored to control or disrupt pathogenic biofilms. Future formulations should be evaluated for infection control, immune responses, vascular development, and bone repair within the same experimental model. The temporal relationships among these responses should be characterized before inferring functional coupling.

Mechanistic studies should use transcriptomic and single-cell analyses to identify candidate pathways, followed by targeted perturbation to assess their functional contribution. Pharmacological inhibition should be complemented, where feasible, by gene silencing or conditional knockout, gain-of-function, and rescue experiments. These approaches should distinguish pathway necessity from sufficiency and separate cellular differentiation mechanisms from those responsible for bone repair in relevant oral defect models. Matrix mechanosensing and mitochondrial responses should be examined within this framework. Translation requires validated, formulation-specific controls for sterility, photocuring, composition, methacryloyl substitution, rheology, cargo release and storage stability. These controls should be established before animal or clinical evaluation and should account for the mechanical, degradation and biological changes introduced by processing.

Indication-specific studies should assess ridge dimensions after extraction, periodontal attachment in periodontal defects, and bone–implant integration in peri-implantitis. Standardized endpoints, active controls, appropriate follow-up and large-animal evaluation under relevant loading should precede clinical studies of safety, feasibility and efficacy.

7. Conclusions

GelMA-based systems provide configurable matrices for cell or molecular delivery and scaffold fabrication. Their biological performance depends on composition, processing, defect geometry and local disease conditions. Network reinforcement, inorganic additives and bioactive cargo address different design requirements while introducing trade-offs among structural stability, transport, degradation and host–cell responses.

Anatomically relevant preclinical studies support several design approaches, including cell-laden GelMA constructs for alveolar defects [59,99], compartmentalized scaffold–membrane architectures and dECM-containing modules for periodontal reconstruction [86,103], bioactive delivery for extraction-socket healing [118], and PGRN delivery as an adjunct to periodontal debridement [122]. The reported outcomes include new bone formation, reconstruction of bone–ligament interfaces, or increased cementum formation, depending on the model. Other formulations remain supported mainly by cellular assays, ectopic implantation, or calvarial repair. These findings identify candidate strategies for indication-specific development.

Further development should prioritize complete formulation reporting, controlled manufacturing and photocuring, and comparison with the established treatment for each intended indication. Longitudinal studies should relate material degradation and constituent clearance to bone maturation, dimensional stability, and tissue integration. Periodontal studies should assess cementum and ligament reconstruction, whereas peri-

implant studies should quantify bone–implant contact where re-osseointegration is intended. Progress toward clinical evaluation will depend on demonstrating sustained repair and acceptable safety for the complete construct and its surgical application.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/doi/s1. Supplementary Methods S1: Bibliometric Data Collection and Analysis; Table S1: Primary Information on Research Literature Analysis; Figure S1: Annual publication trends in GelMA-based bone regeneration research (2011–2025); Figure S2: Publication volume and collaboration patterns of the top 10 most productive countries; Figure S3: Average citations and impact analysis of publications across different countries; Figure S4: Keyword co-occurrence network for the bibliometric dataset; Figure S5: Trend topics in GelMA-related bone-regeneration research; Table S2: Comparison of Formulation Parameters, Photocrosslinking Conditions, Physicochemical Properties, and Biological Outcomes of Representative GelMA-Based Biomaterials.

Author Contributions: J.Y.: Writing—original draft, visualization. Q.L.: Writing—review and editing. Y.G. (Yilin Guo): Writing—review and editing. Y.W.: Writing—review and editing. J.C.: Writing—review and editing. Y.L.: Writing—review and editing, supervision, resources, conceptualization. Y.G. (Yan Gao): Writing—review and editing, supervision, resources, conceptualization. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Scientific Research Talent Cultivation Project of Stomatological Hospital, Southern Medical University (grant number RC202303), and the Science Research Cultivation Program of Stomatological Hospital, Southern Medical University (grant number PY2023023).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new experimental data were generated. The bibliometric analysis used records retrieved from the Web of Science Core Collection. The search strategy and summary results are provided in the Supplementary Materials.

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

References

1. Tsuchida, S.; Nakayama, T. Recent Clinical Treatment and Basic Research on the Alveolar Bone. *Biomedicines* **2023**, *11*, 843. [Google Scholar] [CrossRef] [PubMed]
2. Zhu, S.; Yan, M.-Q.; Masson, A.; Chen, W.; Li, Y.-P. Cell Signaling and Transcriptional Regulation of Osteoclast Lineage Commitment, Differentiation, Bone Resorption and Diseases. *Cell Discov.* **2026**, *12*, 6. [Google Scholar] [CrossRef] [PubMed]
3. Zhu, S.; Chen, W.; Masson, A.; Li, Y.-P. Cell Signaling and Transcriptional Regulation of Osteoblast Lineage Commitment, Differentiation, Bone Formation, and Homeostasis. *Cell Discov.* **2024**, *10*, 71. [Google Scholar] [CrossRef] [PubMed]
4. Wang, L.; You, X.; Zhang, L.; Zhang, C.; Zou, W. Mechanical Regulation of Bone Remodeling. *Bone Res.* **2022**, *10*, 16. [Google Scholar] [CrossRef] [PubMed]
5. de Molon, R.S.; Vernal, R.; Oliveira, G.E.; Steffens, J.P.; Ervolino, E.; Theodoro, L.H.; van den Beucken, J.J.J.P.; Tetradis, S. Inflammatory Bone Loss and Signaling Pathways in Periodontitis: Mechanistic Insights and Emerging Therapeutic Strategies. *Bone Res.* **2026**, *14*, 1. [Google Scholar] [CrossRef] [PubMed]
6. He, L.; Liu, L.; Li, T.; Zhuang, D.; Dai, J.; Wang, B.; Bi, L. Exploring the Imbalance of Periodontitis Immune System from the Cellular to Molecular Level. *Front. Genet.* **2021**, *12*, 653209. [Google Scholar] [CrossRef] [PubMed]
7. Hull, P.S.; Worthington, H.V.; Clerehugh, V.; Tsirba, R.; Davies, R.M.; Clarkson, J.E. The Reasons for Tooth Extractions in Adults and Their Validation. *J. Dent.* **1997**, *25*, 233–237. [Google Scholar] [CrossRef] [PubMed]
8. Araújo, M.G.; Lindhe, J. Dimensional Ridge Alterations Following Tooth Extraction. An Experimental Study in the Dog. *J. Clin. Periodontol.* **2005**, *32*, 212–218. [Google Scholar] [CrossRef] [PubMed]

9. Botticelli, D.; Berglundh, T.; Lindhe, J. Hard-Tissue Alterations Following Immediate Implant Placement in Extraction Sites. *J. Clin. Periodontol.* **2004**, *31*, 820–828. [Google Scholar] [CrossRef] [PubMed]
10. Couso-Queiruga, E.; Stuhr, S.; Tattan, M.; Chambrone, L.; Avila-Ortiz, G. Post-Extraction Dimensional Changes: A Systematic Review and Meta-Analysis. *J. Clin. Periodontol.* **2021**, *48*, 126–144. [Google Scholar] [CrossRef] [PubMed]
11. Ferrus, J.; Cecchinato, D.; Pjetursson, E.B.; Lang, N.P.; Sanz, M.; Lindhe, J. Factors Influencing Ridge Alterations Following Immediate Implant Placement into Extraction Sockets. *Clin. Oral Implants Res.* **2010**, *21*, 22–29. [Google Scholar] [CrossRef] [PubMed]
12. Shakya, A.; Li, Y.; Chang, N.-W.; Liu, X. Supra-Alveolar Bone Regeneration: Progress, Challenges, and Future Perspectives. *Compos. Part B Eng.* **2024**, *283*, 111673. [Google Scholar] [CrossRef] [PubMed]
13. Duda, G.N.; Geissler, S.; Checa, S.; Tsitsilonis, S.; Petersen, A.; Schmidt-Bleek, K. The Decisive Early Phase of Bone Regeneration. *Nat. Rev. Rheumatol.* **2023**, *19*, 78–95. [Google Scholar] [CrossRef]
14. Barootchi, S.; Tavelli, L.; Majzoub, J.; Stefanini, M.; Wang, H.-L.; Avila-Ortiz, G. Alveolar Ridge Preservation: Complications and Cost-Effectiveness. *Periodontology2000* **2023**, *92*, 235–262. [Google Scholar] [CrossRef] [PubMed]
15. Wang, G.; Zhou, Y.; He, X.; Tang, X.; Lin, Z.; Wang, X.; Zhang, Y.; Hu, X.; Liang, K.; Zhang, J.; et al. Bioactive Wet Adhesive Materials for Oral Health: Strategies and Applications. *J. Mater. Chem. B* **2025**, *13*, 14494–14534. [Google Scholar] [CrossRef] [PubMed]
16. Hajishengallis, G. Periodontitis: From Microbial Immune Subversion to Systemic Inflammation. *Nat. Rev. Immunol.* **2015**, *15*, 30–44. [Google Scholar] [CrossRef] [PubMed]
17. Retzepi, M.; Donos, N. Guided Bone Regeneration: Biological Principle and Therapeutic Applications. *Clin. Oral Implants Res.* **2010**, *21*, 567–576. [Google Scholar] [CrossRef] [PubMed]
18. Wang, H.; Kang, J. Bone Grafts and Synthetic Substitutes in Dental Applications: A Comprehensive Review of Molecular Mechanisms, Materials Evolution, and Clinical Perspective. *Front. Bioeng. Biotechnol.* **2025**, *13*, 1759864. [Google Scholar] [CrossRef] [PubMed]
19. Lee, J.-H.; Kim, D.-H.; Jeong, S.-N. Comparative Assessment of Anterior Maxillary Alveolar Ridge Preservation with and without Adjunctive Use of Enamel Matrix Derivative: A Randomized Clinical Trial. *Clin. Oral Implants Res.* **2020**, *31*, 1–9. [Google Scholar] [CrossRef] [PubMed]
20. Marian, D.; Toro, G.; D'Amico, G.; Trotta, M.C.; D'Amico, M.; Petre, A.; Lile, I.; Hermenean, A.; Fratila, A. Challenges and Innovations in Alveolar Bone Regeneration: A Narrative Review on Materials, Techniques, Clinical Outcomes, and Future Directions. *Medicina* **2024**, *61*, 20. [Google Scholar] [CrossRef] [PubMed]
21. Ahmed, E.M. Hydrogel: Preparation, Characterization, and Applications: A Review. *J. Adv. Res.* **2015**, *6*, 105–121. [Google Scholar] [CrossRef] [PubMed]
22. Peppas, N.A.; Hilt, J.Z.; Khademhosseini, A.; Langer, R. Hydrogels in Biology and Medicine: From Molecular Principles to Bionanotechnology. *Adv. Mater.* **2006**, *18*, 1345–1360. [Google Scholar] [CrossRef]
23. Slaughter, B.V.; Khurshid, S.S.; Fisher, O.Z.; Khademhosseini, A.; Peppas, N.A. Hydrogels in Regenerative Medicine. *Adv. Mater.* **2009**, *21*, 3307–3329. [Google Scholar] [CrossRef] [PubMed]
24. Huang, L.; Guo, Z.; Yang, X.; Zhang, Y.; Liang, Y.; Chen, X.; Qiu, X.; Chen, X. Advancements in GelMA Bioactive Hydrogels: Strategies for Infection Control and Bone Tissue Regeneration. *Theranostics* **2025**, *15*, 460–493. [Google Scholar] [CrossRef]
25. Sun, M.; Sun, X.; Wang, Z.; Guo, S.; Yu, G.; Yang, H. Synthesis and Properties of Gelatin Methacryloyl (GelMA) Hydrogels and Their Recent Applications in Load-Bearing Tissue. *Polymers* **2018**, *10*, 1290. [Google Scholar] [CrossRef] [PubMed]
26. Klotz, B.J.; Gawlitta, D.; Rosenberg, A.J.W.P.; Malda, J.; Melchels, F.P.W. Gelatin-Methacryloyl Hydrogels: Towards Biofabrication-Based Tissue Repair. *Trends Biotechnol.* **2016**, *34*, 394–407. [Google Scholar] [CrossRef] [PubMed]
27. Nichol, J.W.; Koshy, S.T.; Bae, H.; Hwang, C.M.; Yamanlar, S.; Khademhosseini, A. Cell-Laden Microengineered Gelatin Methacrylate Hydrogels. *Biomaterials* **2010**, *31*, 5536–5544. [Google Scholar] [CrossRef] [PubMed]
28. Celikkin, N.; Mastrogiacomo, S.; Jaroszewicz, J.; Walboomers, X.F.; Swieszkowski, W. Gelatin Methacrylate Scaffold for Bone Tissue Engineering: The Influence of Polymer Concentration. *J. Biomed. Mater. Res. Part A* **2018**, *106*, 201–209. [Google Scholar] [CrossRef] [PubMed]
29. Xiao, S.; Zhao, T.; Wang, J.; Wang, C.; Du, J.; Ying, L.; Lin, J.; Zhang, C.; Hu, W.; Wang, L.; et al. Gelatin Methacrylate (GelMA)-Based Hydrogels for Cell Transplantation: An Effective Strategy for Tissue Engineering. *Stem Cell Rev. Rep.* **2019**, *15*, 664–679. [Google Scholar] [CrossRef] [PubMed]

30. Bupphathong, S.; Quiroz, C.; Huang, W.; Chung, P.-F.; Tao, H.-Y.; Lin, C.-H. Gelatin Methacrylate Hydrogel for Tissue Engineering Applications-A Review on Material Modifications. *Pharmaceuticals* **2022**, *15*, 171. [Google Scholar] [CrossRef] [PubMed]
31. Kurian, A.G.; Singh, R.K.; Patel, K.D.; Lee, J.-H.; Kim, H.-W. Multifunctional GelMA Platforms with Nanomaterials for Advanced Tissue Therapeutics. *Bioact. Mater.* **2022**, *8*, 267–295. [Google Scholar] [CrossRef] [PubMed]
32. Van Den Bulcke, A.I.; Bogdanov, B.; De Rooze, N.; Schacht, E.H.; Cornelissen, M.; Berghmans, H. Structural and Rheological Properties of Methacrylamide Modified Gelatin Hydrogels. *Biomacromolecules* **2000**, *1*, 31–38. [Google Scholar] [CrossRef] [PubMed]
33. Li, X.; Zhang, J.; Kawazoe, N.; Chen, G. Fabrication of Highly Crosslinked Gelatin Hydrogel and Its Influence on Chondrocyte Proliferation and Phenotype. *Polymers* **2017**, *9*, 309. [Google Scholar] [CrossRef] [PubMed]
34. Abdollahi Baghban, S.; Ebrahimi, M.; Bagheri-Khoulenjani, S.; Khorasani, M. A Highly Efficient Microwave-Assisted Synthesis of an LED-Curable Methacrylated Gelatin for Bio Applications. *RSC Adv.* **2021**, *11*, 14996–15009. [Google Scholar] [CrossRef] [PubMed]
35. Fairbanks, B.D.; Schwartz, M.P.; Bowman, C.N.; Anseth, K.S. Photoinitiated Polymerization of PEG-Diacrylate with Lithium Phenyl-2,4,6-Trimethylbenzoylphosphinate: Polymerization Rate and Cytocompatibility. *Biomaterials* **2009**, *30*, 6702–6707. [Google Scholar] [CrossRef] [PubMed]
36. Mironi-Harpaz, I.; Wang, D.Y.; Venkatraman, S.; Seliktar, D. Photopolymerization of Cell-Encapsulating Hydrogels: Crosslinking Efficiency versus Cytotoxicity. *Acta Biomater.* **2012**, *8*, 1838–1848. [Google Scholar] [CrossRef] [PubMed]
37. Noshadi, I.; Hong, S.; Sullivan, K.E.; Shirzaei Sani, E.; Portillo-Lara, R.; Tamayol, A.; Shin, S.R.; Gao, A.E.; Stoppel, W.L.; Black, L.D.; et al. In Vitro and In Vivo Analysis of Visible Light Crosslinkable Gelatin Methacryloyl (GelMA) Hydrogels. *Biomater. Sci.* **2017**, *5*, 2093–2105. [Google Scholar] [CrossRef] [PubMed]
38. Goto, R.; Nishida, E.; Kobayashi, S.; Aino, M.; Ohno, T.; Iwamura, Y.; Kikuchi, T.; Hayashi, J.-I.; Yamamoto, G.; Asakura, M.; et al. Gelatin Methacryloyl-Riboflavin (GelMA-RF) Hydrogels for Bone Regeneration. *Int. J. Mol. Sci.* **2021**, *22*, 1635. [Google Scholar] [CrossRef] [PubMed]
39. Wang, H.; Li, J.; Qin, R.; Guo, F.; Wang, R.; Bian, Y.; Chen, H.; Yuan, H.; Pan, Y.; Jin, J.; et al. Porous Gelatin Methacrylate Gel Engineered by Freeze-Ultraviolet Promotes Osteogenesis and Angiogenesis. *ACS Biomater. Sci. Eng.* **2024**, *10*, 5764–5773. [Google Scholar] [CrossRef] [PubMed]
40. Hutmacher, D.W. Scaffolds in Tissue Engineering Bone and Cartilage. *Biomaterials* **2000**, *21*, 2529–2543. [Google Scholar] [CrossRef] [PubMed]
41. Bose, S.; Roy, M.; Bandyopadhyay, A. Recent Advances in Bone Tissue Engineering Scaffolds. *Trends Biotechnol.* **2012**, *30*, 546–554. [Google Scholar] [CrossRef] [PubMed]
42. Chen, F.-M.; Jin, Y. Periodontal Tissue Engineering and Regeneration: Current Approaches and Expanding Opportunities. *Tissue Eng. Part B Rev.* **2010**, *16*, 219–255. [Google Scholar] [CrossRef] [PubMed]
43. Engler, A.J.; Sen, S.; Sweeney, H.L.; Discher, D.E. Matrix Elasticity Directs Stem Cell Lineage Specification. *Cell* **2006**, *126*, 677–689. [Google Scholar] [CrossRef] [PubMed]
44. Huebsch, N.; Arany, P.R.; Mao, A.S.; Shvartsman, D.; Ali, O.A.; Bencherif, S.A.; Rivera-Feliciano, J.; Mooney, D.J. Harnessing Traction-Mediated Manipulation of the Cell/Matrix Interface to Control Stem-Cell Fate. *Nat. Mater.* **2010**, *9*, 518–526. [Google Scholar] [CrossRef] [PubMed]
45. Wu, S.; Chai, Z.; Yang, Y.; Ding, R.; Gao, B.; Chen, C.; He, S.; Zhang, Z.; Wan, W.; Zou, R. Effect of Matrix Stiffness on the Osteogenic Differentiation of Human Periodontal Ligament Stem Cells in a Three-Dimensional Culture Hydrogel: A Preliminary Study. *ACS Biomater. Sci. Eng.* **2025**, *11*, 5616–5626. [Google Scholar] [CrossRef] [PubMed]
46. Fu, Y.; Wang, Y.; Cheng, B.; Zou, R.; Wan, W. Substrate Stiffness Regulates the Osteogenesis of PDLSCs via ERK-Mediated YAP Nuclear Translocation. *Int. Dent. J.* **2025**, *75*, 103852. [Google Scholar] [CrossRef] [PubMed]
47. Li, G.; Wang, Y.; Wang, D.; Cui, H.; Qin, M.; Ma, J. GelMA-Based Nanocomposites for Bone Defect Regeneration: Design, Performance, and Clinical Translation Potential. *Int. J. Nanomed.* **2026**, *21*, 583425. [Google Scholar] [CrossRef] [PubMed]
48. Gao, M.; Zhao, P.; Xing, J.; Wang, Z.; Xu, Y.; Yan, Y.; Zhang, H.; Qu, J. GelMA Encapsulating BMSCs-Exosomes Combined with Interference Screw or Suture Anchor Promotes Tendon-Bone Healing in a Rabbit Model. *Sci. Rep.* **2024**, *14*, 28212. [Google Scholar] [CrossRef] [PubMed]
49. Ma, Y.; You, Y.; Cao, L.; Liang, B.; Tian, B.; Dong, J.; Lin, H. Improved Osteogenesis by Mineralization Combined with Double-Crosslinked Hydrogel Coating for Proliferation and Differentiation of Mesenchymal Stem Cells. *Front. Bioeng. Biotechnol.* **2021**,

9, 706423. [Google Scholar] [CrossRef] [PubMed]
50. Kurian, A.G.; Mandakhbayar, N.; Singh, R.K.; Lee, J.-H.; Jin, G.; Kim, H.-W. Multifunctional Dendrimer@nanoceria Engineered GelMA Hydrogel Accelerates Bone Regeneration through Orchestrated Cellular Responses. *Mater. Today Bio* **2023**, *20*, 100664. [Google Scholar] [CrossRef] [PubMed]
51. Yu, H.; Wang, W.; Wang, H.; Zhang, W.; Zheng, Y.; Chen, L.; Huang, S.; Yan, W.; Yao, Q. Immunomodulatory and Anabolic Biphasic Scaffold with Hierarchical Biomimetic Structure Directed Osteochondral Defect Repair. *npj Regen. Med.* **2026**, *11*, 17. [Google Scholar] [CrossRef] [PubMed]
52. Zhu, J.; Wei, Y.; Yang, G.; Zhang, J.; Liu, J.; Zhang, X.; Zhu, Z.; Chen, J.; Pei, X.; Wu, D.; et al. Peptide-Based Rigid Nanorod-Reinforced Gelatin Methacryloyl Hydrogels for Osteochondral Regeneration and Additive Manufacturing. *Nat. Commun.* **2025**, *16*, 7090. [Google Scholar] [CrossRef] [PubMed]
53. Surjadi, J.U.; Aymon, B.F.G.; Carton, M.; Portela, C.M. Double-Network-Inspired Mechanical Metamaterials. *Nat. Mater.* **2025**, *24*, 945–954. [Google Scholar] [CrossRef] [PubMed]
54. Zhu, R.; Zhu, D.; Zheng, Z.; Wang, X. Tough Double Network Hydrogels with Rapid Self-Reinforcement and Low Hysteresis Based on Highly Entangled Networks. *Nat. Commun.* **2024**, *15*, 1344. [Google Scholar] [CrossRef] [PubMed]
55. Wallin, T.J.; Simonsen, L.-E.; Pan, W.; Wang, K.; Giannelis, E.; Shepherd, R.F.; Mengüç, Y. 3D Printable Tough Silicone Double Networks. *Nat. Commun.* **2020**, *11*, 4000. [Google Scholar] [CrossRef] [PubMed]
56. Yuan, Z.; Cao, Z.; Wang, H.; Wu, H.; Zheng, J.; Zhang, R.; Wu, J. Tough Hydrogels Enabled by Transient Entanglements. *Nat. Commun.* **2026**, *17*, 4145. [Google Scholar] [CrossRef] [PubMed]
57. Zhong, D.; Wang, Z.; Xu, J.; Liu, J.; Xiao, R.; Qu, S.; Yang, W. A Strategy for Tough and Fatigue-Resistant Hydrogels via Loose Cross-Linking and Dense Dehydration-Induced Entanglements. *Nat. Commun.* **2024**, *15*, 5896. [Google Scholar] [CrossRef] [PubMed]
58. Wei, A.; Wang, Q.; Liu, J.; Huang, Y.; Li, H.; Zhu, Z.; Wang, T.; Yu, Y. Co-Initiating-System Dual-Mechanism Drives the Design of Printable Entangled Polymer Multinetworks. *Nat. Commun.* **2025**, *16*, 4407. [Google Scholar] [CrossRef] [PubMed]
59. Ma, Y.; Ji, Y.; Zhong, T.; Wan, W.; Yang, Q.; Li, A.; Zhang, X.; Lin, M. Bioprinting-Based PDLSC-ECM Screening for In Vivo Repair of Alveolar Bone Defect Using Cell-Laden, Injectable and Photocrosslinkable Hydrogels. *ACS Biomater. Sci. Eng.* **2017**, *3*, 3534–3545. [Google Scholar] [CrossRef] [PubMed]
60. Aminmansour, S.; Cardoso, L.M.; Anselmi, C.; de Carvalho, A.B.G.; Rahimnejad, M.; Bottino, M.C. Development of Cerium Oxide-Laden GelMA/PCL Scaffolds for Periodontal Tissue Engineering. *Materials* **2024**, *17*, 3904. [Google Scholar] [CrossRef] [PubMed]
61. Zheng, S.; Li, D.; Liu, Q.; Tang, C.; Hu, W.; Ma, S.; Xu, Y.; Ma, Y.; Guo, Y.; Wei, B.; et al. Surface-Modified Nano-Hydroxyapatite Uniformly Dispersed on High-Porous GelMA Scaffold Surfaces for Enhanced Osteochondral Regeneration. *Int. J. Nanomed.* **2023**, *18*, 5907–5923. [Google Scholar] [CrossRef] [PubMed]
62. Wang, J.; Wang, X.; Liang, Z.; Lan, W.; Wei, Y.; Hu, Y.; Wang, L.; Lei, Q.; Huang, D. Injectable Antibacterial Ag-HA/ GelMA Hydrogel for Bone Tissue Engineering. *Front. Bioeng. Biotechnol.* **2023**, *11*, 1219460. [Google Scholar] [CrossRef] [PubMed]
63. Chen, X.; Bai, S.; Li, B.; Liu, H.; Wu, G.; Liu, S.; Zhao, Y. Fabrication of Gelatin Methacrylate/Nanohydroxyapatite Microgel Arrays for Periodontal Tissue Regeneration. *Int. J. Nanomed.* **2016**, *11*, 4707–4718. [Google Scholar] [CrossRef] [PubMed]
64. Ai, Y.; Dai, F.; Li, W.; Xu, F.; Yang, H.; Wu, J.; Yang, K.; Li, L.; Ai, F.; Song, L. Photo-Crosslinked Bioactive BG/BMSCs@GelMA Hydrogels for Bone-Defect Repairs. *Mater. Today Bio* **2023**, *23*, 100882. [Google Scholar] [CrossRef] [PubMed]
65. Mei, N.; Wu, Y.; Chen, B.; Zhuang, T.; Yu, X.; Sui, B.; Ding, T.; Liu, X. 3D-Printed Mesoporous Bioactive Glass/GelMA Biomimetic Scaffolds for Osteogenic/Cementogenic Differentiation of Periodontal Ligament Cells. *Front. Bioeng. Biotechnol.* **2022**, *10*, 950970. [Google Scholar] [CrossRef] [PubMed]
66. Dubey, N.; Ferreira, J.A.; Daghrery, A.; Aytac, Z.; Malda, J.; Bhaduri, S.B.; Bottino, M.C. Highly Tunable Bioactive Fiber-Reinforced Hydrogel for Guided Bone Regeneration. *Acta Biomater.* **2020**, *113*, 164–176. [Google Scholar] [CrossRef] [PubMed]
67. Zhou, J.; Zhao, Y.; Ling, Y.; Zhao, P.; Gao, H.; Yang, Y.; Chen, J. Microsphere-Composite Hydrogel for Recruiting Stem Cells and Promoting Osteogenic Differentiation. *ACS Appl. Bio Mater.* **2024**, *7*, 6520–6528. [Google Scholar] [CrossRef] [PubMed]
68. Luo, A.; Yao, Y.; Chen, Y.; Li, Z.; Wang, X. Gelatin Methacryloyl-Phenylboronic Acid/Hydroxyadamantane Self-Healing Microgels for the Periodontitis Treatment by Promoting Alveolar Bone Regeneration. *Int. J. Biol. Macromol.* **2025**, *303*, 140434. [Google Scholar] [CrossRef] [PubMed]
69. Li, J.; Fan, Z.; Guan, Z.; Ruan, J. Injectable MXene/Ag-HA Composite Hydrogel for Enhanced Alveolar Bone Healing and Mechanistic Study. *Front. Bioeng. Biotechnol.* **2024**, *12*, 1485437. [Google Scholar] [CrossRef] [PubMed]

70. Xia, J.; Yu, J.; Shi, W.; Liu, Y. Molybdenum Facilitates PDLSC-Based Bone Regeneration through the JAK/STAT3 Signaling Pathway. *Sci. Rep.* **2025**, *15*, 22204. [Google Scholar] [CrossRef] [PubMed]
71. Im, G.-B.; Lin, R.-Z. Bioengineering for Vascularization: Trends and Directions of Photocrosslinkable Gelatin Methacrylate Hydrogels. *Front. Bioeng. Biotechnol.* **2022**, *10*, 1053491. [Google Scholar] [CrossRef] [PubMed]
72. Tanadchangsaeng, N.; Pasanaphong, K.; Tawonsawatruk, T.; Rattanapinyopituk, K.; Tangketsarawan, B.; Rawiwet, V.; Kongchanagul, A.; Srikaew, N.; Yoyruerop, T.; Panupinthu, N.; et al. 3D Bioprinting of Fish Skin-Based Gelatin Methacryloyl (GelMA) Bio-Ink for Use as a Potential Skin Substitute. *Sci. Rep.* **2024**, *14*, 23240. [Google Scholar] [CrossRef] [PubMed]
73. Ha, J.H.; Lim, J.H.; Lee, J.M.; Chung, B.G. Electro-Responsive Conductive Blended Hydrogel Patch. *Polymers* **2023**, *15*, 2608. [Google Scholar] [CrossRef] [PubMed]
74. Li, Q.; Wang, R.; Xue, J.; Wang, R.; Zhang, S.; Kang, H.; Wang, Y.; Zhu, H.; Lv, C. ZIF-8-Modified Black Phosphorus Nanosheets Incorporated into Injectable Dual-Component Hydrogels for Enhanced Photothermal Antibacterial and Osteogenic Activities. *ACS Appl. Mater. Interfaces* **2024**, *16*, 32058–32077. [Google Scholar] [CrossRef] [PubMed]
75. Zhu, Y.; Yu, X.; Liu, H.; Li, J.; Gholipourmalekabadi, M.; Lin, K.; Yuan, C.; Wang, P. Strategies of Functionalized GelMA-Based Bioinks for Bone Regeneration: Recent Advances and Future Perspectives. *Bioact. Mater.* **2024**, *38*, 346–373. [Google Scholar] [CrossRef] [PubMed]
76. Roldan, L.; Montoya, C.; Solanki, V.; Cai, K.Q.; Yang, M.; Correa, S.; Orrego, S. A Novel Injectable Piezoelectric Hydrogel for Periodontal Disease Treatment. *ACS Appl. Mater. Interfaces* **2023**, *15*, 43441–43454. [Google Scholar] [CrossRef] [PubMed]
77. Gong, S.; Lang, S.; Wang, Y.; Li, X.; Tian, A.; Ma, J.; Ma, X. pH-Responsive Mesoporous Silica Nanoparticles Loaded with Naringin for Targeted Osteoclast Inhibition and Bone Regeneration. *Int. J. Nanomed.* **2024**, *19*, 6337–6358. [Google Scholar] [CrossRef] [PubMed]
78. Gaglio, C.G.; Baruffaldi, D.; Pirri, C.F.; Napione, L.; Frascella, F. GelMA Synthesis and Sources Comparison for 3D Multimaterial Bioprinting. *Front. Bioeng. Biotechnol.* **2024**, *12*, 1383010. [Google Scholar] [CrossRef] [PubMed]
79. Roldán, E.; Reeves, N.D.; Cooper, G.; Andrews, K. Can We Achieve Biomimetic Electrospun Scaffolds with Gelatin Alone? *Front. Bioeng. Biotechnol.* **2023**, *11*, 1160760. [Google Scholar] [CrossRef] [PubMed]
80. Vurat, M.T.; Şeker, Ş.; Lalegül-Ülker, Ö.; Parmaksiz, M.; Elçin, A.E.; Elçin, Y.M. Development of a Multicellular 3D-Bioprinted Microtissue Model of Human Periodontal Ligament-Alveolar Bone Biointerface: Towards a Pre-Clinical Model of Periodontal Diseases and Personalized Periodontal Tissue Engineering. *Genes Dis.* **2022**, *9*, 1008–1023. [Google Scholar] [CrossRef] [PubMed]
81. Yu, M.; Luo, D.; Qiao, J.; Guo, J.; He, D.; Jin, S.; Tang, L.; Wang, Y.; Shi, X.; Mao, J.; et al. A Hierarchical Bilayer Architecture for Complex Tissue Regeneration. *Bioact. Mater.* **2022**, *10*, 93–106. [Google Scholar] [CrossRef] [PubMed]
82. Ghobadi, F.; Mohammadi, M.; Kalantarzadeh, R.; Ashrafnia Menarbazari, A.; Majidi, J.; Lotfi, E.; Borhan, S.; Fatahi, Y.; Chauhan, N.P.S.; Salehi, G.; et al. Optimized Gradient of Lyophilized Platelet-Rich Plasma in Biomimetic 3D-Printed Triphasic Scaffold Based on Alginate and Gelatin for Osteochondral Tissue Engineering. *Sci. Rep.* **2026**, *16*, 6332. [Google Scholar] [CrossRef] [PubMed]
83. Hossen, S.M.M.; Khaleque, M.A.; Lim, M.-S.; Kang, J.-K.; Kim, D.-K.; Lee, H.-H.; Kim, Y.-Y. Biomimetic Strategies for Bone Regeneration: Smart Scaffolds and Multiscale Cues. *Biomimetics* **2025**, *11*, 12. [Google Scholar] [CrossRef] [PubMed]
84. Xie, X.; Wang, Y.; Li, Z.; Yang, G.; Cheng, G.; Qin, S.; Wang, H.; Zhu, L. Recent Advances in Gradient Biomimetic Scaffolds for Tendon-Bone Interface Regeneration. *Front. Bioeng. Biotechnol.* **2025**, *13*, 1629816. [Google Scholar] [CrossRef] [PubMed]
85. Lai, R.; Jiang, J.; Huo, Y.; Wang, H.; Bosiakov, S.; Lyu, Y.; Li, L. Design of Novel Graded Bone Scaffolds Based on Triply Periodic Minimal Surfaces with Multi-Functional Pores. *Front. Bioeng. Biotechnol.* **2025**, *13*, 1503582. [Google Scholar] [CrossRef] [PubMed]
86. Wei, Y.; Wang, Z.; Han, J.; Jiang, X.; Lei, L.; Yang, X.; Sun, W.; Gou, Z.; Chen, L. Modularized Bioceramic Scaffold/Hydrogel Membrane Hierarchical Architecture Beneficial for Periodontal Tissue Regeneration in Dogs. *Biomater. Res.* **2022**, *26*, 68. [Google Scholar] [CrossRef] [PubMed]
87. Zhang, X.; Hasani-Sadrabadi, M.M.; Zarubova, J.; Dashtimighadam, E.; Haghniaz, R.; Khademhosseini, A.; Butte, M.J.; Moshaverinia, A.; Aghaloo, T.; Li, S. Immunomodulatory Microneedle Patch for Periodontal Tissue Regeneration. *Matter* **2022**, *5*, 666–682. [Google Scholar] [CrossRef] [PubMed]
88. Yi, K.; Zhu, H.; Lian, X.; Tang, Z.; Li, Q. I-PRF Functionalized Gelatin Methacrylate Microspheres for Improving the Proliferation and Osteogenic Differentiation of Human Periodontal Ligament Stem Cells. *Biomed. Mater.* **2025**, *20*, 035023. [Google Scholar] [CrossRef] [PubMed]

89. Cardoso, L.M.; de Carvalho, A.B.G.; Anselmi, C.; Mahmoud, A.H.; Dal-Fabbro, R.; Basso, F.G.; Bottino, M.C. Bifunctional Naringenin-Laden Gelatin Methacryloyl Scaffolds with Osteogenic and Anti-Inflammatory Properties. *Dent. Mater.* **2024**, *40*, 1353–1363. [Google Scholar] [CrossRef] [PubMed]
90. Li, N.; Yang, M.; Feng, M.; Xu, X.; Li, Y.; Zhang, Y.; Xian, C.J.; Li, T.; Zhai, Y. Locally Delivered Hydrogel with Sustained Release of Flavonol Compound Kaempferol Mitigates Inflammatory Progression of Periodontitis and Enhances the Gut Microflora Composition in Rats. *ACS Biomater. Sci. Eng.* **2025**, *11*, 1646–1659. [Google Scholar] [CrossRef] [PubMed]
91. Zhang, Q.; Chu, F.; Xu, Y.; Wu, X.; Yu, J.; Cong, B.; Wu, Y. Osteogenesis Promotion by Injectable Methacryloylated Gelatin Containing Psoralen and Its Bacteriostatic Properties. *IET Nanobiotechnol.* **2023**, *17*, 376–386. [Google Scholar] [CrossRef] [PubMed]
92. Guo, S.; Zhang, G.; Lu, A.; Chen, Q.; Qu, Q.; Liu, M.; Liu, S.; Niu, W.; Wang, L. A Radix Dipsaci-Loaded Gelatin Methacryloyl Nanocomposite Hydrogel with Slow Release and Osteogenic Effects. *Int. J. Biol. Macromol.* **2025**, *330*, 148153. [Google Scholar] [CrossRef] [PubMed]
93. Sun, J.; Sun, M.; Li, Z.; Liu, L.; Liu, X.; Sun, Y.; Ding, G. GelMA@ginsenoside Rb3 Targets Inflammatory Microenvironment in Periodontitis via MAPK Pathway. *Gels* **2025**, *11*, 648. [Google Scholar] [CrossRef] [PubMed]
94. Liu, Y.; Li, T.; Sun, M.; Cheng, Z.; Jia, W.; Jiao, K.; Wang, S.; Jiang, K.; Yang, Y.; Dai, Z.; et al. ZIF-8 Modified Multifunctional Injectable Photopolymerizable GelMA Hydrogel for the Treatment of Periodontitis. *Acta Biomater.* **2022**, *146*, 37–48. [Google Scholar] [CrossRef] [PubMed]
95. Ma, Y.; Ghosh, S.; Kong, X.; Kalimuthu, S.; Pudipeddi, A.; Okuro, K.; Ye, Z.; Dubey, N.; Neelakantan, P. Nanoscale Bismuth Infused Bioadhesive Gelatin Methacryloyl Electrospun Mats Demonstrate Excellent Antibiofilm Activity and Biocompatibility. *Int. J. Biol. Macromol.* **2025**, *312*, 144103. [Google Scholar] [CrossRef] [PubMed]
96. Khademi, R.; Hosseini, M.A.; Kharaziha, M. An Injectable Gelatin Methacrylate Containing Surface-Imprinted Chitosan-Modified Bioglass Microspheres for Potential Periodontitis Treatment. *Int. J. Biol. Macromol.* **2025**, *302*, 140561. [Google Scholar] [CrossRef] [PubMed]
97. Zou, T.; Liang, Y.; Kang, J.; Liu, J.; Kang, W.; Jiang, S.; Zhang, C. Oxygen Enrichment Mediated by Calcium Peroxide Loaded Gelatin Methacrylate Hydrogel Eradicates Periodontal Biofilms. *Int. J. Biol. Macromol.* **2024**, *265*, 130868. [Google Scholar] [CrossRef] [PubMed]
98. Chen, F.-M.; Liu, X. Advancing Biomaterials of Human Origin for Tissue Engineering. *Prog. Polym. Sci.* **2016**, *53*, 86–168. [Google Scholar] [CrossRef] [PubMed]
99. Pan, J.; Deng, J.; Yu, L.; Wang, Y.; Zhang, W.; Han, X.; Camargo, P.H.C.; Wang, J.; Liu, Y. Investigating the Repair of Alveolar Bone Defects by Gelatin Methacrylate Hydrogels-Encapsulated Human Periodontal Ligament Stem Cells. *J. Mater. Sci. Mater. Med.* **2019**, *31*, 3. [Google Scholar] [CrossRef] [PubMed]
100. Aksel, H.; Sarkar, D.; Lin, M.H.; Buck, A.; Huang, G.T.-J. Cell-Derived Extracellular Matrix Proteins in Colloidal Microgel as a Self-Assembly Hydrogel for Regenerative Endodontics. *J. Endod.* **2022**, *48*, 527–534. [Google Scholar] [CrossRef] [PubMed]
101. Wang, W.; Zhu, Y.; Li, J.; Geng, T.; Jia, J.; Wang, X.; Yuan, C.; Wang, P. Bioprinting EphrinB2-Modified Dental Pulp Stem Cells with Enhanced Osteogenic Capacity for Alveolar Bone Engineering. *Tissue Eng. Part A* **2023**, *29*, 244–255. [Google Scholar] [CrossRef] [PubMed]
102. Tang, H.; Bi, F.; Chen, G.; Zhang, S.; Huang, Y.; Chen, J.; Xie, L.; Qiao, X.; Guo, W. 3D-Bioprinted Recombination Structure of Hertwig's Epithelial Root Sheath Cells and Dental Papilla Cells for Alveolar Bone Regeneration. *Int. J. Bioprint.* **2022**, *8*, 512. [Google Scholar] [CrossRef] [PubMed]
103. Yang, X.; Ma, Y.; Wang, X.; Yuan, S.; Huo, F.; Yi, G.; Zhang, J.; Yang, B.; Tian, W. A 3D-Bioprinted Functional Module Based on Decellularized Extracellular Matrix Bioink for Periodontal Regeneration. *Adv. Sci.* **2023**, *10*, e2205041. [Google Scholar] [CrossRef] [PubMed]
104. Miao, G.; Liang, L.; Li, W.; Ma, C.; Pan, Y.; Zhao, H.; Zhang, Q.; Xiao, Y.; Yang, X. 3D Bioprinting of a Bioactive Composite Scaffold for Cell Delivery in Periodontal Tissue Regeneration. *Biomolecules* **2023**, *13*, 1062. [Google Scholar] [CrossRef] [PubMed]
105. Hu, S.; Zhu, Y.; Yu, S.; Guo, Y.; Wang, Y.; Lv, M.; Bai, W.; Ma, P. Osteogenic Effect and Mechanism of IL-10 in Diabetic Rat Jaw Defect Mode. *Oral Dis.* **2024**, *30*, 2695–2707. [Google Scholar] [CrossRef] [PubMed]
106. Han, P.; Raveendran, N.; Liu, C.; Basu, S.; Jiao, K.; Johnson, N.; Moran, C.S.; Ivanovski, S. 3D Bioprinted Small Extracellular Vesicles from Periodontal Cells Enhance Mesenchymal Stromal Cell Function. *Biomater. Adv.* **2024**, *158*, 213770. [Google Scholar] [CrossRef] [PubMed]

107. Liu, H.; Zhu, D.; Lang, L.; Liu, M.; Yang, Z.; Zhang, Z.; Shen, Z. Umbilical Cord Blood-Derived Exosomes Deliver miR-182-5p to Therapeutically Target the MYD88/NF-κB Signaling Pathway in Rat Peri-Implantitis. *Mater. Today Bio* **2025**, *34*, 102246. [Google Scholar] [CrossRef] [PubMed]
108. Deng, D.; Li, X.; Zhang, J.-J.; Yin, Y.; Tian, Y.; Gan, D.; Wu, R.; Wang, J.; Tian, B.-M.; Chen, F.-M.; et al. Biotin-Avidin System-Based Delivery Enhances the Therapeutic Performance of MSC-Derived Exosomes. *ACS Nano* **2023**, *17*, 8530–8550. [Google Scholar] [CrossRef] [PubMed]
109. Zhuo, H.; Zhang, S.; Wang, H.; Deng, J.; Zhang, X. Gelatin Methacryloyl @MP196/Exos Hydrogel Induced Neutrophil Apoptosis and Macrophage M2 Polarization to Inhibit Periodontal Bone Loss. *Colloids Surf. B Biointerfaces* **2025**, *248*, 114466. [Google Scholar] [CrossRef] [PubMed]
110. Liu, Y.; Yan, J.; Chen, L.; Liao, Y.; Huang, L.; Tan, J. Multifunctionalized and Dual-Crosslinked Hydrogel Promotes Inflammation Resolution and Bone Regeneration via NLRP3 Inhibition in Periodontitis. *Small Struct.* **2024**, *5*, 2300281. [Google Scholar] [CrossRef]
111. Ge, X.; Hu, J.; Qi, X.; Shi, Y.; Chen, X.; Xiang, Y.; Xu, H.; Li, Y.; Zhang, Y.; Shen, J.; et al. An Immunomodulatory Hydrogel Featuring Antibacterial and Reactive Oxygen Species Scavenging Properties for Treating Periodontitis in Diabetes. *Adv. Mater.* **2025**, *37*, e2412240. [Google Scholar] [CrossRef] [PubMed]
112. Cui, Y.; Hong, S.; Xia, Y.; Li, X.; He, X.; Hu, X.; Li, Y.; Wang, X.; Lin, K.; Mao, L. Melatonin Engineering M2 Macrophage-Derived Exosomes Mediate Endoplasmic Reticulum Stress and Immune Reprogramming for Periodontitis Therapy. *Adv. Sci.* **2023**, *10*, e2302029. [Google Scholar] [CrossRef] [PubMed]
113. Xiu, Z.; Zhu, Y.; Li, X.; Jiang, X.; Feng, Y.; He, L.; Li, C.; Cai, R.; Tao, G. A Multifunctional Injectable Microsphere with Enhanced Near-Infrared Photo-Antibacterial, ROS Scavenging, and Anti-Inflammatory Properties for Periodontitis Treatment. *Theranostics* **2025**, *15*, 3750–3780. [Google Scholar] [CrossRef] [PubMed]
114. Mahmoud, A.H.; Han, Y.; Dal-Fabbro, R.; Daghrery, A.; Xu, J.; Kaigler, D.; Bhaduri, S.B.; Malda, J.; Bottino, M.C. Nanoscale β-TCP-Laden GelMA/PCL Composite Membrane for Guided Bone Regeneration. *ACS Appl. Mater. Interfaces* **2023**, *15*, 32121–32135. [Google Scholar] [CrossRef] [PubMed]
115. Chen, Y.; Guo, B.; Zhang, Y.; Bao, X.; Li, D.; Lin, J. Injectable Hypoxia-Preconditioned Human Exfoliated Deciduous Teeth Stem Cells Encapsulated within GelMA-AMP Microspheres for Bone Regeneration in Periodontitis. *Colloids Surf. B Biointerfaces* **2025**, *247*, 114452. [Google Scholar] [CrossRef] [PubMed]
116. An, N.; Yan, X.; Qiu, Q.; Zhang, Z.; Zhang, X.; Zheng, B.; Zhao, Z.; Guo, J.; Liu, Y. Human Periodontal Ligament Stem Cell Sheets Activated by Graphene Oxide Quantum Dots Repair Periodontal Bone Defects by Promoting Mitochondrial Dynamics Dependent Osteogenic Differentiation. *J. Nanobiotechnol.* **2024**, *22*, 133. [Google Scholar] [CrossRef] [PubMed]
117. Xu, R.; Zhao, Z.-Y.; Zhou, L.-X.; Chen, L.; Liu, C.-Y.; Liao, Y.-X.; Liao, X.-Y.; Wang, Z.-S.; Yang, Z.-H.; Cao, Y.; et al. GelMA-Based Moldable and Rapid-Curable Osteogenic Paste Inspired by Ceramic Craft for Alveolar Bone Defect Regeneration. *Int. J. Biol. Macromol.* **2024**, *283*, 137058. [Google Scholar] [CrossRef] [PubMed]
118. Yang, Y.; Liu, Y.; Wang, S.; Feng, X.; Lan, J.; Dong, Z. Injectable Dual Network Hydrogel Containing Mg2+-Gallate-Based MOF and Bone Growth Polypeptide for Extraction Socket Site Preservation. *ACS Biomater. Sci. Eng.* **2025**, *11*, 5600–5615. [Google Scholar] [CrossRef] [PubMed]
119. Qi, Y.; Xu, C.; Zhang, Z.; Zhang, Q.; Xu, Z.; Zhao, X.; Zhao, Y.; Cui, C.; Liu, W. Wet Environment-Induced Adhesion and Softening of Coenzyme-Based Polymer Elastic Patch for Treating Periodontitis. *Bioact. Mater.* **2024**, *35*, 259–273. [Google Scholar] [CrossRef] [PubMed]
120. Xing, Z.; Liu, J.; Cai, J.; Jiang, X.; Liang, J.; Fujio, M.; Hadler-Olsen, E.; Wang, J.; Kantarci, A.; Xue, Y. The Application of Resolvin D1-Loaded Gelatin Methacrylate in a Rat Periodontitis Model. *Pharmaceutics* **2024**, *17*, 16. [Google Scholar] [CrossRef] [PubMed]
121. Li, N.; Xie, L.; Wu, Y.; Wu, Y.; Liu, Y.; Gao, Y.; Yang, J.; Zhang, X.; Jiang, L. Dexamethasone-Loaded Zeolitic Imidazolate Frameworks Nanocomposite Hydrogel with Antibacterial and Anti-Inflammatory Effects for Periodontitis Treatment. *Mater. Today Bio* **2022**, *16*, 100360. [Google Scholar] [CrossRef] [PubMed]
122. Liu, W.; Song, A.; Wu, Y.; Gong, P.; Zhao, J.; Zhang, L.; Liu, X.; Wang, R.; Guo, H.; Yang, P. Enhanced Immunomodulation and Periodontal Regeneration Efficacy of Subgingivally Delivered Progranulin-Loaded Hydrogel as an Adjunct to Non-Surgical Treatment for Class II Furcation Involvement in Dogs. *J. Clin. Periodontol.* **2024**, *51*, 774–786. [Google Scholar] [CrossRef] [PubMed]

123. Hu, B.; Qiao, W.; Cao, Y.; Fu, X.; Song, J. A Sono-Responsive Antibacterial Nanosystem Co-Loaded with Metformin and Bone Morphogenetic Protein-2 for Mitigation of Inflammation and Bone Loss in Experimental Peri-Implantitis. *Front. Bioeng. Biotechnol.* **2024**, *12*, 1410230. [Google Scholar] [CrossRef] [PubMed]
124. Nie, R.; Sun, Y.; Lv, H.; Lu, M.; Huangfu, H.; Li, Y.; Zhang, Y.; Wang, D.; Wang, L.; Zhou, Y. 3D Printing of MXene Composite Hydrogel Scaffolds for Photothermal Antibacterial Activity and Bone Regeneration in Infected Bone Defect Models. *Nanoscale* **2022**, *14*, 8112–8129. [Google Scholar] [CrossRef] [PubMed]
125. Luo, D.; Chen, B.; Chen, Y. Stem Cells-Loaded 3D-Printed Scaffolds for the Reconstruction of Alveolar Cleft. *Front. Bioeng. Biotechnol.* **2022**, *10*, 939199. [Google Scholar] [CrossRef] [PubMed]
126. Tu, C.-C.; Chen, M.-H.; Lan, G.-Y.; Lin, Y.-T.; Lin, Y.-T.; Tai, W.-C.; Yu, J.; Chang, P.-C. A GelMA/Polydopamine Hydrogel with PTH and Osteogenically Stimulated Alveolar Mucosa-Derived Stem Cells Promotes Bone Regeneration in MRONJ-Affected Wounds. *Stem Cell Res. Ther.* **2025**, *16*, 524. [Google Scholar] [CrossRef] [PubMed]
127. Rizwan, M.; Chan, S.W.; Comeau, P.A.; Willett, T.L.; Yim, E.K.F. Effect of Sterilization Treatment on Mechanical Properties, Biodegradation, Bioactivity and Printability of GelMA Hydrogels. *Biomed. Mater.* **2020**, *15*, 065017. [Google Scholar] [CrossRef] [PubMed]
128. Monteiro, N.; Thrivikraman, G.; Athirasala, A.; Tahayeri, A.; França, C.M.; Ferracane, J.L.; Bertassoni, L.E. Photopolymerization of Cell-Laden Gelatin Methacryloyl Hydrogels Using a Dental Curing Light for Regenerative Dentistry. *Dent. Mater.* **2018**, *34*, 389–399. [Google Scholar] [CrossRef] [PubMed]
129. Nguyen, A.K.; Goering, P.L.; Elespuru, R.K.; Sarkar Das, S.; Narayan, R.J. The Photoinitiator Lithium Phenyl (2,4,6-Trimethylbenzoyl) Phosphinate with Exposure to 405 Nm Light Is Cytotoxic to Mammalian Cells but Not Mutagenic in Bacterial Reverse Mutation Assays. *Polymers* **2020**, *12*, 1489. [Google Scholar] [CrossRef] [PubMed]
130. Grijalva Garces, D.; Appoldt, L.J.; Egner, J.; Leister, N.; Hubbuch, J. The Effect of Gelatin Source on the Synthesis of Gelatin-Methacryloyl and the Production of Hydrogel Microparticles. *Gels* **2023**, *9*, 927. [Google Scholar] [CrossRef] [PubMed]
131. Zhu, M.; Wang, Y.; Ferracci, G.; Zheng, J.; Cho, N.-J.; Lee, B.H. Gelatin Methacryloyl and Its Hydrogels with an Exceptional Degree of Controllability and Batch-to-Batch Consistency. *Sci. Rep.* **2019**, *9*, 6863. [Google Scholar] [CrossRef] [PubMed]
132. Sharifi, S.; Sharifi, H.; Akbari, A.; Chodosh, J. Systematic Optimization of Visible Light-Induced Crosslinking Conditions of Gelatin Methacryloyl (GelMA). *Sci. Rep.* **2021**, *11*, 23276. [Google Scholar] [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.