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Review

Nanomaterials in Oral Regeneration: Current Advances and Future Directions

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Abstract: Oral regenerative medicine is crucial for restoring damaged enamel, dentin, pulp, and periodontium, yet conventional treatments fail to replicate native tissue hierarchy and bioactivity, causing poor integration and long-term failure. Nanomaterials, with unique properties (high surface-area-to-volume ratio, tunable chemistry, and stimuli responsiveness), address these issues. This review critically assesses the paradigm of nano-enabled strategies to achieve precise spatiotemporal control over the regenerative process. We focus on nanomaterials functional mechanisms within the oral milieu, including biomimetic mineralization, targeted bioactive cargo delivery to specific dental tissues, and intelligent modulation of cellular behavior and the local microenvironment. Inorganic nanoparticles (e.g., nano-hydroxyapatite, mesoporous silica) excel in biomimetic hardening and ion delivery; Organic nanocarriers (e.g., chitosan, PLGA, liposomes) offer superior biocompatibility and controlled release profiles; and biological nanoplatforms (e.g., exosomes, protein cages) provide unparalleled biorecognition and targeting. The review also evaluates translational hurdles (batch heterogeneity, rapid oral clearance, biosafety) and forecasts convergence with AI, 4D bioprinting, and gene editing to advance dentistry from repair to personalized restoration of oral tissues.

Keywords: oral tissue regeneration; nanoparticles; AI; CRISPR-Cas9; stimuli-responsive delivery

1. Introduction

Oral tissue regeneration represents a pivotal frontier in translational dentistry, aiming to restore structural and functional integrity in enamel, dentin, pulp, and periodontium compromised by trauma, caries, or genetic disorders [1,2]. The inherent hierarchical complexity of these tissues—ranging from nanoscale mineralized crystallites in enamel to microvascular networks in pulp—poses significant challenges for conventional restorative approaches [3–5]. Autografts and synthetic implants frequently fail to recapitulate native bioactivity and tissue architecture, resulting in suboptimal integration and long-term failure [6].

Recent advances in nanotechnology have unlocked transformative strategies to overcome these limitations (Figure 1). Engineered nanomaterials enable: Biomimetic extracellular matrix (ECM) replication (e.g., nano-hydroxyapatite for enamel crystallite alignment [7,8]); Spatiotemporally controlled delivery of bioactive factors (e.g., pH-responsive release from mesoporous silica nanoparticles [9]); Dynamic modulation of cellular behavior (e.g., graphene oxide (GO)-enhanced scaffolds activating Wnt/β-catenin signaling [10]). These functionalities arise from unique nanomaterial properties: high surface-area-to-volume ratios, tunable surface chemistry, and

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stimuli-responsive dynamics [11]. For instance, electrospun nanofibers mimic dentin ECM topology to direct odontoblast differentiation [12], while phage-derived nanoparticles enable pathogen-specific microbiome modulation [13].

Despite promising preclinical outcomes, clinical translation requires resolving key challenges: rigorous long-term biosafety assessment, scalable manufacturing, and multifunctional integration [14]. This review synthesizes progress based on the overarching nano-enabled strategy employed. We provide the mechanistic evidence supporting each nano-approach, directly compare the strengths and limitations of different nano-platforms for specific oral applications, and outline the methods for overcoming key barriers—such as batch heterogeneity, rapid clearance in the salivary environment, and long-term biosafety—to accelerate the clinical translation of these transformative technologies.

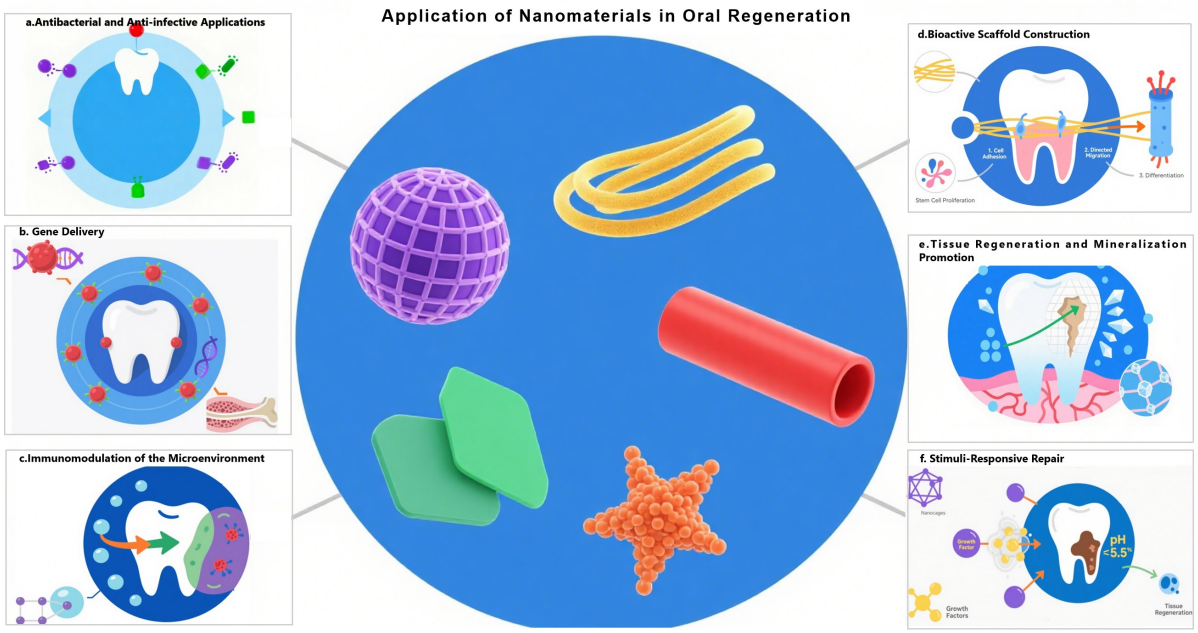

Figure 1. Applications of Nanomaterials in Oral Regeneration. (**a**). Antibacterial and Anti-infective Applications: Nanocomposites efficiently eliminate Porphyromonas gingivalis through a photodynamic mechanism. (**b**). Gene Delivery: Lipid nanoparticles deliver osteogenic genes to enhance osseointegration. (**c**). Immunomodulation of the Microenvironment: Graphene oxide scaffolds inhibit osteoclast activity and promote osteogenic differentiation. (**d**), Bioactive Scaffold Construction: PCL/nHA nanofibers mimic the topology of the dentin extracellular matrix (ECM), guiding dental pulp stem cells to differentiate into odontoblast-like cells. (**e**). Tissue Regeneration and Mineralization Promotion: Calcium phosphate nanocomposites (CPCs) serve as mineralization templates to guide oriented crystal growth. (**f**). Stimuli-Responsive Repair: Ferritin nanocages (which disassemble at pH ≤ 5.5) enable precise release of factor into carious or inflammatory microenvironments.

2. Dental Hard Tissue Regeneration: From Surface Remineralization to Pulp Vitality Preservation

The regeneration of dental hard tissues faces the dual challenges of biomimetic mineralization and deep disinfection/regeneration. This section focuses on the use of nano-strategies to reconstruct the microstructure of enamel/dentin and achieve intelligent therapy within the confined pulp chamber (Figure 1) (Table 1).

Table 1. Key Characteristics of Nanomaterials in Oral Regeneration.

Category of Nanomaterials	Subtype	Key Properties	Target/Application	Mechanism	References
Inorganic Nanoparticles (INPs)	Nano-Hydroxyapatite (nHA)	Mimics enamel/dentin inorganic composition; self-assembly; 20–80 nm size	Enamel/dentin	Guides apatite crystal growth; delivers Ca^{2+}/PO_4^{3-}; adheres to demineralized enamel	[15]
	Calcium Phosphate Composites (CPCs)	Stabilized by polyanionic polymers; tunable Ca/P ratio; rapid assembly	Enamel/dentin	Forms mineralizing membranes; recruits Ca^{2+}/PO_4^{3-}; drives oriented crystal growth	[16,17]

Table 1. *Cont.*

Category of Nanomaterials	Subtype	Key Properties	Target/Application	Mechanism	References
	Mesoporous Silica Nanoparticles (MSNs)	High surface area (≈900 m^2/g); tunable pores (2–10 nm); pH-responsive release	Pulp	Loads BMP-2 (>20 wt%); releases cargo in acidic pulp microenvironments	[18]
	Graphene oxide quantum dots	Activat human periodontal ligament stem cells (hPDLSCs)	Periodontium	Promot mitochondrial dynamics dependent osteogenic differentiation	[19]
Organic Nanoparticles (ONPs)	Chitosan Nanoparticles (CNPs)	Cationic; mucoadhesive; antimicrobial; biodegradable	Periodontium, pulp, bone	Targeted drug delivery; activates Wnt/Notch signaling; induces odontoblast differentiation	[20–22]
	Silk Fibroin Nanoparticles (SFNPs)	High tensile strength; tunable β-sheet crystallinity; biocompatible	Load-bearing oral tissues, gingiva	Provides scaffolding; encapsulates BMP-2; promotes mineral deposition	[23,24]
	PLGA Nanoparticles	FDA-approved; tunable degradation (weeks- months); controlled release	Alveolar bone, pulp, dentin tubules	Stimulates osteogenesis; releases drugs (simvastatin/lovastatin); eradicates biofilms	[25–27]
	Nanofiber Scaffolds (e.g., PCL/nHA)	200–500 nm diameter; mimics ECM topology; Ca^{2+}/PO_4^{3-} release	Dentin	Activates CaSR; phosphorylates Smad1/5/8; promotes integrin-mediated adhesion	[28–30]
	Liposomal Nanocarriers	Phospholipid bilayer; membrane fusion; cargo encapsulation (100–200 nm)	Pulp, periodontium	Delivers DDM/rutin; magneto-responsive BMP-2 release	[31,32]
	Hybrid Organic Nanocarriers	Multifunctional; targeted co-delivery; stimuli-responsive	Diabetic peri-implant sites, bone	Reduces inflammation; enhances angiogenic-osteogenic coupling; inhibits IL-6	[33,34]
Biological Nanomaterials	Protein-Based Nanocarriers (e.g., Ferritin)	pH-responsive (disassemble at ≤5.5); self-assembling; receptor targeting	Enamel, bone, pulp	Releases BMP-2 in carious niches; homes to bone via SPARC receptor	[35,36]
	Polysaccharide Nanosystems	10–500 nm; mucoadhesive; abundant active groups (hydroxyl/carboxyl)	Periodontal pockets, dentin-pulp interface	Loads drugs/growth factors; mimics ECM; directs cellular migration	[37,38]
	Nucleic-Acid Nanostructures	Programmable; biodegradable; pH/enzymatic sensitivity	Pulp, periodontium, jawbone	Delivers gene therapeutics; releases growth factors; CRISPR-Cas9-mediated pathogen clearance	[39,40]
	Lipid-Based Bio-Nanoparticles (e.g., Exosomes)	Phospholipid bilayer; low immunogenicity; barrier permeability	Maxillofacial tissue, pulp, periodontium	Transports signaling molecules; recruits stem cells; enhances differentiation	[41]

2.1. Nanomineralization Templates: Reconstructing the Biomimetic Structure and Properties of Enamel

Strategies represented by nano-hydroxyapatite (nHA) and calcium phosphate nanocomposites (CPCs) have as their core mechanism acting as "nano-seeds" and "structural templates" (Table 2). Nha (Table 3), due to its crystal structure and chemical composition similar to natural enamel, directly adsorbs onto demineralized surfaces, guiding the oriented deposition of calcium phosphate salts to achieve nanoscale defect repair [15]. The liberated Ca^{2+}/PO_4^{3-} ions from nHA mineralize the microenvironment, activating calcium-sensing receptors (CaSR) (Figure 2) and phosphorylating Smad1/5/8 to drive dental pulp stem cell (DPSC) differentiation into odontoblasts [28]. CPCs (Table 3) go a step further; their polyanionic polymers can stabilize amorphous precursors, self-assembling into a negatively charged mineralization membrane on the tooth surface that efficiently recruits calcium and phosphate ions from saliva and drives preferential crystal growth along the c-axis, thereby repairing enamel structure at the micro- and even macro-scale [17,42,43]. From

a critical perspective, the nHA strategy is more suitable for early superficial caries, while CPCs show greater clinical translation potential in terms of repair depth and speed. However, their long-term stability and compatibility with natural enamel still require verification.

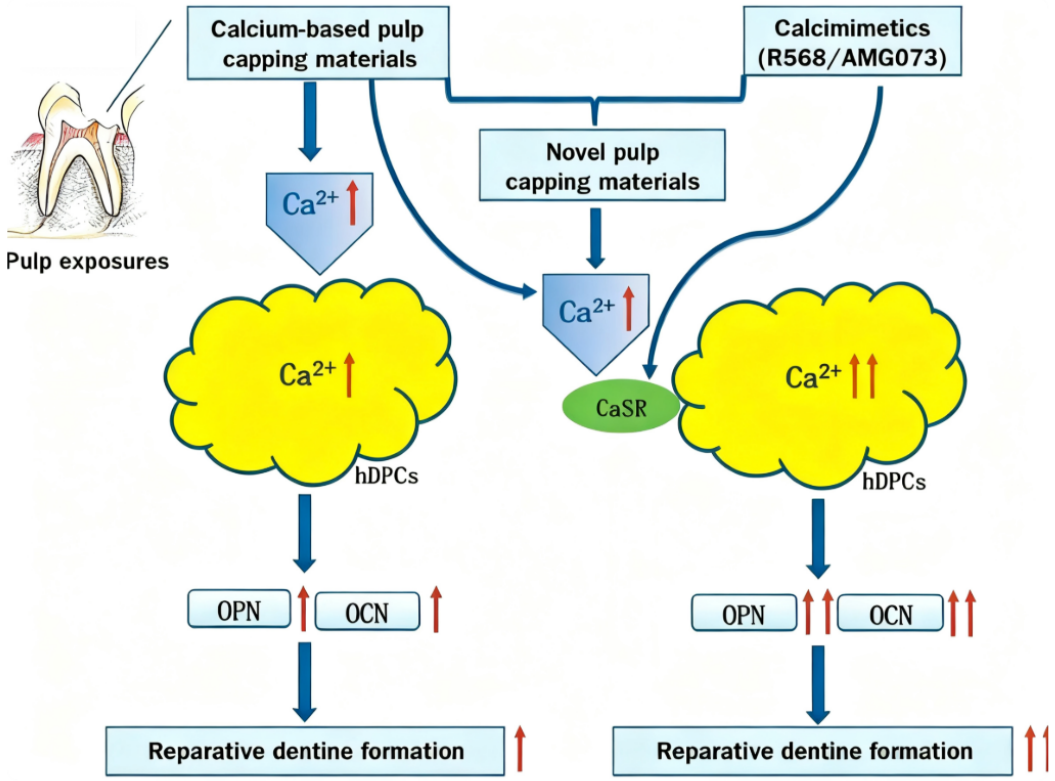

Figure 2. Diagrammatic representation of the hypothesis: CaSR as a Therapeutic Target and Tool in Human Dental Pulp [28]. Trauma would lead to accidental exposure of the dental pulp. Direct pulp capping with calcium-based pulp capping materials is a feasible therapeutic method. Elevated calcium ion (Ca^{2+}) concentrations promote the odontogenic/osteogenic differentiation and mineralisation of human dental pulp cells (hDPCs). Ca^{2+} concentrations released from the currently available direct pulp capping materials is much lower. hDPCs may express the CaSR and respond to extracellular Ca^{2+} via this receptor. Calcimimetics can promote the Ca^{2+} influx of hDPCs from the extracellular space via CaSR. We make a hypothesis that the local use of calcimimetics and calcium-based pulp capping materials could create an option for enhancing the odontogenic/osteogenic differentiation of hDPCs and improving the success rate of direct pulp capping treatments.

Table 2. The mechanism of action and targeted applications of the nanomaterials in Oral Regeneration.

Type	Core Mechanisms of Action	Targeted Applications	References
Inorganic (INPs)	- Biomimetic mineralization (via ion release, e.g., Ca^{2+}/PO_4^{3-}). - Stimuli-responsive cargo release (e.g., pH-sensitive MSNs). - Physical/chemical modulation (e.g., GO's electrical conductivity for antibacterial/osteogenic signaling).	Enamel/dentin repair (nHA, CPCs), pulp regeneration (MSNs), periodontal bone restoration (GO composites).	[16,43–45]
Organic (ONPs)	- Tunable biodegradation for sustained delivery (e.g., PLGA). - Muco-adhesion/tissue targeting (e.g., CNPs' cationic surface). - ECM-mimetic scaffolding (e.g., electrospun nanofibers).	Targeted drug delivery (CNPs, liposomes), load-bearing tissue scaffolds (SFNPs), dentin-pulp complex repair (nanofibers).	[25,26,28,29,32]
Biological	- Native biorecognition (e.g., ferritin's pH-responsive disassembly). - Receptor-guided targeting (e.g., albumin's SPARC binding). - Precision gene editing (e.g., CRISPR-functionalized DNA nanostructures).	Enamel remineralization (ferritin), bone lesion targeting (albumin), periodontal regeneration/gene therapy (DNA origami, exosomes).	[15,37,39,46–48]

Table 3. Nanomaterials in Oral Regeneration: Stages of Translation and Clinical Trials.

Nanomaterial Category	Specific Nanomaterial	Stage of Translation/Clinical Trial	References
Inorganic Nanoparticles (INPs)	Nano-Hydroxyapatite (nHA)	Preclinical with clinical application potential (partial commercial exploration)	[15]
	Calcium Phosphate Nanocomposites (CPCs, e.g., CPIC-nHA)	Advanced preclinical (near translation)	[17,42]
	Mesoporous Silica Nanoparticles (MSNs, e.g., MCM-41)	Preclinical (animal model validation)	[18]
	Graphene Oxide (GO) Nanosheets	Preclinical (with early translational exploration)	[49]
Organic Nanoparticles (ONPs)	Chitosan Nanoparticles (CNPs)	Preclinical (partial translational research)	[20–22]
	Poly (Lactic-co-Glycolic Acid) (PLGA) Nanoparticles	Preclinical (with translational potential)	[27,50]
	Electrospun Nanofiber Scaffolds (e.g., PCL/nHA)	Preclinical (near translation)	[29,30,51]
Biological Nanomaterials	Exosomes (e.g., Dental Pulp-Derived Exosomes)	Preclinical (translational research stage)	[36,38,52]
	DNA Tetrahedral Nanostructures	Preclinical (translational exploration)	[40,53]

2.2. pH-Responsive Nanodelivery Systems: Intelligent Regeneration Targeted to the Pulp Cavity

Aiming at the enclosed structure of the pulp chamber and the acidic microenvironment of inflammation/infection, mesoporous silica nanoparticles (MSNs) (Table 3) exemplify a smart delivery strategy. Their high specific surface area and tunable pore size allow for high loading capacities of bioactive factors. More importantly, through surface functionalization (e.g., amination), they achieve pH-responsive release kinetics [44]. In the mildly acidic environment of inflamed pulp, the release rate of MSNs significantly increases, ensuring precise delivery of therapeutic cargo where and when it is most needed. Critical analysis indicates that while this strategy has demonstrated enhanced pulpal angiogenesis and root maturation in canine models [18], the long-term fate and degradation behavior of silica nanoparticles within the pulp space, as well as the precise matching of release kinetics with the complex timeline of tissue regeneration, remain key challenges for its clinical translation.

3. Periodontal Tissue Repair: Integrating Antibacterial and Osteogenic Functions

Periodontal tissue regeneration occurs in a complex, bacteria-rich environment, requiring materials that simultaneously eliminate pathogens and promote the regeneration of alveolar bone, periodontal ligament, and cementum (Table 1).

3.1. Multifunctional Nanoplatforms with Antibacterial-Osteogenic Synergy

Graphene oxide (GO) nanosheets (Table 3) are a typical representative of this strategy. Their mechanism of action is multi-faceted: (1) As a scaffold component (e.g., GO/collagen composite), it provides a three-dimensional structure supporting cell growth and activates osteogenic differentiation-related signaling pathways (e.g., FAK/ERK) [45,54]; (2) Its photothermal properties enable it, upon near-infrared light irradiation, to generate reactive oxygen species or heat, effectively eliminating periodontal pathogens like *P. gingivalis* (photodynamic antimicrobial action) [19]. This combination of "scaffold function + intrinsic osteogenic induction + exogenous antibacterial activation" creates a synergistic effect favorable for periodontal regeneration. Critically, although GO exhibits excellent multifunctionality in preclinical studies, its long-term biosafety and potential chronic inflammatory responses require rigorous evaluation before clinical application.

3.2. Muco-Adhesive Targeted Delivery Systems

Facing challenges like saliva flushing and complex microflora in periodontal pockets, chitosan nanoparticles (CNPs) offer an effective strategy relying on their inherent cationic properties. Their oral-specific mechanisms include: (1) Muco-adhesion: electrostatic interaction with negatively charged mucosal surfaces, prolonging local residence time [20]; (2) Intrinsic antimicrobial activity: disrupting the cell membranes of pathogens [20]. Furthermore, functionalized CNPs (e.g., mitochondria-targeted guanidylated CNPs) can precisely regulate the intracellular oxidative state of periodontal ligament stem cells, enhancing their osteogenic potential [20]. From a comparative perspective, CNPs offer excellent biocompatibility and multifunctionality, but their degradation rate in the complex enzymatic environment of the oral cavity is difficult to control uniformly, and large-scale

production with consistent quality (molecular weight, deacetylation degree) remains a significant hurdle for industrial translation.

4. Complex Maxillofacial Defect Regeneration: Orchestrating Multi-Tissue Healing

Repairing large maxillofacial defects often requires the coordinated regeneration of multiple tissues (bone, nerve, blood vessels), demanding nano-strategies with superior mechanical properties, sustained release capabilities, and abilities to guide stem cell homing and differentiation (Table 2).

4.1. High-Strength Nanoscaffolds and Controlled-Release Platforms for Load-Bearing Bone Regeneration

Silk fibroin nanoparticles (SFNPs) leverage the inherent high tensile strength and tunable β-sheet crystallinity of silk protein to provide robust mechanical support for load-bearing areas (Table 2). For instance, BMP-2-loaded SFNPs (~200 nm) have been shown to significantly increase alkaline phosphatase activity and achieve complete repair of rabbit calvarial defects [23,55]. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles, as an FDA-approved controlled-release platform, operate through a mechanism based on hydrolytic degradation, allowing drug release profiles (e.g., simvastatin, lovastatin) to be finely tuned from weeks to months, providing a continuous osteogenic signal [25,50]. Critical assessment reveals that SFNPs require balancing mechanical strength with biodegradability, while the acidic degradation products of PLGA may cause a local pH drop, potentially inducing a mild inflammatory response—a factor that must be considered in clinical applications.

4.2. Lipid-Based Bio-Nanoparticles and Stem Cell Homing Strategies

This strategy utilizes natural lipid vesicles, particularly exosomes, as endogenous nanocarriers. Exosomes derived from dental pulp stem cells or mesenchymal stem cells carry a natural cargo of miRNAs, proteins, and lipids. Their core mechanism involves mediating intercellular communication, reprogramming recipient cells, promoting angiogenesis, and modulating immune responses, thereby facilitating the regeneration of pulp-dentin complexes and periodontal tissues (Figure 3) (Table 2) (Table 3) [52,56]. This represents a "cell-free" stem cell therapy strategy centered on bioactive cargo. Comparative perspective: Compared to synthetic nanocarriers, exosomes have lower immunogenicity and a natural ability to cross biological barriers. However, the extreme heterogeneity of exosome populations and the lack of standardized, scalable isolation and purification methods lead to significant batch-to-batch variability, which is currently the biggest obstacle to their clinical translation.

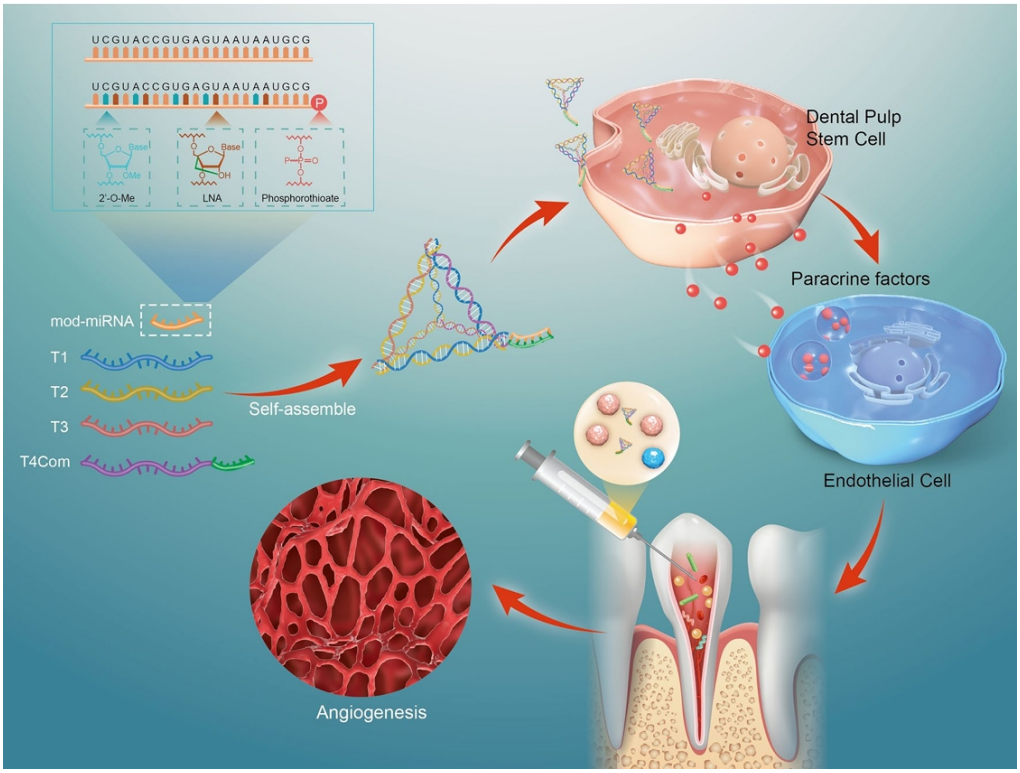

Figure 3. Illustration of microRNA-loaded tetrahedral framework nuclear acid nanostructures applied to oral regeneration [39]. This depicts the process of dental pulp regeneration facilitated by chemically modified

microRNA (miRNA)-loaded tetrahedral-framework nucleic acid nanostructures. The nanostructures enhance the delivery of miR-126-3p into dental pulp stem cells (DPSCs), improving their proliferation, migration, and upregulation of angiogenesis-related genes. This leads to enhanced paracrine signaling effects on endothelial cells, promoting their tube formation, migration, and gene expression.

5. Challenges for Nanomaterials in Oral Tissue Regeneration

5.1. Biosafety, Stability, and Degradation Control

In recent years, safety investigations of nanomaterials for oral regeneration have evolved from preliminary cytotoxicity screening toward comprehensive, long-term multi-species studies that better simulate the human oral environment. In response, mandatory "saliva-simulated stability" (S-cubed) assessment in preclinical studies; 7- and 90-day oral mucosal irritation tests in both healthy and diabetic animal models; and comprehensive mass-balance tracking of degradation products (ions, oligomers, metals) in gingival crevicular fluid and systemic circulation prior to first-in-human trials [57–59].

5.2. Persistent Bottlenecks

Nanomaterial-based therapies for oral regeneration face several persistent translational barriers. Key challenges include:

Manufacturing and Biological Hurdles: The lack of standardized protocols leads to significant batch heterogeneity in size, surface charge, and drug-loading capacity, especially for biological nanoparticles like exosomes. Furthermore, sub-100 nm nanostructures suffer from rapid clearance via enzymatic degradation and phagocytosis, leading to suboptimal biodistribution [58]. Unresolved long-term biocompatibility concerns, such as unintended immune activation, tissue accumulation, and chronic inflammation, also remain critical [57].

The Dynamic Oral Microenvironment: The oral cavity presents a uniquely challenging delivery environment characterized by: (1) Continuous salivary secretion and swallowing, which drastically limit nanocarrier retention at target sites [60,61]; (2) Abundant enzymes (e.g., amylase, lysozyme) that degrade protein- or polysaccharide-based nanocarriers [62]; (3) Dynamic pH variations (pH 5.5-7.5) that can accelerate nanomaterial degradation or cause premature drug release [63]; (4) Dense biofilm extracellular polymeric substance matrices that severely impede nanocarrier penetration [64]; and (5) Complex microbiota capable of metabolizing therapeutic agents and nanocarriers [65].

5.3. Strategic Solutions: Engineering Nano-Responsiveness to the Oral Environment

Emerging strategies are being developed to directly counter the aforementioned barriers, focusing on enhancing stability, retention, and targeted action within the oral cavity.

Combating Salivary Clearance: To overcome rapid clearance, bioadhesive strategies are employed. Chitosan Nanoparticles (CNPs), for instance, leverage their cationic surface to form strong electrostatic interactions with negatively charged salivary mucins, significantly prolonging their retention in periodontal pockets or on oral mucosa [20]. Simultaneously, surface engineering of systems like PLGA nanoparticles with hydrophilic coatings (e.g., PEGylation) creates a steric barrier that reduces both degradation by salivary enzymes and non-specific mucin adsorption, thereby ensuring sustained drug release profiles [25,50,66].

Penetrating the Biofilm Barrier: The dense biofilm matrix is targeted using agents that disrupt its integrity. Graphene Oxide (GO) nanocomposites, upon near-infrared light irradiation, generate reactive oxygen species that not only kill embedded bacteria but also degrade the EPS components, physically loosening the biofilm structure and enhancing penetration. This mechanism is pivotal for achieving high efficacy, such as the reported "99% eradication of Enterococcus faecalis biofilms" [19,27]. Integrating biofilm-degrading enzymes represents a complementary strategy to enhance biofilm penetration [67].

Leveraging pH Fluctuations for Targeted Release: The pH gradients within the oral cavity are harnessed for smart drug delivery. MSNs can be engineered with pH-responsive surface groups. In the neutral pH of healthy saliva, drug release is minimal. However, upon reaching acidic pathological niches, such as an inflamed pulp or carious lesion, the protonation of surface groups triggers pore opening and the specific release of therapeutic cargo like BMP-2, ensuring high local drug concentrations at the disease site [18,44].

Addressing Manufacturing and Systemic Challenges: To tackle batch heterogeneity, microfluidic-assisted continuous-flow reactors enable scalable production of uniform nanoparticles, including biological ones [68]. Surface modifications like PEGylation and CD47 biomimetic coating prolong circulation time and reduce

phagocytic clearance [66,69], while multimodal imaging platforms allow for real-time biodistribution tracking to optimize dosing and safety [59,70].

6. Future Prediction: Precision Oral Tissue Regeneration

Oral regenerative medicine is advancing through three synergistic technological pillars: 4D bioprinting for dynamically adaptive scaffolds, closed-loop gene editing for spatiotemporal precision, and AI-engineered nanosystems for intelligent delivery—collectively enabling functional, patient-specific reconstruction.

6.1. 4D Bioprinting: Dynamically Responsive Structural Frameworks

4D printing fabricates stimuli-responsive scaffolds via biomimetic composites (e.g., mineralized collagen inks) with tunable viscoelastic properties. Machine learning optimizes temperature/pH/mechanical responsiveness to match tissue regeneration timelines, while interfacial engineering resolves multimaterial integration challenges. Intraoperative integration with AI-driven 3D scanning enables patient-specific fabrication, contingent upon standardized biosafety validation for clinical translation.

6.2. Closed-Loop Gene Editing: Autonomous Molecular Regulation

CRISPR-Cas9 combined with nanocarriers, creates a powerful "editing-and-delivery" platform for precision therapy. This strategy, widely explored in oncology, uses nanoparticles to efficiently deliver CRISPR components, enhancing editing efficiency and targeting [71]. Its application is now extending to oral regeneration, showing potential for repairing genetic mutations [72] behind dental defects and guiding cell differentiation [73]. Evolving beyond this, closed-loop gene editing establishes a revolutionary paradigm. This system integrates implantable sensors that monitor microenvironmental signals to dynamically guide CRISPR-Cas9, enabling conditional and spatiotemporal control over gene expression for tissue repair. By synchronizing patient-specific genomic data with machine learning-optimized strategies, the framework enhances targeting precision, autonomously mitigates off-target risks, and ultimately forms a self-regulated "monitoring-decision-intervention" circuit for restoring complex tissues.

6.3. AI-Engineered Nanosystems: Intelligent Therapeutic Delivery

The integration of AI and nanotechnology is advancing the development of intelligent diagnostic systems and personalized therapeutic strategies, with emerging applications in oral regenerative medicine. For instance, AI-integrated cardiac nanosensors enable real-time tracking of heart rhythms and early detection of arrhythmias or ischemic events [74], while in oncology, nanodevices coupled with AI algorithms can detect tumor biomarkers or circulating tumor DNA to monitor cancer progression and treatment response [75,76].

Building on these foundations, AI-driven generative adversarial networks could be applied to design nanovectors that enhance transmucosal delivery efficiency, and federated learning models allow pre-screening of nanotoxicity prior to clinical use. Implantable nanosensors can further trigger the on-demand release of CRISPR-Cas9 lipid nanoparticles for site-specific gene editing, and patient-specific iPSC-derived exosomes loaded with AI-matched regenerative cargo enable precise reprogramming of the cellular microenvironment. Supported by blockchain-standardized microfluidics to ensure batch consistency, these components collectively establish a closed-loop, coordinated system for monitoring, predicting, and adaptively guiding multi-tissue regeneration. This synergistic approach, as also reflected in the work of Wang et al., who integrated machine learning with nanomedicine to decode nanoparticle biodistribution and design targeted drug delivery systems [77], marks a transition toward autonomous, responsive, and predictive oral regenerative therapy.

7. Conclusions

Nanomaterials have fundamentally expanded the toolbox for oral tissue regeneration by uniquely replicating the hierarchical nano-architecture of native dental and periodontal tissues. Their ultra-high surface area enables efficient loading of therapeutic agents, while their stimuli-responsive nature allows for the controlled release of ions, growth factors, or nucleic acids at the desired time and location. These features enable rapid biomineralization, precise control of stem-cell fate and on-demand antimicrobial action capabilities unattainable with conventional grafts or bulk scaffolds. Nevertheless, significant hurdles persist: batch-to-batch variability in size and surface chemistry, rapid endothelial clearance, and incomplete understanding of long-term nanotoxicity. Residual surfactants, endotoxin contamination and degradation products can trigger oxidative stress or immune over-reaction. To overcome these issues, microfluidic continuous-flow synthesis now delivers gram-scale monodisperse particles, while surface engineering strategies such as PEGylation or CD47-mimetic coatings

significantly prolong their retention. Furthermore, rigorous multi-species toxicological studies are helping to define safety thresholds and adverse outcome pathways. In the coming decades, the convergence of nanomaterials with artificial intelligence, 4D bioprinting, and precision gene editing is poised to create an integrated regenerative platform. This synergy will enable data-driven design, autonomous therapeutic regulation, and patient-specific epigenetic modulation, collectively transforming oral medicine from a discipline of repair to one of predictive and lifelong regeneration.

Author Contributions

S.X.: Data curation, writing—original draft preparation; P.L.: Visualization (preparation of figures and illustrations); L.Z.: Data organization (summary of comparative tables); X.F.: Data curation, writing—original draft preparation; Y.L.: Writing, reviewing and editing; Y.W.: Conceptualization, supervision. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

The authors declare no conflicts of interest. The Jilin Province Science and Technology Development Plan Item (20230204048YY) had involvement in data collection. The authors take full responsibility for the content of the published article.

Use of AI and AI-assisted Technologies

No AI tools were utilized for this paper.

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