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REVIEW

Nanoscale Approaches to Oro-Dental Tissue Engineering: A Review of Strategies, Composites, and Translational Challenges

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Abstract: Oral health is vital to human well-being. As a result, various conditions in the oral cavity, including exposure to dentin and edentulous states, lead to diverse oral issues and tissue loss. Although conventional treatments are available, they often have limitations in drug delivery and tissue regeneration. For example, delivered drugs may fail to disrupt bacterial biofilms, thereby increasing resistance within the oral microbiome and weakening immune responses. Additionally, the limited regenerative capacity of dental pulp cells can lead to serious dental emergencies. To address these challenges, innovative nanoarchitectures have been developed to improve their antimicrobial effects and enhance the regenerative potential of oral tissues for oro-dental tissue engineering. This review discusses different nanotechnological strategies for delivery and subsequent tissue engineering in the oral cavity. We first explore concepts to boost regenerative capacity, emphasizing the roles of various nanomaterials that act as antibacterial agents, activate the differentiation of human dental pulp stem cells, and support their integration with soft oral tissues. Beyond nanotherapeutic strategies involving dental implants, we also discuss nanotoxicity issues and remaining challenges in oral health. Finally, we offer perspectives on translating these developments into clinical practice.

Keywords: nanomaterials, tissue regeneration, regenerative medicine, soft tissue integration, supramolecular assemblies

Introduction

Oral health represents the overall health of human beings. Accordingly, the World Health Organization (WHO) reported that 3.5 billion people were affected by various oral-related ailments in 2022.[1,2] Various prevalent oral ailments include gum-related conditions (periodontitis and gingivitis), tooth-related issues (dental caries, enamel erosion, root infection, and edentulousness), and oral cavity-related problems (dry mouth, mouth sores, and oral cancer).[2] In addition to these notable disorders, several other oral ailments include oro-facial clefts, noma (pediatric gangrenous disease), and oro-dental trauma.[2–4] Eventually, all these dental-gum- and buccal-cavity-related ailments lead to damage to oral cavity tissues. Moreover, the limited regenerative capacity of dental pulp cells can lead to serious dental emergencies, requiring various optimal reconstruction strategies, such as scaffolding systems and dental implants.

Prior to exploring the strategies for engineering tissues in oro-dental ailments, it is imperative to understand the oral cavity in terms of specialized cellular organization (the periodontal superficial enamel layer, the middle orthodontic bony layer, and the lower endodontic dentin-pulp layers),[4] physicochemical cues in the microenvironment, aesthetic-functional necessities, and challenges within the healthcare settings.[1,5] The oral tissue cavity presents an intricate soft- and hard-tissue environment with various physicochemical cues (cellular secretions, saliva, altered pH, enzymes, and ions), along with aesthetic and functional requirements, including constant mechanical stimulation and rapid clearance of secretions.[6] The developmental origin and tissue complexity include epithelial-mesenchymal interactions, neural crest-derived ectomesenchyme, precise spatiotemporal signaling, and tight anatomical integration of the complex (multi-fold) tissue

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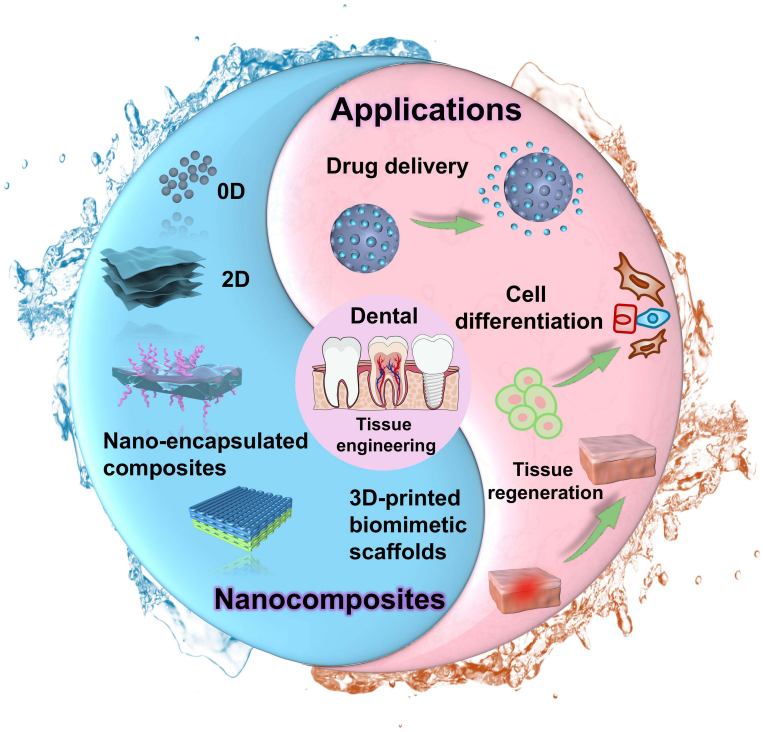
Graphical Abstract



architectures with dentin, cementum, alveolar bone, and pulp. Various specialized cells in the oral environment support the growth of complex tissue structures, including alveolar bone-derived mesenchymal stem cells (ABMSCs), dental pulp stem cells (DPSCs), gingiva-derived MSCs, and periodontal ligament stem cells (PDLSCs).[7] Accordingly, each part of the tissue architecture (periodontal tissue, Alveolar bone, dental pulp, and gingival tissue) faces common challenges and unique limitations. Among them, the major common limitation is microbial and immune-related challenges, in which the dense oral microbiome increases biofilm and infection-based risks.[8] The resultant wounds in the oral microenvironment are frequently exposed to pathogens, leading to immune-related challenges and poor healing due to acquired resistance. The periodontal tissue faces a unique challenge: coordinating the regeneration of bone and the periodontal ligament in a poorly vascularized environment. The alveolar bone is quite challenging to regenerate due to complex defect shapes and high aesthetic needs. The dental pulp in the endodontic layer of the tooth is quite narrow, posing a challenge for revascularization and resulting in undesired outcomes.[7] The gingival tissue lacks a keratinized structure, which makes it difficult to design biomaterial-based strategies. Thus, it is necessary to understand the cellular properties in the regenerative area under development when developing diverse dental-based regenerative materials.[9]

To engineer tissues for oro-dental ailments, various biomimetic scaffolds have been developed to reconstruct damaged tissues.[10,11] Nevertheless, these biomimetic scaffolds merely serve as support for tissue growth, lacking the ability to regenerate. Although various stem cell types have been explored, they lack the odontogenic potential of stem cells, resulting in poor regeneration of dental pulp cells.[12] These limitations often result in recurrent dental emergencies, prompting the need for alternative, innovative therapeutic options that improve drug delivery and enhance remineralization and regeneration capabilities.[13] Notably, the integration of nanotechnology with active species, along with biomimetic scaffolds, has demonstrated its potential for functional tissue restoration.[14–16] Due to their exceptional physicochemical (mechanical, optical, electronic, and magnetic) and morphological properties,[17,18] the encapsulated guest nanoconstructs in the scaffolds enable the host-guest cross-talks, improving the differentiation and soft tissue integration of stem cells.[19] Given their abundant surface chemistry and high surface-to-volume ratio, these nanostructured components facilitate the loading of diverse guest molecules

by either filling their pores or conjugating to the surface for targeted delivery.[20,21] From the host's perspective, the oral tissue controls the 3D topology of the composites, facilitating communication with the scaffold. To this end, the guest species offer the inherent molecular (electrical, mechanical, and physical) properties, enabling the spatiotemporal arrangement of their extracellular cues.[22] In addition to improved intercellular crosstalk, these nanocomposites may regulate mechanical signals in the ECM.[23,24] These nanoarchitectures, with compatibility, as well as colloidal and thermal stabilities, can be synthesized using various precursors, including inorganic (gold, titanium, silver, zinc oxide, calcium phosphates, MXenes, and silica) and organic (polymers and lipids) components.[25–28] Although various fields of science and technology have been using these nanoconstructs, several technological advancements have altered the landscape of medicine, including dentistry.[16,29–32]

Despite the availability of several reviews on dental-related diseases,[33–37] an overview of the use of various nanoscale components and their hybrid composites for the regeneration of oral tissues is rarely presented. Considering the first utilization of nanomaterials for engineering dental tissues in 2002,[38] we have conducted a systematic search based on the keywords "tissue engineering", "dental ailments", "hydrogels", "nanoparticles", using the "Web of Science" search engine from 2002 to 2025. This review discusses several nanotechnologies used for engineering oral tissues (Figure 1), emphasizing the detailed pathological conditions and deficiencies associated with traditional therapeutic modalities. Initially, various concepts to enhance regeneration abilities are presented, highlighting the roles of different nanomaterials, antibacterial nanomaterials, differentiation, and the integration of human dental pulp stem cells into soft tissue. Furthermore, various types of nanotechnological composites for regenerating oral tissues are reviewed, including nanoparticles and supramolecular assemblies that support cell delivery. Additionally, a note on nanotoxicity and its impact on oral health, along with the remaining challenges, is included. Finally, the article is summarized, offering interesting perspectives on its path to clinical translation.

Influence of Nanostructures

Since the advent of nanotechnology,[39] notable advances have been made in recent decades, such as the development of nanotubes by Dr. Sumio Lijima in 1991,[40] and the creation of various multidimensional architectures ranging from 0D (dots) to 3D (spheres) materials.[41] Notably, these advancements and various advantages of morphological and physicochemical features have led to the integration of nanotechnology with dentistry.[42] Several classes of nanomaterials include organic, such as polymeric (polylactic acid, PLA, polylactic-co-glycolic acid, PLGA, and chitosan),[43–47] liposomal

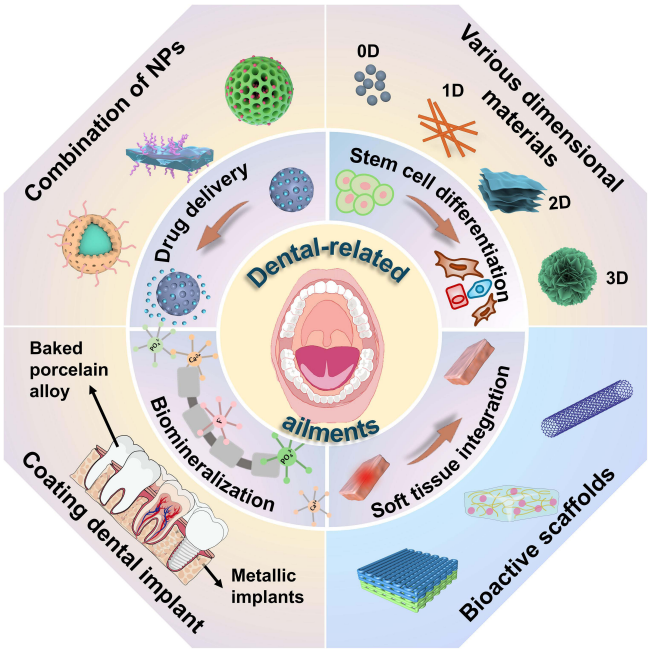


Figure 1 Schematic illustrating various roles of different nanostructures for tissue regeneration applications.

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(DSPE-PEG2000, lecithin, cholesterol),[48] dendrimer (poly(amidoamine), PAMAM),[49] as well as inorganic calcium fluoride, CaF, Au, titanium dioxide, TiO_2, Ag, mesoporous silica nanoparticles, MSNs, and iron oxide nanoparticles, IONPs).[20,25,50,51] It is worth noting that the eventual outcome can be influenced by various factors, including morphological characteristics (size and shape), particle attributes (hydrophobicity and radius), and charge, among others.[52] Accordingly, the modifications have been made by altering the surface with materials of opposite charge or supramolecular assemblies. These surface modifications enhance interactions and crosstalk between the material and cells, thereby improving biological performance. As coined by Dr. Freitas Jr, the term "nano-dentistry" describes the exploration of diverse nanomaterials and nanorobots for the regeneration of dentition, specifically robots in dentifrices, also known as dentifrobots.[53,54] Along this line, ultra-small components facilitate multiple actions in improving oral health, including the delivery of drugs, biomineralization of hard tissues, and enhanced differentiation and integration of soft tissues. In this section, we discuss the influence of several nanostructures, highlighting their roles in engineering tissues for various oral-related ailments.

Drug Delivery

Typically, dental emergencies begin with bacterial infections between the teeth and gums, such as dental caries and gingivitis, which can lead to edentulous conditions and other oral-related ailments.[45] Although traditional antimicrobial solutions act against bacteria, they suffer from several major limitations, including limited solubility of hydrophobic drugs and challenges in eradicating biofilms that develop antibacterial resistance, which limit their successful formulation.[44,55] To address these limitations, various nanomaterials, such as porous (mesoporous silica)[56] and non-porous (polymeric constructs or 1D or 2D materials)[57,58] have been employed to deliver various traditional antibiotics and other antimicrobial drugs.[59] Due to their high surface-to-volume ratio and tunable surface chemistry, several types of antibiotics are either encapsulated in their porous spaces or immobilized on the surface of nanoparticles, releasing the guest species in a spatiotemporal manner. These nanocarriers in the buccal cavity offer several advantages. Firstly, these nano-sized carriers improve the solubility of hydrophobic drugs. Secondly, the ultrasmall constructs improve deep penetration into root canals, providing a long-lasting effect through sustained drug release. These carriers can directly eradicate biofilm and microbes in the mouth, providing localized therapy. Accordingly, the localized delivery of drugs using stronger composites improves bonding, substantially increasing the efficacy and reducing systemic side effects. In recent times, active materials with drug-like features and stimuli-responsive properties facilitate effective ablation of resistant bacteria in tough biofilms, such as TiO_2.[8,60–62] These antibacterial materials act through various mechanisms, including electrostatic interactions between the surfaces of materials and bacterial membrane through crosstalk, disruption of metal ion hemostasis intracellularly, protein denaturation, and genotoxicity, as well as inhibition of signal transduction in the nucleus.[60,63–66] Regarding electrostatic interactions, positively charged nanoparticles interact more strongly with the negatively charged bacterial surface.[67] In addition to damage to the bacteria's membrane, excessive intracellular accumulation of ions (for instance, silver nanoparticles)[68,69] irreversibly affects various metabolic processes, such as respiration, division, and replication.[70] In some instances, the by-products of the designed nanomaterials, such as reactive oxygen species (ROS), can compromise cell membrane integrity, disrupt respiration, and reduce energy production. Moreover, the nanoparticles could interact intracellularly with nucleic acid molecules, inhibiting chromosomal replication and signal transduction.[71]

Biomineralization

In addition to the strategies for regeneration of oral tissues, it is worth noting to explore the treatment options for treating the teeth-related ailments (dental caries), as damaged enamel and teeth subsequently affect the oral tissues due to the uncontrollable bacterial growth. The damaged hard tissues can be treated with biologically active materials, supported by adhesives or resins, as remineralizing agents for anti-caries.[72] Sequentially, the remineralization process proceeds through the following steps: irrigation/cleaning, intracanal medicament, and obturation (filling and sealing). The utilization of nanomaterials often facilitates the remineralization of exposed collagen. These nanomaterials prevent degradation, allowing the controlled release of calcium and phosphate species, as well as encapsulated antibiotics, at low pH values, and exerting antimicrobial action, specifically, nanohydroxyapatite (nHAp) and nano-silver.[47,73] These remineralizing agents offer superior effects in repairing enamel defects by delivering ions, reducing sensitivity and post-bleaching pain,

and eradicating bacteria. Initially, irrigation is performed by explicit cleaning, demineralization, and hemorrhage control using the bleaching agents.[74] Due to the limitations of some traditional bleaching agents, including sodium hypochlorite, ethylenediaminetetraacetic acid,[75] and chlorhexidine,[76] nanoformulations with anti-biofilm efficacy have been developed to inactivate bacterial endotoxins, for instance, chitosan nanoconstructs.[77] Furthermore, the intracanal medicament (typically calcium hydroxide paste), along with antimicrobial (AgNPs)[78] and anti-inflammatory agents,[79] acts as a calcium supplement and protectant, avoiding undesirable infection after remineralization in the root canal.[80] Finally, obturation, referred to as the combination of filling and sealing, is performed using general semi-solid bulk fillers (Guttapercha,[81] and Resilon).[82] Typically, ideal bulk fillers with structural stability based on nanoparticles are encapsulated with antibiotics, thereby enhancing mechanical strength and antimicrobial properties.[11] Finally, the fillers are sealed with sealers to establish a connection with the root dentin, achieving a fluid-tight seal.[83] For instance, ZnO nanoparticles-deposited chitosan nanoconstructs are added to obturating sealers to achieve prolonged mechanical properties and enhanced remineralization.[84,85] To a considerable extent, some non-toxic remineralizing agents have been employed in pastes to deliver Ca/P ions to a liquid enamel. Generally, these nanomaterials (for instance, AgNPs) have been shown to be more effective than traditional fluoride alone at enhancing enamel hardness and fighting decay on a lab scale. It requires further investigation to demonstrate long-term efficacy and safety for clinical usage.

Stem Cell Differentiation

Usually, several oral-related conditions eventually lead to tissue loss, including during surgical interventions to treat them. Although the complex extracellular matrix (ECM) environment guides cell behavior, the regenerative capacity of oral tissues post-surgical remains highly challenging.[12] Oral tissue regeneration can be achieved by altering the oral ECM using various supplements. In several instances, various biomimetic scaffolds have been employed for dental tissue engineering, creating natural tooth-like structures (periodontal tissue, pulp, and dentin). For instance, scaffolds of natural (ECM, gelatin, HA, collagen) and synthetic (PLGA, PCL, and PLA) origin have been used to regenerate lost tissues.[86,87] These scaffolding systems often provide a conducive environment for tissue growth. Nevertheless, these scaffolds often lack cell-surface cohesion and exhibit poor spatiotemporal properties.

To guide periodontal tissue regeneration, various stem cells have been employed, including human dental pulp stem cells (hDPSCs) derived from the dental pulp of permanent teeth and periodontal ligament stem cells (PDLSCs) obtained from wisdom teeth. These stem cells, in combination with various biomimetic scaffolds, guide periodontal tissue regeneration and require stimuli to enhance their differentiation.[14] Integrating various nanotechnological products into the scaffolding system has unlocked exceptional differentiation potential for the structural restoration and functional improvement of oral tissues, ushering in a new paradigm shift in the dental field.[14,88] The integrated nanomaterials enable differentiation by altering the spatial rearrangement of extracellular cues and by improving intercellular host-guest cross-talk, thereby regulating mechanical signals in the ECM.[23,24] In return, the oral tissues can exert control over the administered nanocomposites through intercellular communication.[22] Various nanoconstructs, including organic (dendrimers) and inorganic (nHAp, silicon, calcium-based materials, and amorphous calcium phosphate, ACP), were used to enhance the differentiation of hDPSCs into odontoblastic-like cells.[10,89,90]

These encapsulated nanoparticles within the biomimetic scaffolds, along with the stem cells (hDPSCs), significantly enhance osteogenic (bone-like) and odontogenic (tooth-like) differentiation.[91] These nanoparticles influence differentiation in multiple ways, mimicking ECM-like structure, improving cell behavior, and enhancing biological efficacy. Firstly, these nanoparticles (nHA) with specific topography often replicate a natural bone-like structure, offering physical cues that direct stem cells towards bone formation (ie, osteogenic potential). nHA not only intensifies osteogenic differentiation but also improves mineralization.[92] Secondly, nanoparticles (eg, Au NPs) interact with cells within the biomimetic scaffolds, thereby improving adhesion, enhancing proliferation, and promoting differentiation. Further, the proliferated cells spread, leading to greater production of tissue matrix. Thirdly, nanoparticles (eg, bioactive glass) often release the required components, such as Ca and P species, thereby increasing alkaline phosphatase activity, a key osteogenic marker, and promoting cellular activity to enhance differentiation.[91,93] Given their physicochemical characteristics, nanoparticles can be encapsulated with differentiation enhancers and oro-protective drugs (antibiotics).[94] In a case, hDPSCs encapsulated with mineralized ECM-like components presented improved regeneration efficiency, facilitating

intrafibrillar mineralization of single-layer collagen fibrils.[90] Moreover, specific peptides (RGD) can be functionalized on nanoparticles, resulting in improved mineralization and nerve regeneration of pulp, as well as neuronal differentiation of hDPSCs.[10,89]

Soft-Tissue Integration

The soft-tissue integration of the designed scaffolds with the ECM in the oral cavity requires an understanding of the ECM's role and the influence of modified nanoarchitectures in native oral tissues. On the one hand, the nanofibrous biomolecules in the ECM (collagen, elastin, and other proteins) significantly guide cell movement and behavior, thereby influencing the encapsulated stem cells within the biomimetic scaffolds. On the other hand, integrated nanoassemblies within the scaffolds conveniently regulate mechanical and biochemical cues, thereby altering the ECM environment and providing the spatiotemporal cues for cellular growth in oro-dental regeneration. Specifically, enhanced hydrophobicity achieved by immobilizing organic linkers on nanoparticles improves the interplay between nanoparticles and cellular membranes, thereby activating their differentiation potential and intercellular crosstalk towards tissue integration.[16,46,58] For instance, the altered surface treatment of titanium discs demonstrated varied adhesion to osteoblasts and bacteria, resulting in enhanced osteoinductive performance and antibacterial efficacy.[58,95]

Typically, nanoengineered composites within biomimetic scaffolding systems promote important actions in stem cells, including adhesion, alignment, proliferation, and differentiation.[46,96] Nevertheless, poor integration and subsequent bacterial infection often lead to the failure of implanted scaffolding systems, including dental implants. These nanoengineered architectures with modulated implant-tissue interfaces are necessary to enhance the integration capabilities of implants with oral tissues, thereby promoting the long-term success of implants. In a case, Jayasree et al fabricated dual micro- and nanoscale anisotropic titania nanopores in dental implants via electrochemical anodization, followed by gallium doping.[97] These nanoengineered constructs offered exceptional surface topographical features, promoting enhanced soft-tissue integration and reduced attachment of human salivary biofilm. Nevertheless, the anodized implants with TiO_2 nanopores can significantly impede electrostimulation therapy (EST), which has been used to enhance growth factor expression and promote osseointegration. In another study, TiO_2 nanopores were transformed into conducting porous Ti architectures for EST execution to achieve soft-tissue integration and antibacterial efficacy.[6] EST enhanced the proliferation of gingival fibroblasts and collagen secretion (Figure 2), and a significant reduction in the bacterial growth (1.5 V for 5 min per day) was observed using Ti nanopores in human salivary biofilm. Together, the surface nanotopography and EST enhanced the proliferation efficiency of human gingival fibroblasts and their potential for ligament differentiation. These synergistic treatments facilitated soft-tissue integration and demonstrated exceptional bactericidal activity in a clinically relevant polymicrobial human oral salivary biofilm model. In particular, the effects of various physicochemical properties of nanoparticles in biomimetic scaffolds on cellular behavior and eventual soft integration remain unexplored. Moreover, the fabrication of such nanoengineered composites requires further optimization to enhance their performance in the applications based on oro-dental tissue engineering.

Diverse Composites for TE

Several types of nanoparticles and their composites have been designed to execute various notified functionalities (drug delivery, biomineralization, differentiation, and soft-tissue integration) for engineering oral tissues. Based on the required formulation and relevant performance, we have classified different nanoparticle-based composites, including sole nanoparticles for drug (antimicrobial) delivery and tissue differentiation, as well as nanoparticles-embedded macro-sized biomimetic scaffolds for improved tissue regeneration (osteogenesis and pulp repair). In this section, we discuss different nanoparticle-based composites for oro-dental tissue engineering, highlighting the roles of nanoparticles in improving dental health (Table 1).

Nano-Sized Particles

In terms of dental ailments, the nanoconstructs often enhance antibacterial efficacy, improve ECM, and promote stem cell differentiation with enhanced regenerative abilities.[119] Several kinds of nanoparticles from different precursors are typically classified into organic (polymeric/liposomal/micelle/dendrimer)[120] and inorganic-based materials, such as 0D nanodots

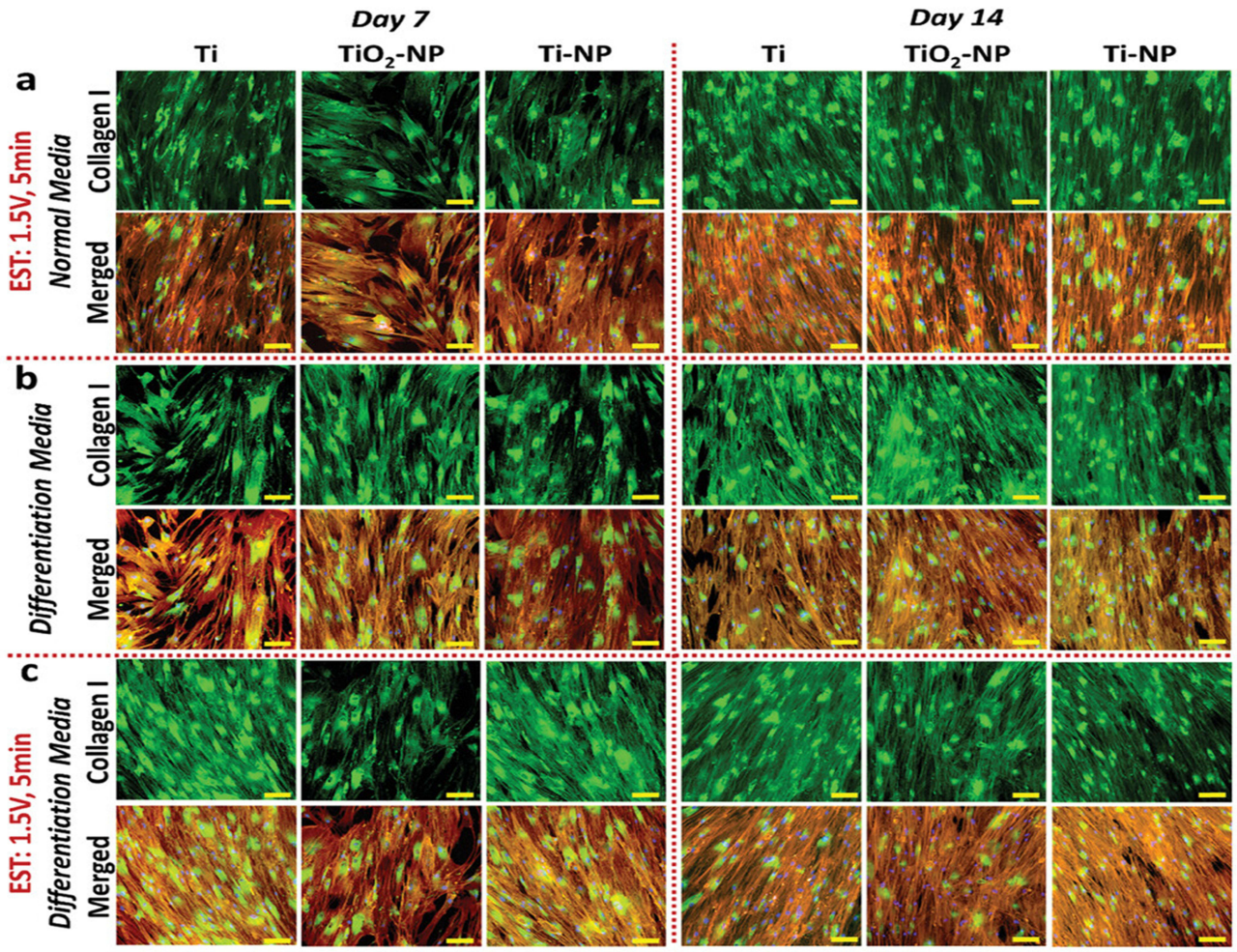

Figure 2 Influence of EST on collagen alignment. (**a**–**c**) Immunofluorescence staining of collagen I (green color), Actin filaments (red color), and nuclei (blue color) imaged by confocal microscope at days 7 and 14 (scale bar represents 100 μm). Reproduced with permission from Ref.[6] Copyright 2024, John Wiley & Sons.

(AuNPs, AgNPs, and ZnO),[105] 1D nanotubes/nanorods (carbon nanotubes and gold nanorods),[58] 2D nanosheets (MXenes and LDHs),[27,28,50] and 3D nanospheres,[93] as well as their composites.[104] Typically, organic-based assemblies are carbon-based materials, while inorganic assemblies are composed of metals and metal oxides that lack carbon/hydrogen in their structures. On the one hand, organic-based nanoassemblies with a carbon-rich environment offer exceptional biocompatibility and degradability, as well as excellent drug-delivery properties, making them suitable for carrying highly sensitive drugs (genes and proteins).[46] Nevertheless, these organic-based nanoassemblies suffer from lower stability and more rapid degradation than inorganic counterparts. Moreover, it is highly challenging to tune the physical properties. These organic-based assemblies, with an inert-like character and lacking specific optoelectrical properties, fail to activate stem cell differentiation, which is necessary for tissue regeneration. Conversely, inorganic nanoarchitectures exhibit superior stability and tunable catalytic/optical/magnetic properties, thereby promoting their growth by enriching the biochemical and mechanical cues in the ECM.[50] However, these inorganic-based structures suffer from a major limitation of accumulation-induced safety risks due to poor compatibility with biological tissues. Owing to the pros and cons of individual components, organic-inorganic composites have emerged as a promising platform for improved therapeutic functionalities in presenting antibacterial effects, inhibiting biofilm integrity, and osteogenesis through stem cell differentiation.[2,18,20]

Predominantly, low-dimensional materials (*eg*, AgNPs, IONPs, ZnO nanorods, and TiO_2 nanotubes) have been employed solely as antibacterial agents or as delivery vehicles for antibiotics against various deadly bacteria.[58,98,121] In one case, Fe_3O_4 magnetic nanoparticles loaded with minocycline were fabricated to explore their effects against bacterial-growth-assisted biofilm in periodontitis rat models.[61] Interestingly, the biofilm integrity was disrupted with the

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Table 1 A Summary of Various Nanoparticle-Based Composites for Various Functional Attributes Towards Oro-Dental Tissue Engineering

Type	Precursor	Size (nm)	Outcome	Reference
Nanoparticles solely	Graphite (for GO), Zinc acetate, Hexamethylenetetramine (HTMA)	~10-20 nm thickness (ZnO nanorods)	It showed antibacterial activity against *S. mutans*. The biocompatible constructs improved flexural strength and modulus.	[98]
	Fe_3O_4 (core), Dopamine (PDA coating), Minocycline (drug)	~273 nm	The results demonstrated magnetically guided biofilm penetration, effective eradication of periodontal pathogens (*P. gingivalis, F. nucleatum*), reduced inflammation, and promoted periodontal tissue recovery in vivo.	[61]
	$ZrOCl_2 \cdot 8H_2O$ (Zirconyl chloride), Fe source (Microwave-assisted sol-gel)	~30 nm	The designed constructs demonstrated antibacterial activity and stabilized the tetragonal phase, making them potentially suitable as dental fillers.	[99]
	Ethanolamine (for PCDs), 2,4-Difluorobenzoic acid (for FCDs), Tetraethyl orthosilicate (TEOS) (for Silica)	~2 nm	The composites presented non-destructive teeth whitening via "afterglow" photodynamic therapy (aPDT), eliminating deep stains without enamel damage or tissue toxicity.	[100]
	Ferumoxytol iron oxide nanoparticles (FerIONP)	–	The designed constructs targeted and disrupted *S. mutans* biofilms, suppressed enamel demineralization (tooth decay) via catalytic ROS generation.	[101]
	Hydroxyapatite nanoparticles (nHAp), Amelotin (AMTN) (or AMTN-Col)	~150 nm (length) ~20-70 nm (wide)	The designed constructs promoted collagen mineralization, significantly enhanced shear bond strength at the dentin-resin interface by stabilizing the hybrid layer.	[102]
	EGCG (Epigallocatechin gallate), ACP (Amorphous Calcium Phosphate)	~68 nm	The composites exhibited dual functionality, promoting enamel remineralization (via Ca/P release) and antibacterial activity against cariogenic biofilms (*S. mutans*) in acidic environments.	[103]
	Dopamine (shell), ZIF-8 (sacrificial template)	~82 nm	High drug loading capacity and sustained release of osteogenic drugs promoted osteogenic differentiation of rBMSCs and effective bone regeneration in vivo (tooth extraction fossa model).	[104]
Nanoparticles in microconstructs	Titanium (Ti) (via electrochemical anodization)	–	These constructs triggered soft-tissue integration (enhanced fibroblast proliferation/collagen secretion) and bactericidal efficacy under electrical stimulation.	[6]
	$CaCO_3$, $Ca(OH)_2$, MTA (Mineral Trioxide Aggregate)	Micro-sized powder inducing nanoscale mineralization	The composites promoted hDPSC differentiation into odontoblast-like cells, significantly upregulated MEPE (early differentiation marker) and ALP activity, and induced calcium deposition via bioactive ion release.	[93]
	ZnO nanoparticles, Mesoporous TiO_2 (on Ti substrate)	~50-100 nm	The sustained Zn^{2+} release and synergistic effect promoted osseointegration (osteogenic activity) and inhibited bacterial infection.	[105]

(*Continued*)

Table 1 (Continued).

Type	Precursor	Size (nm)	Outcome	Reference
	Simvastatin (drug), PLGA (nanoparticle), GelMA (microsphere), SHEDs (cells)	~578 nm	Vascularized pulp-like tissue regeneration, Sustained release of simvastatin promoted odontogenic differentiation and angiogenesis in vivo.	[106]
	$AgNO_3$ (Silver nitrate)	~25 nm	In addition to antibacterial (against *S. aureus* and *E. coli*) effects, these constructs showed enhanced bioactivity (hydroxyapatite formation) and cytocompatibility with osteoblast-like cells.	[70]
	Titanium (substrate, via anodization), Gallium (dopant)	~57 nm	These nanoparticles promoted soft-tissue integration (gingival fibroblast adhesion/ proliferation) and demonstrated significant antibacterial efficacy against salivary biofilms.	[97]
	PEEK (substrate), Silver (Ag) (sputtering target)	~3-12 nm (thickness)	In addition to strong antibacterial activity (>97% against *S. aureus* and *E. coli*), they demonstrated good cytocompatibility and stability, thereby preventing implant-related infections.	[107]
	Boron Nitride Nanosheets (BNNs), DMAHDM (Dimethylaminohexadecyl methacrylate)	~342 nm (lateral size) ~50-80 nm (diameter)	These nanosheets with significantly enhanced mechanical properties (Flexural strength +53%, Compressive strength +97% at 0.8 wt%) offered sustained antibacterial activity against *S. mutans* (>90% inhibition).	[108]
Nanoparticles in macro-sized scaffolds	Chitin (dissolved in NaOH/Urea), ZnO Nanoparticles	~20 nm	In addition to antibacterial (against *P. gingivalis* and *S. aureus*), these composites promoted osteogenesis and periodontal tissue regeneration (in a rat periodontal defect model).	[109]
	Ti_3C_2Tx MXene (nanosheets), Gelatin, ε-Poly-L-lysine (ε-PL)	–	The designed MXene-based nanosheets exhibited multifunctional properties, including strong antibacterial activity, ROS scavenging, and enhanced periodontal bone regeneration in a rat periodontitis model.	[110]
	Carboxymethyl Chitosan (CMCS), Dopamine (oxidized to PDA)	~230 nm	The designed composites offered strong wet adhesion to mucosa, ROS-scavenging, and promoted angiogenesis, thereby accelerating oral ulcer healing.	[111]
	$FeCl_3 \cdot 6H_2O$ (Iron source), Quercetin (Ligand), Hyaluronic acid modified with 3-aminophenylboronic acid (HA-PBA) and PVA (Hydrogel matrix)	~2 nm	The designed composites offered antibacterial, ROS scavenging, anti-inflammatory (promoted M2 macrophage polarization), and alleviated alveolar bone loss (periodontal regeneration).	[112]
	Curcumin (CUR), Polyaminopropyl biguanide (PAPB), Gelatin methacryloyl (GelMA), Oxidized hyaluronic acid (OHA)	~172 nm	The designed composites offered synergistic antibacterial and immunomodulatory effects, accelerated oral tissue repair (ulcers, periodontitis), and robust tissue adhesion.	[113]
	Hollow Mesoporous Silica Nanoparticles (HMSNs) (Carrier), Quercetin (Cargo), ROS-responsive gatekeeper, Pluronic F127 & 4-Terpineol (Hydrogel matrix)	~80-400 nm	The designed composites offered antibacterial activity (pathogen eradication), ROS scavenging, restored ER homeostasis, and promoted periodontal tissue regeneration (increased bone mineral density).	[114]

(*Continued*)

Table 1 (Continued).

Type	Precursor	Size (nm)	Outcome	Reference
	Catechol-conjugated chitosan (CHI-C), Pluronic F-127 (PF-127) (Hydrogel), Copper-containing mesoporous bioactive glass nanoparticles (Cu-BGs)	~100-300 nm	The composites enhanced lymphatic drainage and alveolar bone regeneration and resolved inflammation via Metallo immunotherapy (modulating the COX4i2/ERK pathway).	[115]
	Polyphenols (likely Gallic acid), Zinc ions (forming GZN nanoparticles), Melittin (Peptide), GelMA, OHA (Hydrogel matrix)	~112 nm	The designed constructs regulated oral immunity and flora, targeted mitochondria to rescue cells from oxidative stress, and promoted periodontitis therapy.	[116]
	Chitosan (dissolved in acetic acid), Nano-hydroxyapatite (synthesized with hyperbranched polyethylene imine)	~20-40 nm (diameter), ~80-160 nm (length)	The composites enhanced bone regeneration, increased osteocyte density, and provided effective space for new bone formation in rat calvarial defects.	[43]
	Chitosan, Calcium nitrate tetrahydrate, Diammonium hydrogen phosphate (in situ synthesis)	–	The scaffolds showed osteoconductive properties, promoted new bone formation, and integration in rat tibial defects. The scaffolds were biodegradable and replaced by bone.	[117]
	Chitosan (High MW, in acetic acid), Nano-hydroxyapatite (synthesized with hyperbranched polyethylene imine)	5 mm (diameter) 1 mm (thick)	CBCT effectively visualized the scaffold and new bone formation; histological verification confirmed that nHAp/CS contributes to bone regeneration.	[118]

Abbreviations: ε-PL, Poly-L-lysine; ACP, Amorphous Calcium Phosphate; AMTN, Amelotin; BNNs, Boron Nitride Nanosheets; CBCT, Cone Beam Computed Tomography; CHI-C, Catechol-conjugated chitosan; CMCS, Carboxymethyl Chitosan; COX4i2/ERK, Cytochrome c oxidase subunit 4 isoform 2 (COX4i2) protein and the Extracellular signal-regulated kinase (ERK) pathway; CS, Chitosan; Cu-BGs, Copper-containing mesoporous bioactive glass nanoparticles; CUR, Curcumin; DMAHDM, Dimethylaminohexadecyl methacrylate; *E. coli, Escherichia coli*; EGCG, Epigallocatechin gallate; ER, Endoplasmic reticulum; *F. nucleatum, Fusobacterium nucleatum*; FerIONP, Ferumoxytol iron oxide nanoparticles; GelMA, Gelatin methacryloyl; GO, Graphene oxide; HA-PBA, Hyaluronic acid modified with 3-aminophenylboronic acid; hDPSC, human dental pulp stem cells; HMSNs, Hollow Mesoporous Silica Nanoparticles; HTMA, Hexamethylenetetramine; nHAp, Hydroxyapatite nanoparticles; OHA, Oxidized hyaluronic acid; *P. gingivalis, Porphyromonas gingivalis*; PAPB, Polyaminopropyl biguanide; PDA, polydopamine; PDT, photodynamic therapy; PF-127, Pluronic F-127; PVA, Polyvinyl alcohol; rBMSCs, rat Bone Marrow Mesenchymal Stem Cells; ROS, Reactive oxygen species; *S. aureus, Staphylococcus aureus; S. mutans, Streptococcus mutans*; TEOS, Tetraethyl orthosilicate; TiO_2, Titanium dioxide; ZIF-8, Zeolitic Imidazolate Framework-8; ZnO, Zinc oxide.

release of the loaded minocycline under the influence of a magnetic field by appropriately regulating the expression levels of IL-1β, IL-6, and TNF-α in periodontal tissues. In another case, Li and coworkers reported the promising composites in which ZnO nanorods were decorated on graphene oxide (GO) nanoplatelets for dental resin applications.[98] These composites showed exceptional antibacterial effects against *S. mutans*, presenting a significantly lower concentration (3.9×10^7 CFU/mL) than the unfilled resin (8.5×10^7 CFU/mL). These composites could prevent biofilm formation on their surfaces, which is associated with secondary caries. Similarly, Liu et al synthesized ferumoxytol IONPs (FerIONP) to specifically target biofilms harboring *S. mutans* and ablate them via in situ free-radical generation.[101] These nanoconstructs could act through catalytic activation of intracellular hydrogen peroxide, along with a targeted mechanism based on the interactions with pathogen-specific glucan-binding proteins. Along with their antibacterial efficacy, several efforts have been devoted to exploring the further utility of the designed nanoparticles, including dental fillers, teeth whiteners, remineralizing agents, and dental stabilizers. For instance, Imran et al demonstrated the fabrication of Fe_3O_4-doped ZrO_2 nanoparticles, which exhibited exceptional antibacterial activity against the *Bacillus* strain (inhibition zone of ~32 mm).[99] These mechanically strong nanocomposites presented as excellent dental fillers, playing a crucial role in correcting the teeth's shape and position. In another case, carbon dots embedded in silica nanoparticles were used as whiteners, eliminating deep enamel stains without compromising their structure under PDT.[100] Further efforts have been made on remineralization of enamel using different organic-based composites. In a case, the designed nHAp constructs substantially promoted collagen mineralization, substantially enhanced the shear bond strength at the dentin-resin interface, and stabilized the hybrid layer.[102] In another instance, the composite based on Epigallocatechin gallate (EGCG) and amorphous calcium phosphate (ACP) exhibited dual functionalities, in terms of promoting enamel

remineralization through the release of Ca/P species, as well as strong antibacterial effects against the cariogenic *S. mutans*-assisted biofilm in the acidic environment.

To this end, these nanocomposite-based formulations are employed to explore their ability to confer other functionalities for oro-dental tissue engineering, such as stem cell differentiation and soft-tissue integration towards dental-pulp repair. Inevitably, some of these studies have demonstrated synergistic antibacterial effects, reflecting the diverse oral microbiome and its susceptibility to bacterial attack during treatment. In a case, Spagnuolo et al fabricated calcium-based materials (calcium carbonate, $CaCO_3$, calcium hydroxide, $Ca(OH)_2$, and mineral trioxide aggregate, MTA). They demonstrated their ability to differentiate hDPSCs into odontoblastic-like cells (Figure 3A).[93] These calcium-based materials, particularly MTA, demonstrated exceptional regenerative potential, as evidenced by the expression of specific odontogenic-related genes and by augmented differentiation markers, ie, matrix extracellular phosphoglycoprotein (MEPE) and alkaline phosphatase (ALP) activities. In another case, mesoporous TiO_2 coatings were coated with ZnO nanoparticles (Figure 3B).[105] The regulated release of Zn^{2+} ions through the zinc transporters (ZIP1 and ZnT1) provided excellent antimicrobial activity, promoting the osteogenic efficacy of the bone MSCs (BMSCs). Ilhan and coworkers encapsulated BMP-7 growth factor and clindamycin phosphate in the polymeric nanoparticles for alveolar bone regeneration.[120] Wang et al generated hollow polydopamine nanoparticles using the ZIF-8 metal-organic frameworks (MOFs) as templates (Figure 3C).[104] In terms of bioefficacy, these structures encapsulated with different osteogenic drugs promoted the proliferation of rat BMSCs and their subsequent osteogenic differentiation. Yuan et al fabricated PLGA-based nanoparticles in GelMA cryogel microspheres for vascularized pulp regeneration.[106] These biocompatible nano-in-micro composites encapsulated with stem cells derived from human exfoliated teeth demonstrated exceptional promotion ability of vascularized tissue regeneration in mice. These biocompatible nanoparticles derived from different precursors demonstrated improved antibacterial and differentiation capabilities, enabling the treatment of oro-dental

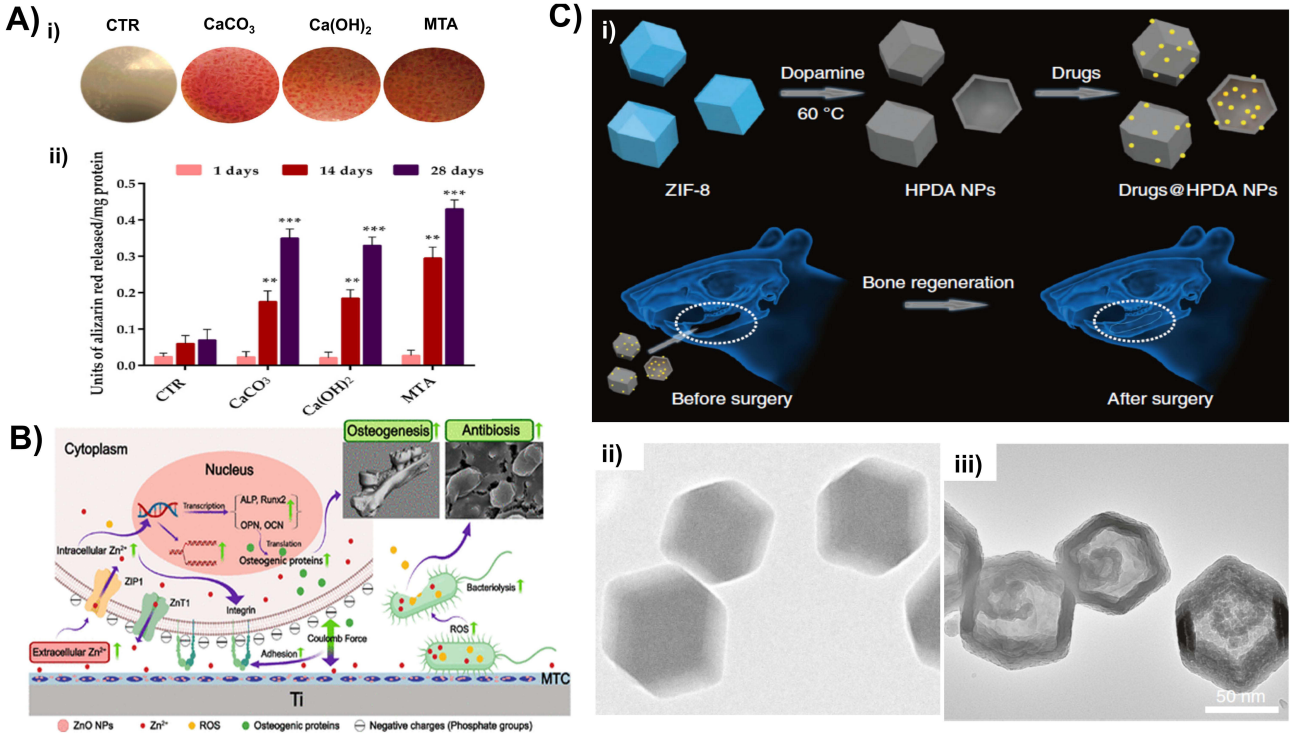

Figure 3 (**A**) Effects of calcium-based materials on hDPSCs mineralization. Photographs of mineral nodules formed after 28 days of culture. (i) Representative pictures of Alizarin Red S-stained sections assessed with transmitted light microscopy at 20 × magnification. (ii) Quantification of Alizarin red staining. The result was the representative of three different experiments. Statistically significant variations ** $p < 0.01$ and *** $p < 0.005$ versus CTR. Reproduced with permission from Ref.[93] Copyright 2023, Elsevier. (**B**) Schematic diagram of nZnO/MTC-Ti regulating Zn^{2+} release, osteogenesis, and antibiosis. Reproduced with permission from Ref.[105] Copyright 2023, American Chemical Society. (**C**) (i) Schematic diagram of the construction of a drug-sustained release system and its application in bone regeneration. Dotted circles show the surgical site before and after surgery. Physical characteristics of hollow polydopamine (HPDA) nanoparticles. (ii) TEM image of ZIF-8. (iii) TEM image of HPDA nanoparticles. Reproduced with permission from Ref.[104] Copyright 2021, Nature Publishing Group.

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defects with regenerative capabilities. Although various formulations, including nanoparticles alone or in combination with microparticles, have been fabricated, strict optimization of their processing and formulation parameters is required to develop suitable morphological features. Moreover, bioefficacy investigations in vivo must be performed, requiring the development of suitable administration methods for practical use towards clinical translation.

Nanoparticle-Encapsulated Macro-Sized Composites

Although nano-sized particles often facilitate exceptional therapeutic potential for dental repair, guided tissue regeneration can effectively treat various oral ailments, such as periodontal defects. Along this line, various macro-sized constructs, such as barrier membranes and hydrogels, among others, are considered. Despite success, these barrier membranes, such as collagen, suffer from several limitations, including instability in a clinical setting, a propensity for bacterial infection, and a failure to promote osteogenesis. In a case, Wu et al generated the nanocomposite system based on the incorporation of ZnO nanoconstructs (1%) in the chitin-based hydrogel homogeneously.[109] Considering the ideal properties of a barrier membrane, the resultant ChT-1%ZnO composites offered appropriate bactericidal effects against *S. aureus* and *P. gingivalis*. In addition, these composites, which exhibit excellent biodegradability, showed osteoconductive effects in vitro. Further, these findings were validated in a rat periodontal defect model in vivo. The cemento-enamel junction value in the ChT-1%ZnO group (1.608 mm) was significantly reduced compared to the ChT group (1.685 mm) after 8 weeks post-operatively. Interestingly, several efforts by Chatzipetros et al have explored the effects of nano-hydroxyapatite and chitosan-based scaffolding systems on rat calvarial defects for bone regeneration.[43,117] In a case, the biological effects of nano-hydroxyapatite/chitosan (nHAp/CS, 75/25 w/w) scaffolds were fabricated and systematically characterized.[43] In addition, various evaluation techniques were used, including the examination of the fraction of bone regeneration (FBR), the total number (Ost), and the cell density (CD; Ost/mm^2) of osteocytes in a rat model. The fabricated nHAp with diameters of 20–40 nm and lengths of 80–160 nm was encapsulated in CS (3%W/W)-based porous scaffolds. These scaffolds, which are biodegradable, showed positive effects, promoting bone regeneration in a timely manner. In another case, these scaffolds (75/25 w/w nHAp/CS) were used to demonstrate the ability of Cone-beam computed tomography to visualize critical-size defects.[118] These findings, with histological and CT-based investigations, presented that nhAP/CS scaffolds promoted the new bone formation.

Typically, various ailments worsen the oral environment by disrupting the physiological balance. For instance, high glucose levels exacerbate periodontitis, resulting in accelerated periodontal bone resorption and compromised bone healing.[61] In an instance, a thermosensitive hydrogel construct based on PDLLA (poly(DL-lactide))-PEG-PDLLA (PPP) hydrogel was incorporated with metformin-encapsulated mesoporous silica nanoparticles (MSNs). These composites resulted in the sequential release of drug cargo towards diabetic periodontal bone regeneration (Figure 4A).[122] These designed constructs emulated the mesenchymal stem cell "recruitment-osteogenesis" cascade by releasing the SDF-1 initially. Further, the degradation of the hydrogel exposes the MSNs to release metformin, scavenging the ROS and reducing the high glucose levels. These consequences substantially inhibited osteogenesis in rBMSCs by reactivating the AMPK/β-catenin pathway. Further, they regulated the diabetic microenvironment and facilitated osteogenesis for diabetic periodontal bone regeneration. Although various macro-sized constructs have been developed, the injectable hydrogels offer exceptional antioxidant and osteoinductive outcomes, promoting bone regeneration for periodontitis treatment. In another instance, an injectable hydrogel system was developed using $Ti_3C_2T_x$ MXene nanosheets in gelatin and poly-L-lysine, based on the facile cross-linking approach (Figure 4B).[110] These composite hydrogels exhibited excellent colloidal stability, moderate tissue adhesion ability, and excellent mechanical properties. These features significantly inhibited *P. gingivalis* growth, attenuated inflammatory responses, scavenged ROS, and enhanced bone tissue regeneration. The periodontal disease group treated with the designed scaffolds recovered to the healthy group levels in terms of junctional epithelium, alveolar bone height, and alveolar bone volume, indicating its potential for bone regeneration and periodontitis treatment (Figure 4C).

Nano-Reinforced Dental Implants

Often, dental-related ailments, whether due to progressive tooth damage from periodontitis or other conditions, eventually result in edentulism and damage to the oral cavity.[99,123] To address the edentulous condition, various dental implants in

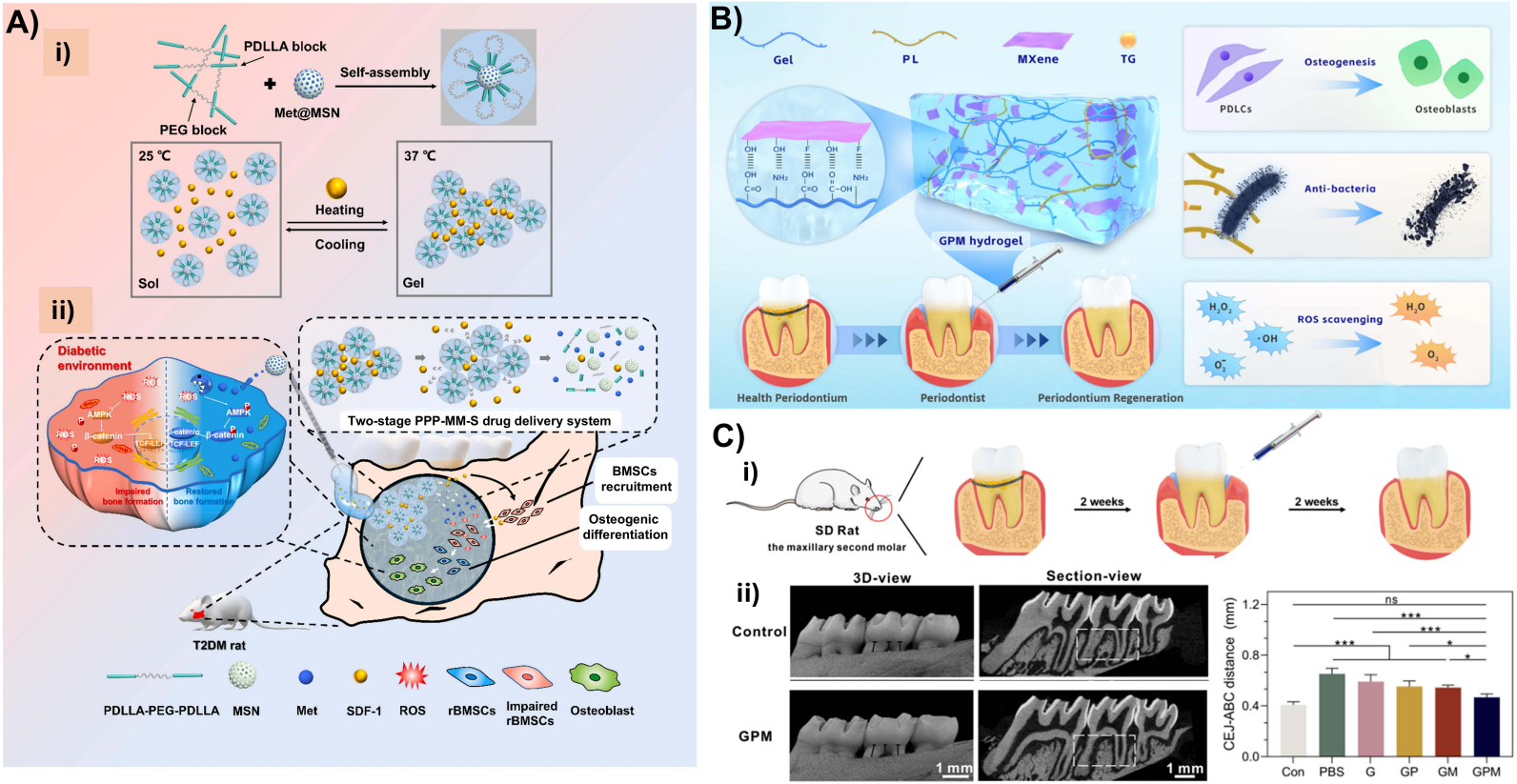

Figure 4 (**A**) Schematic diagram depicting the (i) design principle of the bioinspired hydrogel emulating the cell "recruitment-osteogenesis" cascade for diabetic periodontal bone regeneration and the (ii) mechanism of metformin restoring bone homeostasis through the ROS/AMPK/β-catenin pathway under high-glucose conditions. Reproduced with permission from Ref.[122] Copyright 2023, KeAi Publishers. (**B**) Schematic of the design of injectable nanocomposite hydrogels (GPM) and the application of hydrogels for the treatment of periodontitis. The GPM gels composed of gelatin, PL, and MXene were enzymatically cross-linked using transglutaminase (TG) via a one-pot method, demonstrating high osteoinductivity and robust antibacterial and ROS-scavenging properties to promote periodontium regeneration. (**C**) Effects of injectable hydrogels on in situ periodontal bone formation. (i) Schematic of ligature and *P. gingivalis*-induced periodontitis and the application of hydrogels for the treatment of periodontitis. (ii) Maxillary second molars (M2) were scanned using a micro-CT device after treatment with various hydrogels. Quantitative analysis of the bone-related CEJ–ABC distance parameter of the M2, including from the micro-CT images. Reproduced with permission from Ref.[110] Copyright 2024, American Chemical Society.

appropriate sizes have been developed based on the type of oro-dental condition as well as jaw bone dimensions. These implants facilitate the treatment of damaged teeth by offering solid support to new teeth. Moreover, these structures allow the bone to heal around the implants at the injured sites, thereby improving osseointegration. In this context, various materials have been employed to generate dental implants due to ease of implantation in the jawbone, including porcelain, titanium, zirconium, and ceramic-based materials.[124] Notably, inappropriate fixation may lead to certain complications, such as nerve damage and sinus problems, resulting in undesirable bacterial infections and impaired osseointegration. The fixation of dental implants and their long-term applicability is hampered in several patients with complications, such as osteoporosis and diabetes, or in smokers.

To address these issues, various surface treatments have been employed to enhance the performance of dental implants, including chemical etching and plasma treatment. These surface modification strategies often alter surface chemistry, roughness, wettability, morphology, and compatibility, among other properties. In terms of surface chemistry, the treatment often involves atomic-scale alterations that modify the surface potential of the implants. As a result, these modified surfaces improve cell adhesion rates and enhance soft tissue integration with surrounding tissues, thereby promoting enhanced tissue regenerative capacity. Along this line, diverse nano-engineering strategies can be used to modify the surfaces of dental implants, including the deposition of Ag, Ti, silica, and aluminum oxide (Al_2O_3) nanoparticles.[70,99,102,105] Predominantly, the coating of these metallic nanoconstructs enhances antibacterial efficacy, facilitating improved osseointegration of dental implants.[70,125] For instance, the silver coating on the Ti implants sustained the release of silver ions for 7 days, resulting in exceptional anti-bacterial activity over 12 h.[70] Notably, these Ag-coated Ti implants showed no signs of toxicity in fibroblasts for 10 days, demonstrating their biosafety. Recently, electrochemical anodization has emerged as an innovative surface modification approach owing to its ease of tailoring, scalability, and cost-effectiveness. In a case, titania-based nanostructures were fabricated by electrochemical anodization, simply by immersing a Ti implant and a Pt/Ti (cathode) in a suitable electrolyte (water and fluoride) and applying a voltage/current for a specific duration. The resultant Ti implants modified with TiO_2 nanotube/nanopore structures significantly augmented soft tissue integration.[97] Several reports demonstrated the importance of surface modification of dental implants towards improving osseointegration.[102] In one instance, the dentin was treated with enamel protein amelotin (AMTN)-based bio-nano complex before adhesion. The surface treatment resulted in significant improvements in mechanical properties, accelerated mineral formation, and collagen mineralization. Despite the success, it is necessary to comprehensively explore the long-term behavior of these nano-casted surfaces regarding the risks associated with sophisticated processing and accumulation-induced toxicity, to assess their applicability across various fields of biomedicine.

Challenges in Clinical Translation

Before exploring the challenges in the clinical translation of nanoparticle-based dental materials designed to engineer oral tissues, we provide a brief overview of the formulations in ongoing recent clinical trials, including those recently reported. Predominantly, these nano-engineered composites, alone or within the scaffolds, are often focused on periodontal regeneration, alveolar bone growth, and pulp-dentin repair. Along this line, key nanomaterials for clinical translation include nHA or 3D-printed PCL scaffolds for bone regeneration, bioactive glass nanoparticles for regeneration of the dentin-pulp complex, and chitosan, albumin, TiO_2, silver, and gold-based nanoparticles for modulating bacterial pathogenicity in periodontal diseases to improve immunomodulation and periodontium regeneration. In a case, Farhadian et al reported the effect of Ag NPs decorated acrylic baseplates of orthodontic retainers on the CFU count of *S. mutans* in sixty-six orthodontic patients (registered under the Iranian Clinical Trial Center under the code number IRCT201309239086N2).[126] Compared with conventional acrylic retainers, the deposited silver nanoparticles inhibited *S. mutans* in a clinical setting. Similarly, the polymethyl methacrylate (PMMA)-based orthodontic appliances with in situ-generated silver nanoparticles were tested against carcinogenic bacteria in a randomized, double-anonymized, crossover clinical trial involving 24 patients. Accordingly, NanoAg-IS-PMMA substantially inhibited planktonic growth and biofilm formation.[127] In a recent report, the antibacterial effect of TiO_2 nanoparticles encapsulated in acrylic baseplates was demonstrated in orthodontic patients (https://register.clinicaltrials.gov/ with ID – NCT06051487).[128] Interestingly, the addition of 1% TiO_2 nanoparticles to acrylic baseplates substantially reduced bacterial colony counts after 4 months of application in orthodontic patients. Several nanoparticle-based composites are under trial, including chitosan

nanoparticles on periodontal issues post-steroidal inhalation in asthmatic patients in a Phase-I clinical trial (ClinicalTrials.gov, ID NCT06525363), 3D-printed patient-specific PCL-based resorbable scaffolds (ClinicalTrials.gov, ID: NCT06773923), and nHAp-reinforced glass ionomer in the treatment of root caries in geriatric patients over one year follow-up (ClinicalTrials.gov, ID: NCT04701320).

Despite the success in exploring various treatment strategies with preclinical outcomes, several challenges remain to be addressed when using these nanomaterial-based composites. These shortcomings include analysis, synthesis, sterilization, safety, and storage requirements, towards their utilization in clinics and the commercial market.[5,129] Accordingly, several advancements have led to the generation of various nanoconstructs for improving the solubility of drugs and differentiating cells.[130] On the one hand, the poor solubility of drugs often leads to increased drug resistance, specifically for antibiotics. On the other hand, inappropriate cell differentiation may lead to the development of cancerous tissues,[131] delaying the regeneration process. Encapsulation of hydrophobic antibiotic drugs in porous networks (such as MSNs) to improve their delivery within the tough biofilm network. Several challenges exist in the synthesis of nanoconstructs, including the lack of optimization of synthetic parameters, complex synthesis, the need for sophisticated equipment, and a lack of reproducibility, all of which necessitate further investigation. For example, AgNPs and various anisotropic AuNPs often exhibit poor reproducibility, leading to low yields. Several examples, such as core-shell, dendrimers, liposomes, and polymer-coated nanodots, often require a multi-step complex process, lacking precise control over the parameters. Moreover, various nanoparticles based on plant extracts are challenging to control the exact composition, leading to difficulty in controlling the size and shape. Importantly, the commonly used chemical-based synthesis methods (reduction, sol-gel, and solvothermal) require careful consideration of environmental risks during the synthesis of various nanoparticles (AuNPs, AgNPs, ZnO, TiO_2, PLGA, and gelatin), necessitating the use of eco-friendly techniques, such as supercritical fluid technology.[16] In addition, specific attention must be paid to obtaining cheaper chemical sources and ensuring reproducibility in particle size and drug-loading efficiency for the cost-effective large-scale production of nanoparticles (such as gold). Recently, various innovative techniques for surface-modifying nanoparticles on implants have been proposed. These innovative techniques necessitate the exploration of the optimization and compatibility attributes of such composites.[132,133] For example, these Ag-coated Ti implants showed no signs of toxicity in fibroblasts for 10 days, requiring substantial in vivo investigations.[70]

Further, evaluating the designed components in terms of their responses at the cellular, tissue, and animal levels is important. Despite the reports on compatibility, it is necessary to investigate the comprehensive biological performance of these components, given the complexity of bone and periodontal tissues across various animal models.[70,134] Nevertheless, animal models, typically, small-sized animals (mice), suffer from a major limitation: differences in genetics and anatomical features across species, which make it difficult to predict or extrapolate human responses to these formulations. Although large animals are much closer, conducting animal studies is more expensive and requires animal-specific ethical approval processes. These attributes indicate them as poor indicators for a clinical setting. Accordingly, stem cell engineering has been explored to replicate the physiology of the oral tissues.[135] Nevertheless, investigations across multiple species prior to humans are required for their translation into the clinic.[136] Prior to performance efficacy, the biosafety of nanoparticle-based composites is as important as bioefficacy and requires safety evaluations at various levels to ensure patient compliance. Although 2D monolayers demonstrated cytocompatibility, further investigations are needed to assess blood or tissue compatibility and molecular-level genotoxicity. The degradability of a material goes hand in hand with its safety, and this requires a comprehensive exploration of its environmental influences on degradability kinetics.[137] Eventually, product characteristics, such as sterilization and preservation, play a major role in their clinical translation, as they may influence safety and subsequent efficacy. Although various sterilization procedures are available,[138] it is necessary to validate information by developing standard operating procedures and patents for the biomaterials to avoid critical damage.

In addition to exploring and evaluating the design on a large scale, it is necessary to examine complex regulatory pathways, which often take considerable time. To address this, several accelerated access pathways in regulatory programs have been designed, for instance, the Breakthrough Devices Program (BDP) in the US and the European Union Medical Device Regulation and the Health Technology Assessment Regulation (HTAR), to streamline the pathway to patient access.[139] These programs, designed by concerned authorities, present challenges in balancing rapid access with safety, requiring post-market surveillance and the allowance of regulatory processes across regions. Accordingly, industry stakeholders, regulatory authorities, and insurance organizations must collaborate to rethink the

pathways to ease access to such medical device systems. These solutions may significantly reduce scalability challenges and high production costs. Considering these attributes, it takes considerable time to develop and refine the synthesis, biosafety, bioefficacy, and packaging, achieving the anticipated therapeutic outcomes in clinics and their subsequent market application.

Conclusion

In summary, this review discusses various nanotechnological approaches used to engineer oral tissues. Initially, various concepts for enhancing the regenerative potential of different nanomaterials are discussed, highlighting their roles as antibacterial agents, their capacity to differentiate human dental pulp stem cells, and their potential for soft-tissue integration. Furthermore, various types of nanotechnological composites used for regenerating oral tissues are discussed, including nanoparticles with different supramolecular assemblies that support cell growth. Finally, a note on nanotoxicity in oral health, along with the challenges that remain to be addressed, is emphasized, along with interesting perspectives on their path to clinical translation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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