



Review

Polysaccharide-Based Biomaterials in Oral Regenerative Medicine: Mechanisms, Engineering Strategies, and Translational Perspectives

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Abstract: Oral regenerative medicine seeks to repair or regenerate the pulp-dentin complex, periodontal tissues, jawbone, and oral mucosa. Nevertheless, this field confronts considerable challenges, including the intricate oral microenvironment, the body's limited intrinsic regenerative capacity, and the requirement for coordinated regeneration across multiple tissue types. Natural and engineered polysaccharides have emerged as highly promising regenerative platforms, owing to their excellent biocompatibility, extracellular matrix-mimicking properties, chemical tunability, and capacity for local delivery. This review systematically highlights recent advances in polysaccharide-mediated regeneration of oral and craniofacial tissues. First, polysaccharides are classified into three categories: linear non-sulfated polysaccharides, nitrogen-containing cationic polysaccharides, and sulfated polysaccharides, with an analysis of their structure–function relationships. Second, the key mechanisms through which polysaccharides modulate cellular behavior, reshape the immune microenvironment, regulate biomineralization, and enable the spatiotemporal delivery of bioactive molecules and cell-free therapeutic cargo are clarified. Third, tissue-specific applications of polysaccharide-based materials in pulp-dentin complex regeneration, periodontal tissue regeneration, and craniofacial bone regeneration are systematically reviewed. Furthermore, engineering design strategies—including chemical functionalization, physical assembly, and smart and bioinstructive engineering—alongside advanced manufacturing technologies such as 3D printing, electrospinning, and microsphere-based delivery systems, are discussed. Finally, this review highlights critical challenges in clinical translation, including material standardization, manufacturability, and clinical validation, while proposing future directions centered on mechanism-guided rational design, personalized precision therapy, and AI-assisted development. These insights aim to provide a theoretical framework and practical guidance for advancing next-generation polysaccharide-based biomaterials in oral regenerative medicine.

Keywords: polysaccharides; pulp-dentin complex regeneration; periodontal regeneration; craniofacial bone regeneration; immunomodulation; biomineralization



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1. Introduction

The oral and maxillofacial region performs complex functions such as mastication, phonation, and swallowing while playing a crucial role in facial esthetics, and tissue defects from caries, periodontal disease, trauma, and tumor resection markedly impair quality of life. Oral regenerative medicine aims to repair or regenerate the pulp–dentin complex, periodontal tissues (alveolar bone, periodontal ligament (PDL), and cementum), jawbone, and oral mucosa, restoring structure and function. The oral microenvironment imposes further constraints: continuous salivary flushing, masticatory forces, and a microbial community entrenched in chronic inflammation place exacting demands on any material. Moreover, intrinsic regenerative capacity is modest: enamel cannot regenerate, dentin mounts only slow reparative activity, periodontal wounds heal through a long junctional epithelium, and inflamed alveolar bone is prone to resorption rather than regeneration [1,2]. Developing biomaterials that mimic the native extracellular matrix, regulate cellular behavior, exert antimicrobial effects, and direct tissue regeneration therefore represents a central challenge in this field [3,4].

Natural and engineered polysaccharides are therefore especially appealing, simultaneously satisfying several demanding criteria: biocompatibility, extracellular-matrix mimicry, chemical tunability, local delivery capability, and responsiveness to inflammatory or mineralizing microenvironments. Their advantages stem from four interrelated features. First, polysaccharides derived from animals, plants, algae, or microorganisms exhibit favorable biocompatibility and biodegradability, and several products—hyaluronic acid (HA) fillers, alginate dressings, and chitosan-containing hemostatic materials—are already in clinical practice [5,6]. Second, they display considerable structural and functional diversity: cationic polysaccharides (e.g., chitosan) are antimicrobial and mucoadhesive [7]; linear non-sulfated polysaccharides (e.g., HA, alginate) serve as biomimetic extracellular matrix scaffolds; and sulfated polysaccharides (e.g., chondroitin sulfate, heparan sulfate) enrich and stabilize growth factors electrostatically while regulating biomineralization [8]. Third, their abundant hydroxyl, amino, and carboxyl groups enable modifications such as carboxymethylation, phosphorylation, sulfation, and cross-linking to tailor mechanical properties, degradation rates, and environmental responsiveness [6,9]. Fourth, they can be fabricated into hydrogels, microspheres, nanofibers, and 3D-printed scaffolds, accommodating the repair requirements of various tissues.

This review highlights the role of polysaccharides in oral and craniofacial tissue regeneration, focusing on the pulp–dentin complex, periodontal tissues, and craniofacial bone. We first classify polysaccharides by chemical structure and analyze their structure–function relationships, then summarize the mechanisms through which they regulate cell behavior, the immune microenvironment, biomineralization, and bioactive delivery, and their tissue-specific applications. Engineering strategies, advanced fabrication platforms, and barriers to clinical translation are discussed in turn, providing a systematic framework and practical guidance for researchers.

Notably, although the opening paragraph lists the oral mucosa among the tissues targeted by oral regenerative medicine, a systematic discussion of mucosal wound healing and repair is beyond the scope of this review. This review focuses on the three scenarios involving mineralized and attachment tissues described above. Readers interested in polysaccharide-based mucoadhesive and mucosal repair systems should consult recent comprehensive reviews on this topic [10,11]. Nevertheless, polysaccharide-based materials do show considerable promise for oral mucosal wound healing and defect repair. In particular, mucoadhesive hydrogels and membranes based on chitosan and hyaluronic acid exploit the properties highlighted in this review: biocompatibility, mucoadhesion, maintenance of a moist wound environment, and drug delivery.

2. Classification of Polysaccharides and Structure-Function Relationships

In the context of oral and craniofacial regeneration, the regenerative performance of polysaccharide-based biomaterials is fundamentally dictated by their chemical structure, encompassing backbone composition, functional groups, charge characteristics, molecular weight, and chain conformation [6,12]. These structural parameters critically govern hydrogel formation, cell-material interactions, growth factor binding, immune modulation, and mineralization guidance. To provide a structure-function framework for the subsequent sections, the polysaccharides commonly employed in this field are classified into three representative categories: linear non-sulfated polysaccharides, nitrogen-containing cationic polysaccharides, and sulfated polysaccharides, as summarized in Table 1.

Table 1. Classification of Polysaccharides used in oral regeneration.

Polysaccharide Category	Chemical Characteristics	Key Functions	Representative Polysaccharides	Applications
Linear Non-Sulfated Polysaccharides	Linear backbone rich in carboxyl/hydroxyl groups; negatively charged under physiological conditions; MW (esp. HA) governs biological function; alginate M/G block ratio regulates gel stiffness and degradation [11,13]	Enable ionic or physical cross-linking into ECM-mimetic hydrogels [14]	Alginate	Ca ²⁺ cross-linking of carboxyl groups yields hydrogels for cell encapsulation and 3D bioprinting [15,16]; injectable TDM/alginate hydrogel achieved dentin bridge in direct pulp capping [17,18].
			Hyaluronic acid (HA)	High-MW HA (>1000 kDa) is anti-inflammatory; low-MW (<20 kDa) fragments are pro-angiogenic via TLR4 [11,13]; CD44-mediated TGF-beta1 upregulation promotes odontoblastic differentiation [19].
Nitrogen-Containing Cationic Polysaccharides	Free amino groups; protonated and positively charged under mildly acidic conditions; degree of deacetylation predicts antimicrobial efficacy; MW modulates adhesion and carrier capacity [7,20,21]	Positive charge mediates antimicrobial activity and mucoadhesion [7,20]; versatility enhanced by quaternization, enzymatic or catechol modification [22–24]	Chitosan	Antimicrobial, mucoadhesive [7,20]; enzyme-modified chitosan + blood clots enhanced vital pulp tissue formation and periapical healing [23,25]
			Quaternized chitosan	Permanent positive charges improve solubility and EV loading [22]; 3D-printed scaffolds adsorbing MSC exosomes for vascularized bone regeneration [26]
			Chitin *	Chitosan precursor; structural homology and convertibility [27]; Janus bilayer hydrogel (anti-adhesive outer + osteogenic inner) achieved superior periodontal regeneration vs collagen [28]
Sulfated Polysaccharides	Backbone bears sulfate groups conferring strong negative charge; sulfate density and position (C-2, C-4, C-6) determine charge density and biological activity [8,29]	Higher sulfation enhances growth-factor binding (e.g., FGF-2); no universally applicable sulfation threshold exists [29–32]	Chondroitin sulfate	Carrier for bioactive molecules in osseointegration and mineralized tissue repair [8,33]; injectable HA/CS hydrogels shift cytokine balance from TNF-alpha to IL-10 in periodontitis [34]
			Carrageenan	Sulfate-mediated electrostatics support polyelectrolyte complexation and Ca ²⁺ -associated mineralization [35]; multilayer barrier membranes add antimicrobial and Ca ²⁺ -releasing functions [36,37]; lambda-carrageenan/low-MW fractions can be pro-inflammatory, requiring MW and sulfate control [38,39]
			Fucoidan	Anti-inflammatory, growth-factor-binding, and pro-osteogenic activity [40,41]; fucoidan-chitosan hydrogel superior to CGF in intrabony defect fill (RCT) [41]; bioactivity varies with species and extraction [42,43]
			Heparin	Highly sulfated with strong growth-factor/cytokine affinity; anticoagulant activity must be weighed [44]; immobilized in composite scaffolds for sustained release [45]

* Chitin itself is not a cationic polysaccharide; however, due to its structural homology with chitosan and its convertibility to chitosan through deacetylation, it is commonly discussed alongside chitosan in this field.

2.1. Linear Non-Sulfated Polysaccharides

In linear non-sulfated polysaccharides, primarily alginate and HA, carboxyl and hydroxyl groups impart hydrophilicity, a negative charge, and hydrogen-bonding capacity, enabling ionic or physical cross-linking into hydrogels that mimic the native extracellular matrix (ECM) [14]. Alginate, a copolymer of β -D-mannuronic and α -L-guluronic acid from brown seaweed, forms hydrogels through Ca^{2+} cross-linking of its carboxyl groups [15]; this Ca^{2+} -mediated gelation, combined with tunable viscosity, injectability, and printability, makes alginate a versatile matrix for cell encapsulation, local bioactive delivery, and 3D bioprinting [16]. The ratio and distribution of mannuronic and guluronic acid blocks further regulate gel stiffness, degradation, and mechanical stability, offering key design parameters for tissue-specific regeneration. HA, a repeating disaccharide of D-glucuronic acid and N-acetylglucosamine [46], is a key ECM component contributing to hydration, viscoelasticity, and cell-interactive signaling via receptors such as CD44. Its biological functions depend strongly on molecular weight: high-molecular-weight HA (typically >1000 kDa) mainly exerts anti-inflammatory, anti-edematous, and tissue-protective effects, whereas low-molecular-weight fragments (especially < 20 kDa) are pro-inflammatory and pro-angiogenic and modulate the immune microenvironment via pattern recognition receptors such as Toll-like receptor 4 (TLR4) [11,13]. These molecular-weight-dependent properties render HA valuable not only as a passive hydrogel scaffold but also as a bioactive modulator of cellular behavior and immune microenvironment remodeling in pulp-dentin, periodontal, and craniofacial bone regeneration.

2.2. Nitrogen-Containing Cationic Polysaccharides

Nitrogen-containing cationic polysaccharides are primarily represented by chitosan and its derivatives. Chitosan, produced by partial deacetylation of chitin, carries a positive charge under mildly acidic conditions through its free amino groups [11,17]. This cationic character underpins its antimicrobial activity (electrostatic interactions with negatively charged bacterial membranes) and its interfacial adhesion in moist oral environments, making it among the most widely applied polysaccharide classes in oral regeneration [7,20]. Molecular weight modulates solubility, adhesion, and carrier capacity [21]. A recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-guided synthesis of 127 in vitro antimicrobial assays showed that the degree of deacetylation is the dominant predictor of antibacterial efficacy in soluble chitosans (>60%): minimum inhibitory concentration decreases by approximately 0.04 log units per 1% increase, whereas poorly soluble fractions below 60% display unreliable activity [20].

Chemical modification further enhances chitosan's functional versatility. Quaternized chitosan introduces permanent positive charges, improving water solubility, antibacterial activity, and electrostatic loading of bioactive cargos such as extracellular vesicles [22]. Enzyme- or catechol-modified chitosan strengthens hydrophobic interactions, wet adhesion, and scaffold-cell interactions pertinent to pulp-dentin and periodontal regeneration [23,24]. Although chitin, the precursor of chitosan, is not inherently cationic, its structural homology and convertibility to chitosan explain why chitin-based systems are frequently discussed alongside chitosan derivatives [27].

2.3. Sulfated Polysaccharides

Sulfated polysaccharides, as defined here, comprise natural or synthetic macromolecules bearing sulfate groups, which confer a strong negative charge under physiological conditions. This class includes glycosaminoglycans (GAGs) such as chondroitin sulfate and heparin, and seaweed-derived carrageenan and fucoidan [8]. Their bioactivities depend on sulfate density and substitution pattern: higher sulfation generally enhances electrostatic binding to growth factors and cations, while site-specific sulfation at C-2, C-4, or C-6 modulates tissue selectivity and signaling [29]. Quantitatively, sulfated alginates with degrees of sulfation from 0.8 to 2.6 bind fibroblast growth factor-2 (FGF-2) dose-dependently, highly sulfated derivatives retaining significantly more growth factor than low-sulfated or unmodified counterparts [30,31]; sulfation alone can confer de novo heparin-like binding, as unmodified alginate and hyaluronan show negligible affinity for heparin-binding proteins [32]. Nevertheless, no universally applicable sulfation threshold for growth-factor binding exists; the effective level varies with backbone chemistry, sulfate positioning, and target protein identity. Systematically mapping sulfation degree and pattern to growth-factor binding most relevant to oral regeneration (bone morphogenetic protein-2 (BMP-2), vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β)) remains a key knowledge gap.

Chondroitin sulfate, composed of repeating glucuronic acid and N-acetylgalactosamine units, is a key extracellular matrix component of cartilage and bone, and serves as a carrier for bioactive molecules in osseointegration and mineralized tissue repair [8,33]. Heparin is highly sulfated and strongly binds growth factors

and cytokines, but its anticoagulant activity warrants caution in regenerative applications [44]. It is frequently immobilized in composite scaffolds to enhance local retention and sustained release of bioactive molecules [45].

Seaweed-derived sulfated polysaccharides, such as carrageenan and fucoidan, perform complementary roles. Carrageenan facilitates sulfate-mediated electrostatic interactions and gel formation, supporting polyelectrolyte complexes and Ca^{2+} -associated mineralization [35]. Its biological profile is not uniformly benign: λ -carrageenan is widely used as a pro-inflammatory inducer via TLR4-mediated signaling, and degraded low-molecular-weight carrageenan has been linked to intestinal inflammation in animal models [38,39]. Fucoidan, primarily sulfated α -L-fucose units, exhibits anti-inflammatory, growth-factor-binding, and pro-osteogenic properties; fucoidan-containing chitosan hydrogels show translational potential in periodontal intrabony defect repair [40,41]. Nevertheless, its therapeutic effects are strongly structure-dependent: bioactivity varies with algal species, harvest conditions, and extraction protocols, and molecular weight and sulfation pattern differences have been linked to divergent anticoagulant and immunomodulatory outcomes [42]. Rigorous characterization of purity, molecular weight, and sulfation is essential for batch-to-batch consistency and reproducible clinical translation [43].

3. Core Mechanisms of Polysaccharide-Mediated Oral Tissue Regeneration

In the context of oral and craniofacial regeneration, polysaccharide-based materials exert their effects through structure-dependent interactions with cells, immune components, minerals, and bioactive molecules. These interactions operate via four interrelated mechanisms: modulating cell-material crosstalk and stem cell fate, reshaping the inflammatory and immune microenvironment, guiding biomineralization, and enabling spatiotemporal delivery of bioactive molecules and cell-free therapeutic cargo. Acting synergistically, these mechanisms coordinate infection control, inflammation resolution, vascularization, matrix deposition, and functional tissue repair. Figure 1 schematically summarizes these four core mechanisms and their synergistic roles in polysaccharide-mediated oral regeneration.

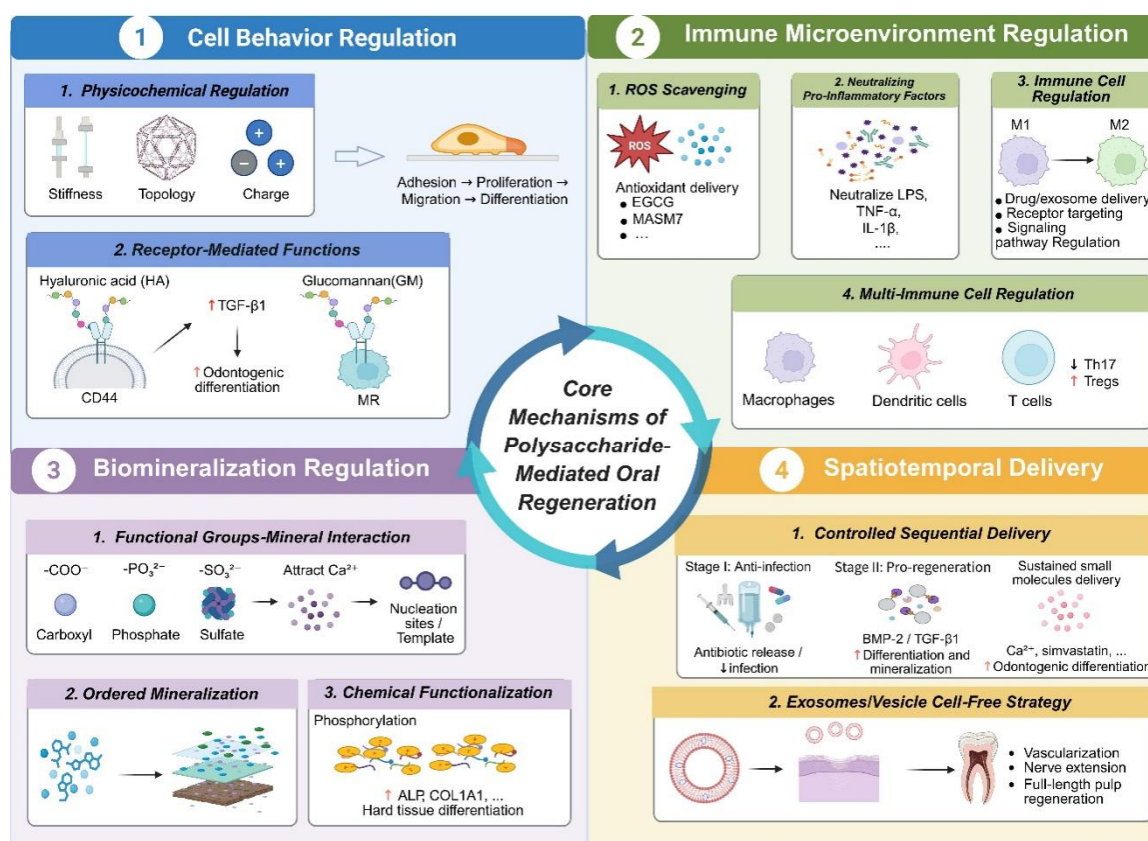


Figure 1. Core mechanisms of polysaccharide-mediated oral regeneration.

3.1. Cell Behavior Regulation

Polysaccharides can directly regulate stem cell adhesion, proliferation, migration, and differentiation via their physicochemical properties, such as stiffness, topography, and charge. A pulp-like double-network polysaccharide hydrogel activated TGF- β 1/Smad3 signaling and promoted vascularized pulp-like tissue formation in vivo,

underscoring the importance of stiffness-matched matrices [47]. Similarly, a viscoelastic alginate-based hydrogel with PDL-like stress relaxation delivered time-dependent mechanical cues that organized PDL fibers [48].

Beyond physicochemical regulation, polysaccharides can also exert biological effects through direct interactions with cell surface receptors, a distinctive advantage over synthetic polymers. For instance, HA binds to CD44 receptors on human dental pulp stem cells (DPSCs), upregulating TGF- β 1 expression to induce odontoblastic differentiation and mineralized nodule formation [19]. Such receptor-mediated mechanisms establish polysaccharides as bioactive matrices combining structural support with cell-instructive signaling.

3.2. Immune Microenvironment Regulation

Oral and craniofacial regeneration typically occurs in microenvironments characterized by microbial challenge, excessive inflammation, and oxidative stress. Consequently, polysaccharide-based materials are increasingly designed as immunomodulatory platforms that actively reshape this environment, rather than serving solely as scaffolds or delivery vehicles.

One key approach involves oxidative stress regulation. Polysaccharide hydrogels can lower reactive oxygen species (ROS) levels via intrinsic antioxidant moieties or controlled antioxidant delivery. ROS/glucose-responsive alginate-chitosan hydrogels loaded with epigallocatechin gallate (EGCG) mitigate oxidative stress and alveolar bone loss in diabetic periodontitis models [49]. Likewise, chitosan-based antioxidant hydrogels integrate ROS scavenging with macrophage phenotype modulation, supporting repair of inflamed pulp tissue [50].

Beyond ROS scavenging, neutralizing pro-inflammatory cytokines represents another key strategy. Because oral inflammatory lesions involve complex cytokine networks rather than a single mediator, materials simultaneously targeting bacterial components, cytokines, and oxidative stress may outperform single-factor blockade. For example, catechol-modified chitosan/platelet-rich plasma artificial blood clot hydrogels neutralize lipopolysaccharide (LPS) and pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β), while scavenging ROS and promoting pro-resolving immune responses [51].

Macrophage reprogramming is a central mechanism linking inflammation resolution to tissue regeneration. Although the M1/M2 dichotomy oversimplifies a broader activation continuum, promoting a pro-resolving (M2-like) phenotype remains a key objective. Polysaccharide-based systems can achieve this through drug or extracellular vesicle delivery, modulation of inflammatory pathways, or direct receptor engagement. Glucosaminoglycan-modified nanohydroxyapatite (nHAp) can target macrophage mannose receptors, induce M2-like polarization, and enhance pro-osteogenic signaling, directly linking glycan recognition to bone regeneration [52,53]. Beyond macrophages, polysaccharide-based systems modulate dendritic cell activity and the Th17/Treg balance, suggesting broader coordination of innate and adaptive immunity [54,55].

Polysaccharides also regulate immune responses under explicit LPS exposure, a dominant component of the polymicrobial biofilm microenvironment in periodontal and pulpal lesions. Their effects depend strongly on material, size, and structure. HA shows bidirectional behavior. High-molecular-weight HA restrains inflammatory activation, whereas enzymatically generated low-molecular-weight fragments act as endogenous danger signals, activating innate immune cells through TLR-mediated signaling [56]. Structure-activity analysis indicates that the smallest pro-inflammatory fragment is the tetrasaccharide, while disaccharides competitively block TLR4-dependent signaling [57]. This bidirectionality supports the molecular-weight thresholds discussed in Section 2.1 and suggests that HA materials intended for infected sites must resist premature fragmentation. Chitosan mainly acts as an LPS antagonist. Engineered chitosan nanoparticles reprogrammed macrophage polarization in LPS-exposed periodontal fibroblast-macrophage co-cultures and inhibited root resorption and ankylosis in a delayed tooth-replantation model [58]. This is the strongest oral-context evidence that chitosan-mediated immunomodulation remains active under pathogen-associated molecular patterns (PAMP) challenge. Sulfated polysaccharides shift LPS-activated macrophages toward a pro-resolving phenotype. λ - and κ -carrageenan oligosaccharides suppress TNF- α , IL-6, and IL-1 β through the TLR4/nuclear factor- κ B (NF- κ B) and p38/c-Jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK) pathways [59,60]. 2-N,6-O-sulfated chitosan promotes M2 polarization and protects against LPS-driven inflammatory bone loss [61]. Fucoidan suppresses LPS-induced inflammatory mediators in vitro and in vivo [62], and as hybrid hydroxyapatite nanoparticles, it promotes osteogenic differentiation of PDL stem cells (PDLSCs) under inflammatory conditions [63]. Most of these findings, however, derive from purified LPS stimulation, and their translation to complex polymicrobial biofilm settings cannot be assumed. Accordingly, recent periodontitis-targeted designs combine fucoidan-based matrices with antimicrobial or photothermal components rather than relying on immunomodulation alone [64,65].

3.3. Biomineralization Regulation

Biomineralization is central to regenerating hard tissues such as dentin, alveolar bone, and cementum, acting in concert with cell recruitment, matrix deposition, and vascularization to restore functional tissue. Through native or engineered functional groups such as carboxyl, phosphate, and sulfate moieties, polysaccharides electrostatically attract calcium ions, serving as nucleation sites for mineralization or biomimetic templates that direct ordered mineral formation.

Representative studies illustrate these mineralization-directing roles: a hydroxypropyl methylcellulose/carboxymethyl chitosan double-network hydrogel stabilized amorphous calcium phosphate precursors and guided the intrafibrillar mineralization of demineralized dentin, highlighting their potential as biomimetic templates for dentin remineralization [66]. In another example, phosphate-functionalized cellulose nanofibers stimulated hard-tissue-related gene expression in human DPSCs without exogenous mineralization inducers, demonstrating that chemical modification transforms otherwise bioinert polysaccharides into mineralization-instructive scaffolds [67].

3.4. Spatiotemporal Delivery of Bioactive Molecules and Cell-Free Therapeutic Cargos

Polysaccharides serve as effective carriers for localized, controlled, and sequential release of drugs, growth factors, and exosomes. By fine-tuning release kinetics and spatial distribution, polysaccharide-based systems can orchestrate distinct stages of regeneration, including early infection control, inflammation resolution, stem cell recruitment, odontogenic or osteogenic differentiation, angiogenesis, and neural ingrowth. Sequential-release polysaccharide hydrogels first release antibiotics for infection control and then deliver BMP-2 and TGF- β 1 to promote odontogenic differentiation [68]. Polysaccharide hydrogels can also deliver cell-free regenerative cargo, as exemplified by the apoptotic-vesicle-laden silk fibroin/alginate system in Section 4.1.2, which circumvents the limitations of exogenous stem cell transplantation [69].

4. Tissue-Specific Applications of Polysaccharide-Based Biomaterials

4.1. Pulp-Dentin Complex Regeneration

Regeneration of the pulp-dentin complex remains a central challenge in oral regenerative medicine, as it requires both vascularization and innervation of pulp tissue alongside the induction of reparative dentin with a regular tubular structure. Application strategies of polysaccharide-based biomaterials fall into three clinical scenarios: direct pulp capping and pulpotomy, revascularization of immature necrotic teeth, and integrated pulp-dentin construction.

4.1.1. Pulp Capping and Reparative Dentin Formation

Pulp capping aims to induce a reparative dentin bridge at the injury site, preserving pulpal vitality. As natural biomacromolecules, polysaccharides facilitate the recruitment, proliferation, and odontogenic differentiation of DPSCs by mimicking the extracellular matrix, delivering bioactive molecules, and providing a mineralization-supportive microenvironment.

Clinically, a sodium alginate hydrogel incorporating treated dentin matrix (TDM) has shown outstanding dentin bridge formation capacity: in a 2-year randomized trial, this TDM/alginate hydrogel achieved outcomes comparable to Biodentine and mineral trioxide aggregate (MTA) while generating thicker, more radiodense bridges, and histology confirmed tubular reparative dentin after direct pulp capping [17,18]. Chitosan scaffolds have also attracted attention: their cationic charge, biocompatibility, and modifiability enable integration with cells, inorganic particles, or mineral-releasing coatings, and chitosan hydrogels encapsulating stem cells and TiO₂ nanoparticles promoted complete dentin bridge formation and neovascularization in pulp exposure models [70].

Other polysaccharide systems also exhibit dentin regeneration capacity: hydroxypropyl methylcellulose/carboxymethyl chitosan double-network hydrogels stabilize amorphous calcium phosphate precursors and promote dentin remineralization, highlighting how polysaccharide networks establish a mineralization-conducive microenvironment [66].

4.1.2. Pulp Regeneration and Revascularization

For immature permanent teeth with necrotic pulp or periapical pathology, the core strategy of revascularization is to induce blood clot formation and facilitate stem cell homing, ultimately restoring viable pulp

tissue with functional vascular and neural components. Polysaccharide-based hydrogels can serve as scaffolds to stabilize the blood clot, provide a three-dimensional microenvironment, and deliver bioactive molecules.

Chitosan hydrogels are among the most extensively studied materials for pulp regeneration. Enzyme-modified chitosan combined with blood clots enhanced vital tissue formation and periapical healing relative to native chitosan or clots alone, with clinical data indicating improved recovery of pulp sensitivity [23,25]. Beyond clot stabilization, they can also serve as carriers for cell-free regenerative signals. Silk fibroin/sodium alginate hydrogels loaded with apoptotic vesicles facilitated vascularized and innervated pulp-like tissue regeneration, underscoring the potential of cell-free cargo delivery [69]. HA hydrogels have likewise been investigated: in a clinical case, combining an HA hydrogel with a blood clot resulted in apical closure and restoration of normal periapical structures [71]. However, different HA formulations may elicit distinct inflammatory responses, indicating that molecular weight, purity, and formulation design critically determine therapeutic efficacy [72].

Beyond these single-purpose approaches, integrated strategies—combining composite scaffolds, sequential delivery systems, and spatially organized fabrication—are being explored to synchronously orchestrate mineralization, vascularization, innervation, and cell recruitment within the pulp–dentin complex [73–76].

4.2. Periodontal Tissue Regeneration

Periodontitis progressively destroys the periodontal tissues (gingiva, alveolar bone, PDL, and cementum), compromising the alveolar bone-PDL-cementum complex responsible for tooth stability. Periodontal regeneration therefore demands coordinated infection control, inflammation resolution, maintenance of regenerative space, and guided reconstruction of the periodontal attachment. Polysaccharide-based biomaterials are well suited to these tasks, given their biocompatibility, biodegradability, chemical tunability, and capacity for localized delivery. Their applications are reviewed below as barrier membranes and spatially organized scaffolds, injectable hydrogels, and integrated systems for bone-PDL-cementum reconstruction.

4.2.1. Barrier Membranes and Spatially Organized Scaffolds

Guided tissue regeneration (GTR)/guided bone regeneration (GBR) membranes act as physical barriers that block epithelial cells and fibroblasts from invading the defect site, creating space for preferential migration of PDL cells and osteoblasts. Polysaccharides are promising membrane materials given their biocompatibility and ample modification sites, and have been developed into active platforms that go beyond barrier function: delivering drugs, resisting infection, modulating immunity, guiding bone formation, and compartmentalizing tissue repair.

One key approach is functionalization with antimicrobial, anti-inflammatory, or pro-osteogenic agents. Chitosan-based nanofibrous membranes incorporating doxycycline or other antimicrobials suppress major periodontal pathogens while providing sustained release and biocompatibility [77]. Bilayer polysaccharide films composed of gellan gum/hydroxyethyl cellulose or HA enable staged delivery of antimicrobial and pro-regenerative agents [78,79]. Antioxidant and osteogenic functionalization has also been explored. Chitosan/gelatin membranes incorporating α -arbutin protected osteoblast function under oxidative stress and promoted bone formation [80], whereas simvastatin- or mogroside V-loaded chitosan electrospun membranes enhanced bone healing and reduced inflammatory responses, even in compromised regenerative environments such as diabetes [81,82].

Spatially designed membrane architecture is another key direction. An ideal periodontal membrane must fulfill distinct functions on opposing sides: the soft-tissue-facing surface should resist bacterial colonization and protein adhesion, while the bone-facing surface should promote cell attachment, osteogenic differentiation, and mineralized tissue formation. Chitin-based Janus hydrogel membranes, for instance, combine an anti-adhesive, antimicrobial outer layer with an osteogenic inner layer, achieving superior periodontal bone regeneration versus commercial collagen membranes in preclinical models [28]. Agarose-based asymmetric and carrageenan-containing multilayer membranes add antimicrobial and calcium-releasing functions [36,37].

Beyond drug loading and architecture, mineralization-enhanced membranes are designed to recapitulate the mineralized extracellular matrix of bone. Biomimetic hydroxyapatite coatings on fish-scale collagen/chitosan electrospun membranes enhanced PDL cell adhesion, migration, proliferation, and osteogenic differentiation, outperforming commercial Bio-Gide® membranes in periodontal defects [83]. Chitosan/xanthan gum polyelectrolyte membranes incorporating hydroxyapatite further show that mineral content and surface roughness can be tuned to balance mechanical stability and biological activity [84].

4.2.2. Injectable Hydrogels for Inflammation Control and Periodontal Regeneration

Injectable hydrogels suit periodontal regeneration: they conformally fill irregular defects, gel in situ, and deliver bioactive molecules. Current designs reshape the inflamed niche, deliver pro-regenerative cargos, or

integrate multiple functions in stimulus-responsive platforms. The first converts the lesion into a regeneration-permissive microenvironment: HA/chondroitin sulfate hydrogels capture stem cell-derived factors and shift the cytokine balance from TNF- α toward interleukin-10 [34]; thermosensitive chitosan gels co-loaded with granulocyte-macrophage colony-stimulating factor (GM-CSF) and resveratrol restore dendritic-cell and T-cell homeostasis in high-fat-diet periodontitis [55]; and, in diabetic settings, oxidized HA/gelatin methacrylate (GelMA) and alginate/carboxymethyl chitosan systems pair ROS scavenging with macrophage M2 polarization, attenuating inflammatory bone loss [85,86].

Clinical evidence is strongest for pro-regenerative cargo delivery. A fucoidan-chitosan thermosensitive hydrogel produced greater intrabony defect fill than concentrated growth factor controls in a randomized trial [41], and chitosan thermosensitive gels with hydroxyapatite and poly(lactic-co-glycolic acid) (PLGA) showed promise in chronic periapical periodontitis [87]. In canine furcation defects, melatonin-loaded alginate/chitosan hydrogels and BMP-7-delivering chitosan thermogels regenerated bone, cementum, and organized PDL fibers [88,89]—tri-tissue evidence considered further in Section 4.2.3. Other formulations deliver ions, small molecules, stem cells, and extracellular vesicles [90,91].

Microenvironment-responsive systems use dynamic bonds or degradable linkages that sense ROS, pH, glucose, or hydrogen sulfide and release therapeutics on demand [49,92–94].

A further class of multicomponent hydrogels operates without external fields or stimulus-responsive designs: integrating antimicrobial agents, anti-inflammatory drugs, bioactive ions, growth factors, natural products, or adhesive networks to concurrently enhance wet adhesion, local retention, antimicrobial efficacy, immune modulation, and osteogenesis [95–98]. Most remain at the small-animal proof-of-concept stage, and compositional complexity may complicate manufacturing, quality control, and regulatory translation.

Clinical data are accumulating beyond the fucoidan-chitosan hydrogel [41]: an oscillating chitosan brush combined with an adjunctive chitosan hydrogel achieved greater probing-depth reduction and pocket closure than debridement alone in residual pockets of stage III/IV periodontitis [99]. Polysaccharide systems may thus serve as both regenerative scaffolds and adjuncts to nonsurgical therapy; both roles await confirmation in larger trials with histological or long-term functional endpoints.

4.2.3. Toward Functional Regeneration of the Bone-PDL-Cementum Complex

The ultimate goal of periodontal regeneration is concurrent, well-organized reconstruction of alveolar bone, PDL, and cementum, establishing functional attachment in which inserting collagen fibers anchor into both new cementum and alveolar bone. Nevertheless, intrinsic disparities among these tissues in developmental origin, cellular composition, and regenerative capacity make this integration technically demanding: in practice, most studies still rely on bone regeneration as the primary endpoint, with systematic assessment of cementum and PDL formation, especially interfacial integration, remaining scarce; studies demonstrating concurrent regeneration of all three tissues in a single model are especially valuable.

Injectable polysaccharide-based composite hydrogels show considerable promise in large-animal furcation defects. Melatonin-loaded alginate-chitosan/ β -tricalcium phosphate (β -TCP) hydrogels induced lamellar new bone formation, well-organized PDL-like fibers, and continuous acellular cementum coverage in canine class II furcation defects [88]. Likewise, BMP-7-loaded chitosan thermosensitive hydrogels promoted coordinated regeneration of new bone, new cementum, and organized PDL fibers in canine class III furcation defects, without obvious ankylosis or inflammatory response [89].

Beyond biochemical induction, scaffold architecture critically guides PDL fiber orientation and preserves compartmentalized healing. Freeze-cast, aligned chitosan-oxidized chondroitin sulfate porous scaffolds promoted more organized PDL-like tissue formation and cementum-like matrix deposition than randomly structured scaffolds [100]. Multilayer systems, such as chitosan/polyglutamic acid/nHAp hydrogels combined with nanofibrous barrier membranes and platelet-rich fibrin, further integrate spatial maintenance, growth-factor delivery, and soft-tissue exclusion for bone-PDL-cementum regeneration [101].

Overall, functional periodontal regeneration requires histological and biomechanical evidence of new cementum, functionally oriented PDL fibers, and stable attachment to both hard tissues. Future polysaccharide-based systems should therefore prioritize spatially patterned architectures and temporally regulated bioactive delivery. To operationalize this shift, we propose a minimum evidence set that future studies of all periodontal regenerative materials should adopt: (1) histological co-localization of all three attachment components in the same defect and section, namely new cementum on the denuded root surface, functionally oriented PDL fibers inserting into new cementum and new bone (Sharpey's-fiber-type insertion), and new bone filling the defect, evaluated at two or more time points, with the final assessment performed no earlier than 8-12 weeks post-implantation, as

achieved in canine models with cross-linked hyaluronic acid gels [102] and, ectopically, with orthogonally fiber-guided biphasic scaffolds [103]; (2) explicit exclusion of repair-type healing: the long junctional epithelium and ankylosis or root resorption reported as absent or quantified, since their absence distinguishes regeneration from repair [104]; (3) defect model stringency: a critical-size or furcation-type defect in a large animal (canine/minipig) or human histological block study, because rodent defects heal spontaneously [105]; (4) reporting standardization following American Academy of Periodontology (AAP) Regeneration Workshop recommendations, which define defect fill and clinical attachment level as primary and secondary outcomes and require histologic proof of principle [106]; and (5) functional evidence where feasible, meaning at least one biomechanical readout (e.g., tooth mobility or ex vivo attachment strength) demonstrating that the regenerated attachment transmits load [107].

Admittedly, few current studies of polysaccharide-based periodontal materials meet all five criteria simultaneously, which is itself an accurate measure of the field's distance from demonstrated functional periodontal regeneration.

4.3. Craniofacial Bone Regeneration

Craniofacial bone defects may arise from trauma, tumor resection, congenital anomalies such as alveolar cleft, or other etiologies. Conventional graft materials often fall short for irregular craniofacial defects. Polysaccharide-based materials, benefiting from excellent biocompatibility, biodegradability, processability, and versatile functionalization, have demonstrated distinct advantages in craniofacial bone regeneration. Three functional strategies are discussed below: osteoconductive and structurally biomimetic scaffolds, bioactive molecule delivery and functionalized systems, and immunomodulatory and microenvironment-responsive materials.

4.3.1. Structural and Osteoconductive Scaffold Design

Structural and osteoconductive scaffolds provide space maintenance, appropriate porosity, mechanical support, and mineralization cues, without relying primarily on exogenous growth factors. Polysaccharides such as alginate, chitosan, HA, chondroitin sulfate, bacterial cellulose, and mucilage-based polymers can be integrated with hydroxyapatite, bioactive glass, calcium phosphate, or synthetic polymers to fabricate bone-mimetic scaffolds. For instance, bilayer calcium alginate scaffolds with differential degradation rates replicate the cortical-cancellous bone architecture, preserving the external contour while facilitating internal tissue ingrowth [108], and gelatin/alginate-bioactive glass scaffolds enhance bone formation in mandibular and cranial defect models [109].

Composite reinforcement further enhances the mechanical strength and osteoconductive properties of these scaffolds: bacterial cellulose-reinforced polycaprolactone (PCL) scaffolds and eggshell membrane/laponite/chitosan/alginate nanocomposites improve cell adhesion, mineral deposition, macrophage modulation, and new bone formation in craniofacial and extraction socket models [110,111].

Although most evidence remains preclinical, early clinical investigations suggest translational relevance. Acemannan sponges for extraction socket preservation and injectable dextrin-based hydrogels combined with synthetic bone substitutes for alveolar ridge preservation have demonstrated favorable results in maintaining ridge dimensions, promoting new bone formation, or enhancing implant primary stability [112,113]. Long-term studies with standardized outcome measures are warranted.

4.3.2. Delivery of Bioactive Molecules, Ions, and Cell-Free Cargos

Polysaccharide-based scaffolds serve as versatile delivery platforms for pro-osteogenic, pro-angiogenic, antimicrobial, or immunomodulatory agents. Their hydrophilic networks, tunable charge, biodegradability, and readily modifiable functional groups support sustained release, electrostatic adsorption, or microenvironment-responsive delivery. Representative cargos include growth factors, drugs, bioactive ions, small molecules, exosomes, and other cell-free entities.

For cell-free therapy, quaternized chitosan has been incorporated into 3D-printed scaffolds to electrostatically adsorb mesenchymal stem cell-derived exosomes, enhancing vascularized bone regeneration in cranial defects [26], while alginate/HA hydrogels support near-infrared-regulated exosome secretion from encapsulated cells [114]. Drug- and growth factor-delivery scaffolds, including dextran-, chitosan-, and polyethylene glycol (PEG)-containing composite systems, have been used to release simvastatin, vancomycin, or insulin-like growth factor-1 (IGF-1), promoting osteogenesis, angiogenesis, and infection control in cranial or mandibular defects [115,116].

Bioactive ion and small-molecule delivery offers another strategy. ROS-responsive HA/poly(vinyl alcohol) (PVA) hydrogels, methacrylated HA hydrogels incorporating DNA tetrahedra, and Zn²⁺-cross-linked alginate hydrogels have delivered peptides, asiatic acid, EGCG, or metal ions to regulate oxidative stress, macrophage

polarization, collagen deposition, and osteogenic differentiation [117,118]. These platforms coordinate osteogenic and angiogenic signals while adapting to infected or oxidatively stressed microenvironments.

4.3.3. Immunomodulatory and Microenvironment-Responsive Materials

Craniofacial bone defects frequently arise in inflammatory, infected, diabetic, or metabolically compromised microenvironments. Accordingly, immunomodulation has become a key design principle. Beyond simple osteoconductive support, these systems aim to regulate macrophage polarization, alleviate oxidative stress, enhance angiogenesis, and dynamically recruit or guide endogenous stem cells.

Representative examples include polyhedral oligomeric silsesquioxane (POSS)-functionalized carboxymethyl chitin microspheres and chondroitin sulfate lithium hydrogels, which promote M2-like macrophage polarization and enhance osteogenic or pro-angiogenic responses under challenging conditions [119,120]. Dynamic alginate/PVA-bioactive glass hydrogels further illustrate how mechanical evolution can coordinate sequential regeneration: an initially soft matrix favors mesenchymal stem cell recruitment, while subsequent ion-triggered stiffening supports osteogenic differentiation [121].

Overall, polysaccharide-based materials offer versatile strategies for craniofacial bone regeneration, spanning structural support, osteoconductive mineralization, therapeutic delivery, and immune microenvironment modulation. Future efforts should aim to reduce unnecessary system complexity while clarifying each component's contribution, and to validate performance in clinically relevant large-animal or patient-specific defect models.

5. Engineering Design Strategies for Polysaccharide-Based Oral Regenerative Biomaterials

Although natural polysaccharides exhibit favorable biocompatibility and biological activity, their mechanical properties, degradation behavior, hydrophilicity/hydrophobicity, and functional versatility are often insufficient to directly meet the demands of complex oral tissue regeneration. Through targeted engineering strategies, including chemical, physical, and specialized approaches, polysaccharides can be purposefully endowed with novel functionalities such as antimicrobial activity, pro-mineralization capacity, cross-linkability, and stimuli-responsive release in oral tissue regeneration.

Each strategy in this section should be read against the oral-specific constraints introduced in the Introduction. Continuous salivary flow and masticatory shear demand materials that either adhere tenaciously to wet hard and soft tissues or gel rapidly *in situ* before being displaced; catechol- and quaternary-ammonium-mediated wet adhesion (Section 5.1) and fast ionic or thermosensitive cross-linking (Sections 5.1 and 5.2) answer this constraint directly. The enzymatic landscape of saliva and inflamed tissue (hyaluronidase, lysozyme, collagenase, and bacterial proteases) sets a lower bound on network stability and explains why cross-linking density, chain length, and degree of substitution are tuned not only for mechanics but for enzymatic resistance (Sections 5.1 and 5.2). The polymicrobial biofilm that colonizes most defect sites shifts the design objective from sterile-scaffold to infection-tolerant performance, motivating antimicrobial functionalization, microenvironment-responsive cargo release, and bacterial-component-neutralizing capacity (Sections 3.2, 5.1, and 5.3). Finally, the intermittent high loads of mastication constrain scaffold stiffness and fatigue behavior at load-bearing craniofacial sites, driving composite reinforcement (Section 5.2) and patient-specific fabrication (Section 6.1).

A second design principle concerns the temporal relationship between scaffold degradation and new-tissue formation. As a general rule, degradation should lag slightly behind tissue formation, so that the material maintains space, mechanical support, and barrier function until the regenerating tissue assumes structural competence; scaffolds that degrade too rapidly collapse the defect space, whereas those that persist too long obstruct ingrowth and can elicit foreign-body reactions [122]. This principle must be calibrated against the very different formation kinetics of the three target tissues. Pulp-like connective tissue and a reparative dentin bridge form within weeks, favoring fast, cleanly resorbable matrices that do not obstruct reinstrumentation. The organization of functionally oriented PDL fibers and new cementum requires far longer than bone filling alone, which is why barrier membranes must remain occlusive during the early weeks of healing; the tendency of non-crosslinked collagen membranes to degrade within two to four weeks, before the attachment apparatus can reform, is a recognized limitation that crosslinking strategies are designed to overcome [123]. Critical-size craniofacial defects at load-bearing sites require months for structural competence, favoring slower, controllably degrading systems; differential rates have been exploited deliberately, as in bilayer alginate scaffolds that preserve cortical contour while degrading faster in the cancellous interior (Section 4.3.1). Polysaccharides are unusually well suited to this kinetic matching because degradation can be tuned continuously through cross-link density, molecular weight, oxidation degree, and sulfation or acetylation pattern, as demonstrated experimentally by alginate-*b*-polylactic acid (PLA) diblock copolymers whose degradation rate is set by the PLA block size and diblock content [124].

Systematic studies that simultaneously quantify degradation and tissue-formation kinetics over time in oral defect models remain scarce, and we regard this synchronization problem as an important open question for the field.

5.1. Chemical Functionalization for Bioactivity and Cross-Linkability

Chemical functionalization broadens the design space of natural polysaccharides by introducing bioactive or reactive moieties (carboxymethyl, phosphate, sulfate, aldehyde, methacryloyl, quaternary ammonium, catechol) onto polymer backbones or by forming interchain covalent cross-links, fine-tuning solubility, charge density, mineral affinity, wet adhesion, cross-linkability, degradation, and environmental responsiveness.

Direct functionalization introduces moieties conferring biological or physicochemical activity. Carboxymethylation enhances water solubility and calcium-chelating capacity, rendering carboxymethyl chitosan particularly suitable for mineralization-guided pulp-dentin and bone regeneration. For instance, carboxymethyl chitosan combined with nano-hydroxyapatite synergistically provides calcium-binding sites and nucleation cues for mineral deposition, promoting human DPSCs adhesion, proliferation, and odontogenic differentiation [74]. Phosphorylation offers a parallel mineralization-oriented route: phosphate-functionalized cellulose nanofibers transform bioinert cellulose into a scaffold promoting hard-tissue gene expression without exogenous odontogenic inducers [67]. Quaternization introduces permanent positive charges onto chitosan, enhancing solubility, antimicrobial activity, and electrostatic adsorption of negatively charged cargo such as extracellular vesicles; quaternized chitosan has thus served as an exosome-binding component in bone-regenerative scaffolds [26].

Other modifications mainly introduce reactive sites for network formation. Methacrylation introduces photo-cross-linkable double bonds, enabling polysaccharides such as HA or chitosan to form in situ gelling injectable scaffolds for periodontal regeneration [125,126]. Aldehyde modification, typically via periodate oxidation, allows Schiff base formation with amino-containing polymers and is widely used for injectable, self-healing, pH-responsive hydrogels. For example, the oxidized alginate/PVA-bioactive glass hydrogel in Section 4.3.3 achieves ion-triggered stiffening within an injectable dynamic network, coordinating cell homing with subsequent osteogenic differentiation [121]. Oxidized alginate microgels can also act as rapidly degradable microcarriers promoting high-density cell aggregation and self-organization [127].

Cross-linked network construction enables precise control of mechanical stability, degradation, injectability, and release kinetics. Dynamic covalent cross-linking, notably Schiff base chemistry, suits injectable and self-healing hydrogels, as reversible bonds facilitate shear-thinning, defect filling, and gradual remodeling. For instance, the pulp-like double-network hydrogel in Section 3.1 illustrates how combining glycol chitosan-based Schiff base cross-linking with alginate- Ca^{2+} ionic cross-linking yields stiffness-matched, injectable matrices for pulp regeneration [47]. In contrast, stable covalent cross-linking yields more durable networks suited to sustained therapeutic delivery. For example, 1,4-butanediol diglycidyl ether (BDDE)-cross-linked HA/carboxymethyl chitosan hydrogels form stable injectable matrices for local delivery of antibiotics and pro-angiogenic factors [128].

Beyond these categories, grafting with catechol or gallic acid further enhances wet adhesion, antioxidant activity, antibacterial efficacy, and immune regulation. For instance, gallic acid-modified chitosan systems integrate antioxidant, antimicrobial, and pro-osteogenic functions in periodontal regeneration [97]. Chemical functionalization thus serves as a toolbox for tailoring properties to each target tissue.

5.2. Composite and Physical Assembly Strategies

Physical assembly strategies broaden polysaccharide function without altering primary chemical structure, modulating performance through non-covalent interactions, blending, surface coating, or altered molecular organization and topography. Compared with covalent modification, it is milder for integrating cells, vesicles, drugs, and inorganic particles, enabling injectable or in situ gelation, mechanical strength, osteoconductivity, and localized delivery.

A major route is physical cross-linking via ionic, hydrogen-bonding, hydrophobic, or thermosensitive interactions. Representative examples—alginate- Ca^{2+} ionic networks and chitosan/ β -glycerophosphate thermogels—undergo sol-gel transition under physiological conditions and conformally fill pulp, periodontal, or bone defects. Such matrices stabilize blood clots and retain cells or therapeutics, providing minimally invasive platforms for localized regeneration [96,129]. Hybrid systems adding secondary covalent or supramolecular interactions further improve mechanical stability, self-healing, and controlled release, as illustrated by alginate double-network hydrogels for antibacterial, antioxidant, and periodontal bone-regenerative applications [130].

Blending, compositing, and coating offer modular strategies for integrating complementary functionalities. Inorganic particles—hydroxyapatite, bioactive glass, calcium phosphate, magnesium-containing compounds—supply mineral nucleation cues and bioactive ions for osteo/odontogenic stimulation, while synthetic polymers

(PCL, PLA, PVA, PEG) and gelatin enhance mechanical strength, shape stability, and barrier or multilayer architecture [77,131]. Matrices can also be loaded with drugs, growth factors, small molecules, cells, extracellular vesicles, or probiotics, with release governed by mesh size, electrostatics, degradation, or carrier incorporation [26,81,132]. Surface coating and physical deposition add hydrophilicity, ion release, antimicrobial or anti-inflammatory activity, and osseointegration to preformed scaffolds and implants without altering bulk architecture [133,134].

5.3. Smart and Bioinstructive Engineering

Beyond chemical functionalization and physical assembly, a third set of strategies endows polysaccharide materials with specific biomolecular recognition, active cell instruction, or self-tracing. These smart and bioinstructive designs differ from the physicochemical stimulus-responsive systems discussed in Sections 5.1 and 4.2.2 (e.g., pH-, ROS-, glucose-, or light-triggered release) in that function is governed by defined molecular-recognition events (enzymatic cleavage, aptamer-ligand binding, or glycan-receptor interactions) rather than by bulk physicochemical changes.

Enzyme-responsive designs exploit elevated host or microbial enzyme activity at diseased sites as a built-in disease-state-dependent trigger. A chitosan membrane incorporating polyphosphoester and minocycline released its antibiotic payload in response to enzymatic activity within infected periodontal pockets and supported alveolar bone repair in a rat periodontal defect model [135]. Likewise, an enzyme-triggered chitosan-based delivery system for peri-implantitis prevention releases its payload upon enzymes characteristic of the peri-implant biofilm [136]. These examples show how the enzymatic signature of inflamed oral tissues can align therapeutic release with disease activity.

Aptamer- and glycan-functionalized systems introduce molecular-recognition motifs that actively recruit or instruct defined cell populations. In a rat periodontal defect model, hyaluronic acid/polyethylene glycol hydrogels bearing fibronectin-recognizing aptamers selectively adsorbed fibronectin from blood, promoted platelet activation, and enhanced new bone formation, demonstrating that aptamers give otherwise passive matrices a dynamic dialogue with the host milieu [137]. An aptamer (Pt-1) selected by cell-based systematic evolution of ligands by exponential enrichment (SELEX) against human DPSCs was immobilized on a chondroitin sulfate methacrylate hydrogel, enabling precise in situ homing of endogenous mesenchymal stem cells and enhancing osteo/odontogenic differentiation [138]. Glycan-mediated recognition offers a natively polysaccharide route to bioinstruction: as discussed in Section 3.2, glucomannan-modified nHAp targets macrophage mannose receptors to induce pro-resolving polarization and enhance osteogenic signaling [52,53].

Carbonization/nanomerization converts polysaccharides into fluorescent carbon dots, integrating fluorescence tracing with biological activity. Carboxymethyl chitosan/citric-acid carbon dots synthesized by one-step hydrothermal treatment reach a quantum yield of 52.93% and were internalized by MC3T3 cells, while upregulating osteogenesis-related genes and promoting bone regeneration in rat cranial defects [139].

Decellularization offers another bioinstructive approach by preserving tissue-derived ECM components, including GAGs such as HA and chondroitin sulfate. A decellularized bovine dental pulp ECM hydrogel, confirmed by Alcian blue staining to retain GAGs, self-assembled after pepsin digestion and sustained release of endogenous VEGF, FGF-2, TGF- β 1, and BMP-2 for 14 days. In a canine mature-tooth periapical periodontitis model, this hydrogel formed more orderly, highly vascularized connective tissue with significantly less periapical inflammation than the blood-clot control [140].

Overall, smart and bioinstructive engineering marks a shift from conventional modification toward functionally programmed regenerative systems, yet these strategies remain at an early stage. For carbon dots, how precursor chemistry and carbonization conditions govern fluorescence behavior, biodegradation, and long-term biosafety remains unclear. For decellularized ECM hydrogels, batch variability, sterilization, and standardization pose major translational challenges. Future efforts should integrate smart responsiveness, traceability, and tissue-specific bioinstruction while preserving material simplicity, safety, and regulatory feasibility.

6. Advanced Fabrication Platforms

This section reviews three fabrication platforms for oral tissue regeneration: 3D bioprinting, electrospinning, and microsphere-based delivery systems. Although each works by distinct principles and builds structures at different scales, they complement one another in recreating the native microenvironment of oral tissues. Figure 2 summarizes their key characteristics and representative applications.

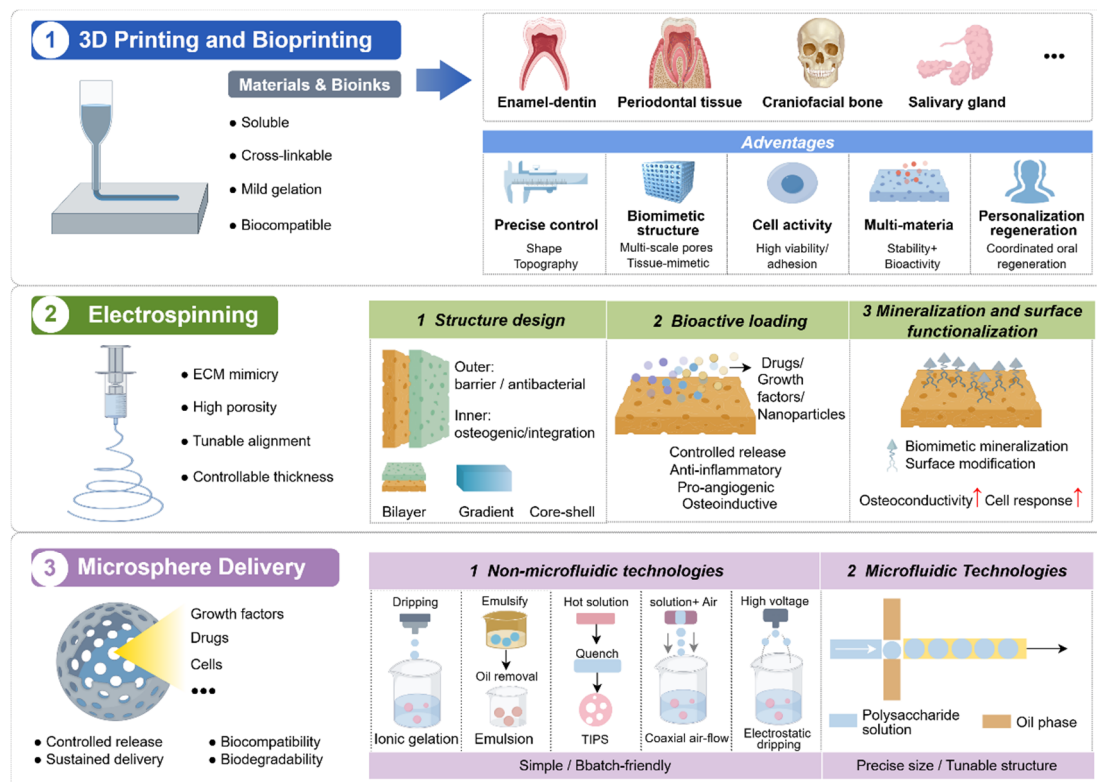


Figure 2. Overview of advanced fabrication platforms for oral regeneration.

6.1. 3D Printing and Bioprinting for Personalized and Spatially Organized Regeneration

In oral and craniofacial regeneration, 3D printing and bioprinting precisely control patient-specific scaffold geometry, internal pore architecture, spatial compartmentalization, and multi-material organization. Polysaccharides are central to printable bioinks: water solubility, tunable viscosity, ionic or photo-cross-linkability, and mild gelation facilitate cell encapsulation, bioactive molecule delivery, and defect-conforming construction, while often dictating print fidelity, degradation, cell compatibility, and spatiotemporal presentation of regenerative signals.

In pulp-dentin and periodontal regeneration, 3D printing predominantly fabricates compartmentalized models or multi-phase scaffolds replicating tissue interfaces. For the pulp-dentin complex, printed constructs of GelMA, alginate, collagen, dentin powder, or modified chitosan reconcile external structural integrity with internal cell viability and odontogenic capacity [141,142]. In periodontal applications, polysaccharide-containing bioinks enhance protein-based matrix printability and incorporate bioactive glass microspheres, stem cells, or growth factors, supporting coordinated regeneration of periodontal soft tissue, PDL, and alveolar bone [143,144]. Hybrid PCL/chitosan scaffolds combine 3D-printed macroporous frameworks with polysaccharide-based microporous networks, achieving mechanical support, antimicrobial function, and PDLSC responsiveness [145].

For craniofacial bone regeneration, the most prominent application domain, 3D-printed polysaccharide scaffolds enable patient-specific defect matching, bilayer structures mimicking cortical and cancellous bone, oriented channels, mechanical reinforcement, and localized osteogenic or antimicrobial delivery. Alginate, bacterial cellulose, GelMA, gelatin, HA, and carboxymethyl chitosan enhance printability, ion-cross-linked stability, cell adhesion, and bioactive cue retention. Representative strategies include aligned nanopatterned and channel-containing alginate/bacterial cellulose/GelMA scaffolds for vascularized bone repair [146], bilayer calcium alginate scaffolds with differential degradation profiles for mandibular defect reconstruction [108], gelatin-alginate bioinks carrying BMP-2 delivery systems [143], bioactive glass-alginate-gelatin composites [147], and antimicrobial ECM-based hydrogels loaded onto printed nHAp/PLA scaffolds [148]. Polysaccharide-assisted 3D printing is thus progressing beyond shape fabrication toward spatially programmed, multifunctional constructs integrating structural, therapeutic, and microenvironmental functions.

The primary value of 3D/bioprinting thus lies less in fabricating scaffolds than in organizing polysaccharide-based materials, cells, minerals, and bioactive cargos into spatially defined architectures meeting the biological requirements of oral and craniofacial tissues. Future efforts should prioritize printable formulations with simplified

compositions, reproducible cross-linking, predictable degradation, and patient-specific imaging compatibility, while preclinical evidence must advance to large-animal models with functional endpoints (Section 7.2).

6.2. Electrospinning for Barrier Membranes and Fibrous ECM Mimicry

Electrospinning fabricates nanofibrous membranes that emulate extracellular matrix architecture, offering high surface area and porosity, tunable fiber alignment, and controllable thickness. In oral and craniofacial regeneration, polysaccharide-containing membranes serve primarily as barrier membranes for GTR and GBR and as periodontal scaffolds. Because most natural polysaccharides are difficult to electrospin alone, they are blended with PCL, gelatin, or silk fibroin. In these blends, polysaccharides impart hydrophilicity, antimicrobial activity, bioactive molecule retention, mineralization sites, and cell-interactive cues.

A key advantage is the capacity to fabricate multilayer, gradient, or core-shell membranes with spatially segregated functions. As in Section 4.2.1, the soft-tissue-facing side should resist invasion while the bone-facing side promotes osteogenesis. Bilayer or functionally graded membranes of PCL/chitosan, silk fibroin, poly(D, L-lactide) (PDLA), or chitosan nanospheres integrate antimicrobial protection, sustained bioactive molecule delivery, mechanical support, and osteogenic guidance [131,149]. Core-shell fibers with magnesium-containing cores and gelatin shells further combine controlled ion release with cell-adhesive surfaces, facilitating PDLSCs proliferation and osteogenic differentiation [150].

Electrospun membranes also function as localized delivery systems for antimicrobial agents, growth factors, natural products, or functional nanoparticles. For instance, PVA/sodium alginate membranes loaded with concentrated growth factors and nHAp were applied in extraction socket repair, combining rapid wound coverage, fibrin-associated bioactivity, and mineralization support [151]. Chitosan-based nanofibrous membranes incorporating doxycycline enable sustained local antimicrobial release against periodontal pathogens [77].

An alternative strategy enhances the osteoconductivity of electrospun membranes through biomimetic mineralization and surface functionalization. As discussed in Section 4.2.1, hydroxyapatite deposition on fish-scale collagen/chitosan fibers outperformed commercial collagen membranes in periodontal defects [83]. Likewise, chemically or physically modified chitosan membranes exhibited enhanced bone formation relative to conventional collagen membranes in cranial defect models [152]. Carboxymethyl chitosan combined with mesoporous bioactive glass nanoparticles enabled ion release, immune modulation, and sustained pro-osteogenic stimulation [153].

6.3. Microsphere-Based Delivery Systems

Microsphere-based systems enable localized, sustained, and tunable delivery of drugs, growth factors, ions, cells, extracellular vesicles, or mineralization precursors for pulp-dentin, periodontal, and craniofacial bone regeneration. They can be injected into irregular defects, incorporated into hydrogels or printed constructs, while protecting labile cargos. Polysaccharides such as alginate, chitosan, HA, and carboxymethyl chitosan suit microsphere fabrication, offering biocompatibility, biodegradability, mild gelation, and ionic or electrostatic cargo retention. Fabrication strategies comprise scalable conventional non-microfluidic methods and microfluidic approaches for finer control of particle size, morphology, and internal architecture.

Conventional non-microfluidic approaches include ionic gelation, emulsion cross-linking, thermally induced phase separation (TIPS), coaxial airflow extrusion, and electrostatic microencapsulation, among which ionic gelation dominates periodontal and pulp-dentin applications. For instance, chitosan-gentamicin microspheres incorporated into β -TCP/gelatin scaffolds promoted new bone, cementum, and periodontal tissue regeneration in canine furcation defects [154]. Likewise, chitosan microspheres loaded with ginsenoside Rg1, combined with Tideglusib-loaded HA hydrogel, delivered staged angiogenic and odontogenic signaling for pulp-dentin complex regeneration [75].

By regulating droplet generation, cross-linking, and architecture through two-phase flow and chip design, microfluidic technologies produce monodisperse microspheres with tailored concave, core-shell, porous, or stimulus-responsive structures. Microfluidic electrospray has produced concave alginate microspheres combining wet adhesion, photothermal responsiveness, and minocycline delivery for periodontitis treatment [155]. Similarly, droplet-microfluidic systems generate black phosphorus-tagged carboxymethyl chitosan-strontium thermosensitive microspheres whose near-infrared-triggered shrinkage enables pulsatile Sr^{2+} release and osteogenic stimulation in cranial defect model [156]. BMP-2-loaded alginate microspheres in GelMA-based 3D-printed scaffolds prolonged growth factor release and, combined with VEGF and bone marrow mesenchymal stem cells (BMSCs), supported synergistic angiogenesis and bone regeneration [157].

7. Clinical Translation and Future Perspectives

7.1. Material Standardization, Manufacturability, and Regulatory Considerations

Although polysaccharide-based materials hold promise for oral and craniofacial regeneration, clinical translation is limited by standardization, manufacturing, and regulatory challenges. Most polysaccharides vary batch-to-batch in molecular weight, degree of deacetylation, sulfation pattern, degree of substitution, charge density, and impurity profile. Such variability affects degradation, immunomodulation, and delivery, and makes quality control critical [158–160]. Only a few HA- or chitosan-based products have been approved for oral or related indications; most remain at the laboratory or preclinical stage [161,162]. Future efforts should standardize raw-material grading, define critical quality attributes, and develop registration guidelines for these devices.

Manufacturability is another critical bottleneck. Although laboratory-scale techniques such as freeze-drying, electrospinning, microfluidics, and 3D printing generate prototypes, scaling them up while preserving consistent morphology, mechanics, degradation, sterility, and release kinetics is challenging [163,164]. Polysaccharide-based materials are also highly susceptible to humidity, temperature, sterilization, enzymatic degradation, and storage, affecting molecular weight, network architecture, cargo bioactivity, and mechanics. Future efforts should prioritize scalable, automated manufacturing, sterilization-compatible, shelf-stable formulations, and simplified designs that reconcile biological functionality with regulatory and industrial feasibility.

7.2. Clinical Validation and Functional Outcome Assessment

In line with the constraint-to-design framework established at the beginning of Section 5, preclinical testing protocols for these materials should incorporate challenge conditions that recreate the oral-specific constraints introduced above (dynamic saliva exposure, enzymatic degradation, and polymicrobial biofilm co-culture), so that the constraint-to-design-to-testing chain is closed end-to-end. Such testing is now feasible: saliva-derived polymicrobial biofilm models have been established on three-dimensional scaffold substrates and shown to reproduce *in vivo* biofilm-formation dynamics with reasonable fidelity [165,166], while *in situ* comparisons indicate that static, sterile *in vitro* conditions can substantially misrepresent both enzymatic challenge and biofilm colonization [167].

Polysaccharide-based materials have demonstrated regenerative potential in preclinical models. Nevertheless, the current evidence is insufficient for clinical translation. The majority of *in vivo* investigations are short-term assessments conducted in small-animal models, typically spanning 4 to 12 weeks, and lack comprehensive data on long-term safety, degradation behavior, immune responses, and functional outcomes derived from large-animal or clinically relevant defect models [168]. Moreover, considerable heterogeneity in defect size, disease models, control groups, evaluation methodologies, and statistical approaches hampers cross-study comparability and limits the feasibility of meta-analysis [168,169]. Standardized models, reporting standards, and multicenter trials are therefore prerequisites for translation.

Functional outcome assessment should extend beyond radiographic bone fill and short-term histological repair. For pulp-dentin regeneration, evaluation should encompass vascularized and innervated pulp-like tissue, controlled inflammation, organized odontoblast-like cells, and sustained tooth vitality. In periodontal regeneration, success requires the minimum evidence set defined in Section 4.2.3 rather than bone fill alone. For craniofacial bone repair, clinically relevant endpoints should include long-term volume maintenance, vascularization, mechanical integration, infection control, implant-related outcomes, and patient-centered functional recovery. Establishing these tissue-specific endpoints is essential to distinguish genuine functional regeneration from partial structural repair.

7.3. Future Directions: Mechanism-Guided, Personalized, and Artificial Intelligence (AI)-Assisted Design

Future polysaccharide-based materials should move beyond empirical formulation screening and functional stacking toward mechanism-guided, simplified, and clinically oriented design. Many current systems incorporate multiple components, from antimicrobial agents to extracellular vesicles, yet the specific contribution of each component remains unclear. Accordingly, new materials should be designed against defined biological barriers: infection, excessive inflammation, impaired mineralization, poor vascularization, and insufficient space maintenance. Each functional module should have a clear purpose, measurable effect, and justifiable translational value. This approach can balance biological performance with manufacturability, regulatory feasibility, and clinical practicality.

In this context, AI presents a valuable tool to facilitate such a transition. The development of polysaccharide-based materials involves complex, nonlinear relationships among composition, processing, structure, degradation,

mechanical properties, release behavior, and biological responses. Machine learning models can be trained on experimental datasets to predict scaffold mechanical performance, degradation profiles, cellular responses, or drug-release kinetics as functions of variables such as polymer concentration, molecular weight, degree of deacetylation, cross-linking density, additive characteristics, and environmental conditions [144,170,171].

In the context of fabrication and personalization, AI-assisted optimization plays a significant role. In 3D bioprinting, process outcomes are influenced by printing parameters such as pressure, speed, nozzle geometry, and cross-linking conditions. AI-based optimization tools can establish parameter-performance relationships from relatively small experimental datasets, thereby reducing the number of iterations needed to achieve printable and biologically compatible formulations [144,172,173]. When integrated with CT/cone-beam computed tomography (CBCT) or intraoral scanning data, AI can further facilitate the reverse design of patient-specific scaffolds that conform to defect geometry, and assist clinicians in selecting appropriate material formats, including injectable hydrogels, barrier membranes, microspheres, or printed constructs [174–176].

Nevertheless, AI-assisted design should serve as a complement to rather than a replacement for biological validation. Current datasets for polysaccharide-based oral regenerative materials remain fragmented, heterogeneous, and frequently too limited in scale to support robust model development. Future progress will depend on standardized data reporting, shared repositories linking material parameters to biological outcomes, interpretable modeling approaches, and prospective validation in clinically relevant preclinical and human settings.

8. Conclusions

With their biocompatibility, structural diversity, and modifiability, polysaccharides are among the most promising biomaterials for oral regenerative medicine. Building on the classification, mechanisms, applications, engineering strategies, and fabrication platforms discussed above, three priorities stand out: first, a shift from empirical trial-and-error toward mechanism-guided design supported by AI-assisted material screening and formulation optimization; second, personalized scaffold design based on patient-specific imaging and clinical profiles; and third, standardized grading of raw materials and end products, alongside multicenter clinical trials and long-term safety assessment, to enable clinical translation. At the interface of materials science, AI, and clinical dentistry, polysaccharide-based systems are well positioned to move from laboratory platforms toward regenerative therapies that restore the form and function of oral tissues.

Author Contributions

Conceptualization, Y.Z. and F.Y.; Investigation (literature search and screening), D.Q. and Y.W.; Data curation, D.Q. and Y.W.; Writing—original draft, D.Q.; Writing—review & editing, D.Q., X.C., Y.Z. and F.Y.; Visualization, D.Q. and X.C.; Supervision, Y.Z. and F.Y. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Not applicable. This is a narrative review; no new studies involving humans or animals were performed.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this review, the authors used AI-assisted tools to support literature retrieval, screening, and reference management, and to assist with language editing and readability polishing of the manuscript. All AI-generated outputs were critically reviewed, verified, and revised by the authors, who take full responsibility for the content of this article. No AI tool was used to generate scientific content, interpret data, or formulate conclusions, and no AI tool is listed as an author.

References

1. Mohabatpour, F.; Chen, X.; Papagerakis, S.; et al. Novel trends, challenges and new perspectives for enamel repair and regeneration to treat dental defects. *Biomater. Sci.* **2022**, *10*, 3062–3087. <https://doi.org/10.1039/d2bm00072e>.
2. Kao, R.T.; Nares, S.; Reynolds, M.A. Periodontal Regeneration – Intrabony Defects: A Systematic Review from the AAP Regeneration Workshop. *J. Periodontol.* **2015**, *86*, S77–104. <https://doi.org/10.1902/jop.2015.130685>.
3. Huang, X.; Lou, Y.; Duan, Y.; et al. Biomaterial scaffolds in maxillofacial bone tissue engineering: A review of recent advances. *Bioact. Mater.* **2024**, *33*, 129–156. <https://doi.org/10.1016/j.bioactmat.2023.10.031>.
4. Hazrati, P.; Mirtaleb, M.H.; Boroojeni, H.S.H.; et al. Current Trends, Advances, and Challenges of Tissue Engineering-Based Approaches of Tooth Regeneration: A Review of the Literature. *Curr. Stem Cell Res. Ther.* **2024**, *19*, 473–496. <https://doi.org/10.2174/1574888x17666220818103228>.
5. Fallacara, A.; Durini, E.; Vertuani, S.; et al. Hyaluronic Acid Fillers in Soft Tissue Regeneration. *Facial Plast. Surg.* **2017**, *33*, 087–096. <https://doi.org/10.1055/s-0036-1597685>.
6. Jin, M.; Shi, J.; Zhu, W.; et al. Polysaccharide-Based Biomaterials in Tissue Engineering: A Review. *Tissue Eng. Part B Rev.* **2021**, *27*, 604–626. <https://doi.org/10.1089/ten.teb.2020.0208>.
7. Ali, A.; Ahmed, S. A review on chitosan and its nanocomposites in drug delivery. *Int. J. Biol. Macromol.* **2018**, *109*, 273–286. <https://doi.org/10.1016/j.ijbiomac.2017.12.078>.
8. Sodhi, H.; Panitch, A. Glycosaminoglycans in Tissue Engineering: A Review. *Biomolecules* **2020**, *11*, 29. <https://doi.org/10.3390/biom11010029>.
9. Li, Z.W.; Du, Z.M.; Wang, Y.W.; et al. Chemical Modification, Characterization, and Activity Changes of Land Plant Polysaccharides: A Review. *Polymers* **2022**, *14*, 4161. <https://doi.org/10.3390/polym14194161>.
10. Liu, Z.; Wang, S.; Yang, S.; et al. Bridging Gaps in Oral Mucosa Regeneration: Advances and Challenges. *Tissue Eng. Part B Rev.* **2025**, 19373368251405708. <https://doi.org/10.1177/19373368251405708>.
11. Constantin, V.; Luchian, I.; Virvescu, D.I.; et al. Hyaluronic Acid-Based Gels and Biomaterial Systems for Oral Wound Healing: Design and Clinical Translation. *Gels* **2026**, *12*, 262. <https://doi.org/10.3390/gels12030262>.
12. Brovold, M.; Almeida, J.I.; Pla-Palacín, I.; et al. Naturally-Derived Biomaterials for Tissue Engineering Applications. *Adv. Exp. Med. Biol.* **2018**, *1077*, 421–449.
13. Tavianatou, A.G.; Caon, I.; Franchi, M.; et al. Hyaluronan: molecular size-dependent signaling and biological functions in inflammation and cancer. *FEBS J.* **2019**, *286*, 2883–2908. <https://doi.org/10.1111/febs.14777>.
14. Gomez-Florit, M.; Pardo, A.; Domingues, R.M.A.; et al. Natural-Based Hydrogels for Tissue Engineering Applications. *Molecules* **2020**, *25*, 5858. <https://doi.org/10.3390/molecules25245858>.
15. Ren, Y.; Wang, Q.; Xu, W.; et al. Alginate-based hydrogels mediated biomedical applications: A review. *Int. J. Biol. Macromol.* **2024**, *279*, 135019. <https://doi.org/10.1016/j.ijbiomac.2024.135019>.
16. Rastogi, P.; Kandasubramanian, B. Review of alginate-based hydrogel bioprinting for application in tissue engineering. *Biofabrication* **2019**, *11*, 042001. <https://doi.org/10.1088/1758-5090/ab331e>.
17. Holiel, A.A.; Mahmoud, E.M.; Abdel-Fattah, W.M. Tomographic evaluation of direct pulp capping using a novel injectable treated dentin matrix hydrogel: a 2-year randomized controlled clinical trial. *Clin. Oral Investig.* **2021**, *25*, 4621–4634. <https://doi.org/10.1007/s00784-021-03775-1>.
18. Holiel, A.A.; Mahmoud, E.M.; Abdel-Fattah, W.M.; et al. Histological evaluation of the regenerative potential of a novel treated dentin matrix hydrogel in direct pulp capping. *Clin. Oral Investig.* **2021**, *25*, 2101–2112. <https://doi.org/10.1007/s00784-020-03521-z>.
19. Bagio, D.A.; Lestari, N.A.; Putra, W.A.; et al. The effect of hyaluronic acid conditioned media on hDPSCs differentiation through CD44 and transforming growth factor- β 1 expressions. *J. Adv. Pharm. Technol. Res.* **2023**, *14*, 89–93. https://doi.org/10.4103/japtr.japtr_649_22.

20. Czajkowska, K.; Rybicki, M.; Kłosiński, K.K.; et al. Factors Determining the Antimicrobial Effectiveness of Chitosan: A Critical Analysis of the Impact of Molecular Weight and Degree of Deacetylation. *Molecules* **2026**, *31*, 2412. <https://doi.org/10.3390/molecules31142412>.
21. Aghbashlo, M.; Amiri, H.; Moosavi Basri, S.M.; et al. Tuning chitosan's chemical structure for enhanced biological functions. *Trends Biotechnol.* **2023**, *41*, 785–797. <https://doi.org/10.1016/j.tibtech.2022.11.009>.
22. Pathak, K.; Misra, S.K.; Sehgal, A.; et al. Biomedical Applications of Quaternized Chitosan. *Polymers* **2021**, *13*, 2514. <https://doi.org/10.3390/polym13152514>.
23. Alshahhoud, A.; Rikab, M.S.; Issa, N.; et al. A Comparison Between Three Types of Scaffolds for Pulp Regeneration: A Histological Study on Dogs. *Clin. Exp. Dent. Res.* **2024**, *10*, e70031. <https://doi.org/10.1002/cre2.70031>.
24. Wu, J.; Wang, P.; Yin, Y.; et al. Cationic Biopolymeric Scaffold of Chelating Nanohydroxyapatite Self-Regulates Intraoral Microenvironment for Periodontal Bone Regeneration. *ACS Appl. Mater. Interfaces* **2023**, *15*, 55409–55422. <https://doi.org/10.1021/acsami.3c13047>.
25. Alshahhoud, A.; Rekab, M.S.; Issa, N.; et al. Application of Three Types of Scaffolds in Pulp Regeneration for Permanent Mature Teeth with Periapical Lesions: A Randomized Controlled Trial. *Eur. Endod. J.* **2024**, *9*, 352–364. <https://doi.org/10.14744/eej.2024.60783>.
26. Kang, Y.; Xu, J.; Meng, L.A.; et al. 3D bioprinting of dECM/Gel/QCS/nHAp hybrid scaffolds laden with mesenchymal stem cell-derived exosomes to improve angiogenesis and osteogenesis. *Biofabrication* **2023**, *15*, 024103. <https://doi.org/10.1088/1758-5090/acb6b8>.
27. Huang, K.X.; Zhou, L.Y.; Chen, J.Q.; et al. Applications and perspectives of quaternized cellulose, chitin and chitosan: A review. *Int. J. Biol. Macromol.* **2023**, *242*, 124990. <https://doi.org/10.1016/j.ijbiomac.2023.124990>.
28. Huang, L.; Wu, T.; Sun, J.; et al. Biocompatible chitin-based Janus hydrogel membranes for periodontal repair. *Acta Biomater.* **2024**, *190*, 219–232. <https://doi.org/10.1016/j.actbio.2024.10.038>.
29. Alizadeh, S.; Ameri, Z.; Daemi, H.; et al. Sulfated polysaccharide as biomimetic biopolymers for tissue engineering scaffolds fabrication: Challenges and opportunities. *Carbohydr. Polym.* **2024**, *336*, 122124. <https://doi.org/10.1016/j.carbpol.2024.122124>.
30. Mhanna, R.; Becher, J.; Schnabelrauch, M.; et al. Sulfated Alginate as a Mimic of Sulfated Glycosaminoglycans: Binding of Growth Factors and Effect on Stem Cell Behavior. *Adv. Biosyst.* **2017**, *1*, 1700043. <https://doi.org/10.1002/adbi.201700043>.
31. Malaeb, W.; Bahmad, H.F.; Abou-Kheir, W.; et al. The sulfation of biomimetic glycosaminoglycan substrates controls binding of growth factors and subsequent neural and glial cell growth. *Biomater. Sci.* **2019**, *7*, 4283–4298. <https://doi.org/10.1039/c9bm00964g>.
32. Freeman, I.; Kedem, A.; Cohen, S. The effect of sulfation of alginate hydrogels on the specific binding and controlled release of heparin-binding proteins. *Biomaterials* **2008**, *29*, 3260–3268. <https://doi.org/10.1016/j.biomaterials.2008.04.025>.
33. Ye, J.; Huang, B.; Gong, P. Nerve growth factor-chondroitin sulfate/hydroxyapatite-coating composite implant induces early osseointegration and nerve regeneration of peri-implant tissues in Beagle dogs. *J. Orthop. Surg. Res.* **2021**, *16*, 51. <https://doi.org/10.1186/s13018-020-02177-5>.
34. Liu, T.; Gao, Y.; Guo, Z.; et al. An injectable hyaluronic acid/chondroitin sulfate hydrogel capturing stem cell factors attenuates periodontitis. *Colloids Surfaces B Biointerfaces* **2026**, *264*, 115641. <https://doi.org/10.1016/j.colsurfb.2026.115641>.
35. Jafari, A.; Farahani, M.; Sedighi, M.; et al. Carrageenans for tissue engineering and regenerative medicine applications: A review. *Carbohydr. Polym.* **2022**, *281*, 119045. <https://doi.org/10.1016/j.carbpol.2021.119045>.
36. He, Z.; Zhou, X.; Wang, Y.; et al. Asymmetric barrier membranes based on polysaccharide micro-nanocomposite hydrogel: Synthesis, characterization, and their antibacterial and osteogenic activities. *Carbohydr. Polym.* **2021**, *273*, 118525. <https://doi.org/10.1016/j.carbpol.2021.118525>.
37. Kikionis, S.; Iliou, K.; Karra, A.G.; et al. Development of Bi- and Tri-Layer Nanofibrous Membranes Based on the Sulfated Polysaccharide Carrageenan for Periodontal Tissue Regeneration. *Mar. Drugs* **2023**, *21*, 565. <https://doi.org/10.3390/md21110565>.
38. Wahnou, H.; Chgari, O.; Ndayambaje, M.; et al. Carrageenan and TLR4 Crosstalk: A Comprehensive Review of Inflammatory Responses in Animal Models. *Recent Adv. Inflamm. Allergy Drug Discov.* **2025**, *19*, 5–17. <https://doi.org/10.2174/0127722708303188240708071523>.
39. Guo, J.; Shang, X.; Chen, P.; et al. How does carrageenan cause colitis? A review. *Carbohydr. Polym.* **2022**, *302*, 120374. <https://doi.org/10.1016/j.carbpol.2022.120374>.
40. Wang, Y.; Xing, M.; Cao, Q.; et al. Biological Activities of Fucoidan and the Factors Mediating Its Therapeutic Effects: A Review of Recent Studies. *Mar. Drugs* **2019**, *17*, 183. <https://doi.org/10.3390/md17030183>.
41. Eshwar, S.; Konuganti, K.; Manvi, S.; et al. Evaluation of Osteogenic Potential of Fucoidan Containing Chitosan Hydrogel in the Treatment of Periodontal Intra-Bony Defects—A Randomized Clinical Trial. *Gels* **2023**, *9*, 573. <https://doi.org/10.3390/gels9070573>.

42. Zayed, A.; Ulber, R. Fucoidan production: Approval key challenges and opportunities. *Carbohydr. Polym.* **2019**, *211*, 289–297. <https://doi.org/10.1016/j.carbpol.2019.01.105>.
43. Zayed, A.; El-Aasr, M.; Ibrahim, A.R.S.; et al. Fucoidan Characterization: Determination of Purity and Physicochemical and Chemical Properties. *Mar. Drugs* **2020**, *18*, 571. <https://doi.org/10.3390/md18110571>.
44. Wang, P.; Chi, L.; Zhang, Z.; et al. Heparin: An old drug for new clinical applications. *Carbohydr. Polym.* **2022**, *295*, 119818. <https://doi.org/10.1016/j.carbpol.2022.119818>.
45. Ying, Y.; Li, B.; Liu, C.; et al. Shape-Memory ECM-Mimicking Heparin-Modified Nanofibrous Gelatin Scaffold for Enhanced Bone Regeneration in Sinus Augmentation. *ACS Biomater. Sci. Eng.* **2022**, *8*, 218–231. <https://doi.org/10.1021/acsbomaterials.1c01365>.
46. Litwiniuk, M.; Krejner, A.; Speyrer, M.S.; et al. Hyaluronic Acid in Inflammation and Tissue Regeneration.. *Wounds* **2016**, *28*, 78–88.
47. Han, B.; Cao, C.; Wang, A.; et al. Injectable Double-Network Hydrogel-Based Three-Dimensional Cell Culture Systems for Regenerating Dental Pulp. *ACS Appl. Mater. Interfaces* **2023**, *15*, 7821–7832. <https://doi.org/10.1021/acsami.2c20848>.
48. Zhang, S.; Jia, Y.; Liu, J.; et al. A viscoelastic alginate-based hydrogel network coordinated with spermidine for periodontal ligament regeneration. *Regen. Biomater.* **2023**, *10*, rbad009. <https://doi.org/10.1093/rb/rbad009>.
49. Feng, Q.; Zhang, M.; Zhang, G.; et al. A whole-course-repair system based on ROS/glucose stimuli-responsive EGCG release and tunable mechanical property for efficient treatment of chronic periodontitis in diabetic rats. *J. Mater. Chem. B* **2024**, *12*, 3719–3740. <https://doi.org/10.1039/d3tb02898d>.
50. Wang, D.; Lv, Y.; Xie, F.; et al. An antioxidant, injectable hydrogel with mitochondrial fusion effect promotes inflamed dental pulp repair via immunomodulation and reactive oxygen species scavenging. *Biomaterials* **2026**, *329*, 123985. <https://doi.org/10.1016/j.biomaterials.2026.123985>.
51. Huangfu, Y.; Zhao, Z.; Liu, X.; et al. An Off-the-Shelf Artificial Blood Clot Hydrogel Neutralizing Multiple Proinflammatory Mediators for Pro-Regenerative Periodontitis Treatment. *Adv. Sci.* **2025**, *12*, e04106. <https://doi.org/10.1002/advs.202504106>.
52. Qiao, D.; Cheng, S.; Xing, Z.; et al. Bio-inspired glycosylated nano-hydroxyapatites enhance endogenous bone regeneration by modulating macrophage M2 polarization. *Acta Biomater.* **2023**, *162*, 135–148. <https://doi.org/10.1016/j.actbio.2023.03.027>.
53. Qiao, D.; Cheng, S.; Song, S.; et al. Polarized M2 macrophages induced by glycosylated nano-hydroxyapatites activate bone regeneration in periodontitis therapy. *J. Clin. Periodontol.* **2024**, *51*, 1054–1065. <https://doi.org/10.1111/jcpe.13999>.
54. Wang, S.; Chen, X.; Li, Q.; et al. Longan polysaccharides promote Th1 and Treg cell differentiation via dendritic cells. *Int. J. Biol. Macromol.* **2025**, *321*, 146462. <https://doi.org/10.1016/j.ijbiomac.2025.146462>.
55. Zhu, Y.; Ali, A.; Mulinari dos Santos, G.; et al. A Chitosan-based Hydrogel to Modulate Immune Cells and Promote Periodontitis Healing in the High-Fat Diet-induced Periodontitis Rat Model. *Acta Biomater.* **2025**, *200*, 452–463. <https://doi.org/10.1016/j.actbio.2025.05.034>.
56. Romo, M.; López-Vicario, C.; Pérez-Romero, N.; et al. Small fragments of hyaluronan are increased in individuals with obesity and contribute to low-grade inflammation through TLR-mediated activation of innate immune cells. *Int J Obes Lond* **2022**, *46*, 1960–1969. <https://doi.org/10.1038/s41366-022-01187-z>.
57. Han, W.; Lv, Y.; Sun, Y.; et al. The anti-inflammatory activity of specific-sized hyaluronic acid oligosaccharides. *Carbohydr. Polym.* **2021**, *276*, 118699. <https://doi.org/10.1016/j.carbpol.2021.118699>.
58. Hadagalu Revana Siddappa, R.; Bishop, E.; Ali, A.; et al. Engineered Immunomodulatory Nanoparticles Inhibit Root Resorption and Ankylosis. *J. Endod.* **2024**, *50*, 1579–1592.e3. <https://doi.org/10.1016/j.joen.2024.08.006>.
59. Wang, Z.; Zhang, A.; Chen, L.; et al. Preparation and anti-inflammation activity of λ -carrageenan oligosaccharides degraded by a novel λ -carrageenase Car3193. *Int. J. Biol. Macromol.* **2024**, *293*, 139282. <https://doi.org/10.1016/j.ijbiomac.2024.139282>.
60. Yao, Z.; Xu, L.; Jin, L.; et al. κ -Carrageenan Oligosaccharides Inhibit the Inflammation of Lipopolysaccharide-Activated Microglia Via TLR4/NF- κ B and p38/JNK MAPKs Pathways. *Neurochem. Res.* **2021**, *47*, 295–304. <https://doi.org/10.1007/s11064-021-03443-6>.
61. Liu, Y.; Ji, L.; Zhu, F.; et al. Sulfated chitosan mitigates acute lung injury induced bone loss via immunoregulation. *Bone Res.* **2026**, *14*, 18. <https://doi.org/10.1038/s41413-025-00475-4>.
62. Zhang, W.; Lee, P.C.W.; Jin, J.O. Anti-Inflammatory Effect of Fucoidan from *Costaria costata* Inhibited Lipopolysaccharide-Induced Inflammation in Mice. *Mar. Drugs* **2024**, *22*, 401. <https://doi.org/10.3390/md22090401>.
63. Xie, Y.; Wang, Z.; Liu, L.; et al. Fucoidan-hybrid hydroxyapatite nanoparticles promote the osteogenic differentiation of human periodontal ligament stem cells under inflammatory condition. *Int. J. Biol. Macromol.* **2024**, *270*, 132416. <https://doi.org/10.1016/j.ijbiomac.2024.132416>.
64. Zhai, J.; Yang, X.; Ren, S.; et al. Spatiotemporally programmable hydrogel enables NIR-triggered biofilm disruption and mitophagy-driven immunometabolic remodeling for periodontitis. *Biomaterials* **2026**, *334*, 124281. <https://doi.org/10.1016/j.biomaterials.2026.124281>.

65. Liu, Y.; Li, J.; Guo, R.; et al. Bioinspired nanomicelles with octopus-like adhesion for microenvironmental reprogramming in periodontitis. *J. Control. Release* **2026**, *392*, 114649. <https://doi.org/10.1016/j.jconrel.2026.114649>.
66. Cui, Z.; Liu, Z.; Zhang, Z.; et al. On-demand amorphous calcium phosphate-mediated regeneration of dentin and enamel using ion-regulated hydroxypropyl methylcellulose and carboxymethyl chitosan hydrogels. *Carbohydr. Polym.* **2026**, *381*, 125170. <https://doi.org/10.1016/j.carbpol.2026.125170>.
67. Iwasaki, A.; Hatakeyama, M.; Liu, Q.; et al. Proliferation and differentiation of human dental pulp stem cells on phosphorylated cellulose nanofiber scaffolds. *Carbohydr. Polym.* **2025**, *359*, 123593. <https://doi.org/10.1016/j.carbpol.2025.123593>.
68. Shamszadeh, S.; Asgary, S.; Akrami, M.; et al. Development of a Thermoresponsive Core–Shell Hydrogel for Sequential Delivery of Antibiotics and Growth Factors in Regenerative Endodontics. *Front. Biosci.-Elite* **2024**, *16*, 32. <https://doi.org/10.31083/j.fbe1604032>.
69. Fei, Y.; Wang, X.; Ling, Z.; et al. Angiogenic apoptotic vesicle-laden silk fibroin /sodium alginate hydrogel for pulp regeneration. *Mater. Today Bio* **2025**, *33*, 102060. <https://doi.org/10.1016/j.mtbio.2025.102060>.
70. Hoveizi, E.; Naddaf, H.; Ahmadianfar, S.; et al. Encapsulation of human endometrial stem cells in chitosan hydrogel containing titanium oxide nanoparticles for dental pulp repair and tissue regeneration in male Wistar rats. *J. Biosci. Bioeng.* **2023**, *135*, 331–340. <https://doi.org/10.1016/j.jbiosc.2022.12.009>.
71. Singh, H.; Rathee, K.; Kaur, A.; et al. Pulp Regeneration in an Immature Maxillary Central Incisor Using Hyaluronic Acid Hydrogel. *Contemp. Clin. Dent.* **2021**, *12*, 94–98. https://doi.org/10.4103/ccd.ccd_149_20.
72. Abdelsalam, M.; Elgendy, A.; Seida, A.; et al. Histological evaluation of the regenerative potential of injectable hyaluronic acid hydrogel or collagen with blood clot as scaffolds during revascularization of immature necrotic dog's teeth. *Open Vet. J.* **2024**, *14*, 3004–3016. <https://doi.org/10.5455/ovj.2024.v14.i11.29>.
73. Loukelis, K.; Machla, F.; Bakopoulou, A.; et al. Kappa-Carrageenan/Chitosan/Gelatin Scaffolds Provide a Biomimetic Microenvironment for Dentin-Pulp Regeneration. *Int. J. Mol. Sci.* **2023**, *24*, 6465. <https://doi.org/10.3390/ijms24076465>.
74. Saravana Karthikeyan, B.; Madhubala, M.M.; Rajkumar, G.; et al. Physico-chemical and biological characterization of synthetic and eggshell derived nanohydroxyapatite/carboxymethyl chitosan composites for pulp-dentin tissue engineering. *Int. J. Biol. Macromol.* **2024**, *271*, 132620. <https://doi.org/10.1016/j.ijbiomac.2024.132620>.
75. Atila, D.; Chen, C.Y.; Lin, C.P.; et al. In vitro evaluation of injectable Tideglusib-loaded hyaluronic acid hydrogels incorporated with Rg1-loaded chitosan microspheres for vital pulp regeneration. *Carbohydr. Polym.* **2022**, *278*, 118976. <https://doi.org/10.1016/j.carbpol.2021.118976>.
76. Bordini, E.A.F.; Cassiano, F.B.; Bronze-Uhle, E.S.; et al. Chitosan in association with osteogenic factors as a cell-homing platform for dentin regeneration: Analysis in a pulp-in-a-chip model. *Dent. Mater.* **2022**, *38*, 655–669. <https://doi.org/10.1016/j.dental.2022.02.004>.
77. Mirzaeei, S.; Pourfarzi, S.; Saeedi, M.; et al. Development of a PVA/PCL/CS-Based Nanofibrous Membrane for Guided Tissue Regeneration and Controlled Delivery of Doxycycline Hydrochloride in Management of Periodontitis: In Vivo Evaluation in Rats. *AAPS PharmSciTech* **2024**, *25*, 27. <https://doi.org/10.1208/s12249-024-02735-8>.
78. Li, A.; Khan, I.N.; Khan, I.U.; et al. Gellan Gum-Based Bilayer Mucoadhesive Films Loaded with Moxifloxacin Hydrochloride and Clove Oil for Possible Treatment of Periodontitis. *Drug Des. Dev. Ther.* **2021**, *15*, 3937–3952. <https://doi.org/10.2147/dddt.s328722>.
79. Eftimie Totu, E.; Mănuc, D.; Totu, T.; et al. Considerations on the Controlled Delivery of Bioactive Compounds through Hyaluronic Acid Membrane. *Membranes* **2022**, *12*, 303. <https://doi.org/10.3390/membranes12030303>.
80. Xu, G.; Xi, L.; Huang, X.; et al. Anti-aging chitosan/gelatin film crosslinked by α -arbutin for bone regeneration by free radical scavenging to prevent osteoblast senescence. *Biomed. Mater.* **2025**, *20*, 025019. <https://doi.org/10.1088/1748-605x/ad66d>.
81. Murali, V.P.; Guerra, F.D.; Ghadri, N.; et al. Simvastatin loaded chitosan guided bone regeneration membranes stimulate bone healing. *J. Periodontal Res.* **2021**, *56*, 877–884. <https://doi.org/10.1111/jre.12883>.
82. Zhong, X.; Lu, Y.; Lin, H.; et al. Electrospun Nanofiber Membrane with Sustained Release of Mogroside V Enhances Alveolar Bone Defect Repair in Diabetic Rats. *ACS Biomater. Sci. Eng.* **2025**, *11*, 1660–1674. <https://doi.org/10.1021/acsbiomaterials.4c01918>.
83. Li, M.; Cheng, G.; Xiao, S.; et al. Biomimetic Mineralized Hydroxyapatite–Fish-Scale Collagen/Chitosan Nanofibrous Membranes Promote Osteogenesis for Periodontal Tissue Regeneration. *ACS Biomater. Sci. Eng.* **2024**, *10*, 5108–5121. <https://doi.org/10.1021/acsbiomaterials.4c00569>.
84. Barbosa, R.M.; da Rocha, D.N.; Bombaldi de Souza, R.F.; et al. Cell-Friendly Chitosan-Xanthan Gum Membranes Incorporating Hydroxyapatite Designed for Periodontal Tissue Regeneration. *Pharmaceutics* **2023**, *15*, 705. <https://doi.org/10.3390/pharmaceutics15020705>.
85. Ge, X.; Hu, J.; Qi, X.; et al. An Immunomodulatory Hydrogel Featuring Antibacterial and Reactive Oxygen Species Scavenging Properties for Treating Periodontitis in Diabetes. *Adv. Mater.* **2025**, *37*, 2412240. <https://doi.org/10.1002/adma.202412240>.

86. Yang, Y.; Zhu, Y.; Yuan, H.; et al. Asiatic Acid-Loaded Hydrogel Ameliorates Diabetic Periodontitis via Mitophagy-Mediated M2 Macrophage Polarization. *ACS Omega* **2026**, *11*, 12229–12241. <https://doi.org/10.1021/acsomega.5c11543>.
87. Dobrzyńska-Mizera, M.; Knitter, M.; Kamińska, M.; et al. Thermosensitive hydrogel doped with osteoconductive fillers for the treatment of periodontitis periapicalis chronica: from synthesis to clinical trial. *Biomater. Sci.* **2024**, *12*, 6063–6081. <https://doi.org/10.1039/d4bm00927d>.
88. Abdelrasoul, M.; El-Fattah, A.A.; Kotry, G.; et al. Regeneration of critical-sized grade II furcation using a novel injectable melatonin-loaded scaffold. *Oral Dis.* **2023**, *29*, 3583–3598. <https://doi.org/10.1111/odi.14314>.
89. Badr, A.M.; Shalaby, H.K.; Awad, M.A.; et al. Assessment of bone morphogenetic protein-7 loaded chitosan/ β -Glycerophosphate hydrogel on periodontium tissues regeneration of class III furcation defects. *Saudi Dent. J.* **2023**, *35*, 760–767. <https://doi.org/10.1016/j.sdentj.2023.05.027>.
90. Sun, Y.; Zhao, Z.; Qiao, Q.; et al. Injectable periodontal ligament stem cell-metformin-calcium phosphate scaffold for bone regeneration and vascularization in rats. *Dent. Mater.* **2023**, *39*, 872–885. <https://doi.org/10.1016/j.dental.2023.07.008>.
91. Liu, S.; Wang, Z.; Li, Y.; et al. Erythropoietin-Stimulated Macrophage-Derived Extracellular Vesicles in Chitosan Hydrogel Rescue BMSCs Fate by Targeting EGFR to Alleviate Inflammatory Bone Loss in Periodontitis. *Adv. Sci.* **2025**, *12*, 2500554. <https://doi.org/10.1002/adv.202500554>.
92. Zhu, Y.; Xiu, Z.; Jiang, X.; et al. Injectable hydrogels with ROS-triggered drug release enable the co-delivery of antibacterial agent and anti-inflammatory nanoparticle for periodontitis treatment. *J. Nanobiotechnology* **2025**, *23*, 205. <https://doi.org/10.1186/s12951-025-03275-4>.
93. Tang, R.; Ren, Y.; Zhang, Y.; et al. Glucose-driven transformable complex eliminates biofilm and alleviates inflamm-aging for diabetic periodontitis therapy. *Mater. Today Bio* **2023**, *20*, 100678. <https://doi.org/10.1016/j.mtbio.2023.100678>.
94. Xie, C.; Zhang, Q.; Bianco, A.; et al. H₂S-Scavenging Hydrogel Alleviating Mitochondria Damage to Control Periodontitis. *J. Dent. Res.* **2025**, *104*, 172–182. <https://doi.org/10.1177/00220345241291540>.
95. Chen, H.; Zhao, Z.; Zhang, R.; et al. Adaptable Hydrogel with Strong Adhesion of Wet Tissue for Long-Term Protection of Periodontitis Wound. *Adv. Mater.* **2025**, *37*, 2413373. <https://doi.org/10.1002/adma.202413373>.
96. Ma, S.; Lu, X.; Yu, X.; et al. An injectable multifunctional thermo-sensitive chitosan-based hydrogel for periodontitis therapy. *Biomater. Adv.* **2022**, *142*, 213158. <https://doi.org/10.1016/j.bioadv.2022.213158>.
97. Chen, J.; Guan, X.; Chen, L.; et al. Customized Hydrogel System for the Spatiotemporal Sequential Treatment of Periodontitis Propelled by ZEB1. *Adv. Sci.* **2025**, *12*, 2503338. <https://doi.org/10.1002/adv.202503338>.
98. Zhou, J.; Li, H.; Li, S.; et al. Convertible Hydrogel Injection Sequentially Regulates Diabetic Periodontitis. *ACS Biomater. Sci. Eng.* **2025**, *11*, 916–929. <https://doi.org/10.1021/acsbomaterials.4c01784>.
99. Klein, O.; Balta, M.G.; Wohlfahrt, J.C. Treatment of Residual Pockets in Stage III and IV Periodontitis Using an Oscillating Chitosan Device with or Without a Chitosan Gel—A Randomised Parallel-Arms Clinical Trial. *J. Clin. Periodontol.* **2026**, *53*, 706–718. <https://doi.org/10.1111/jcpe.70086>.
100. Wang, W.; Wang, A.; Hu, G.; et al. Potential of an Aligned Porous Hydrogel Scaffold Combined with Periodontal Ligament Stem Cells or Gingival Mesenchymal Stem Cells to Promote Tissue Regeneration in Rat Periodontal Defects. *ACS Biomater. Sci. Eng.* **2023**, *9*, 1961–1975. <https://doi.org/10.1021/acsbomaterials.2c01440>.
101. Zhang, L.; Dong, Y.; Liu, Y.; et al. Multifunctional hydrogel/platelet-rich fibrin/nanofibers scaffolds with cell barrier and osteogenesis for guided tissue regeneration/guided bone regeneration applications. *Int. J. Biol. Macromol.* **2023**, *253*, 126960. <https://doi.org/10.1016/j.ijbiomac.2023.126960>.
102. Shirakata, Y.; Imafuji, T.; Nakamura, T.; et al. Cross-linked hyaluronic acid gel with or without a collagen matrix in the treatment of class III furcation defects: A histologic and histomorphometric study in dogs. *J. Clin. Periodontol.* **2022**, *49*, 1079–1089. <https://doi.org/10.1111/jcpe.13694>.
103. Staples, R.; Ivanovski, S.; Vaquette, C. Fibre-guiding biphasic scaffold for perpendicular periodontal ligament attachment. *Acta Biomater.* **2022**, *150*, 221–237. <https://doi.org/10.1016/j.actbio.2022.07.023>.
104. Schüpbach, P.; Gaberthüel, T.; Lutz, F.; et al. Periodontal repair or regeneration: structures of different types of new attachment. *J. Periodontol. Res.* **1993**, *28*, 281–293. <https://doi.org/10.1111/j.1600-0765.1993.tb02095.x>.
105. Benatti, B.B.; Neto, J.B.C.; Casati, M.Z.; et al. Periodontal healing may be affected by aging: a histologic study in rats. *J. Periodontol. Res.* **2006**, *41*, 329–333. <https://doi.org/10.1111/j.1600-0765.2006.00872.x>.
106. Reynolds, M.A.; Kao, R.T.; Camargo, P.M.; et al. Periodontal Regeneration – Intrabony Defects: A Consensus Report From the AAP Regeneration Workshop. *J. Periodontol.* **2015**, *86*, S105–S107. <https://doi.org/10.1902/jop.2015.140378>.
107. Rasperini, G.; Tavelli, L.; Barootchi, S.; et al. Interproximal attachment gain: The challenge of periodontal regeneration. *J. Periodontol.* **2020**, *92*, 931–946. <https://doi.org/10.1002/jper.20-0587>.
108. Ke, S.; Sun, X.; Qian, J.; et al. The Experimental Study of Double-Layer Heterogeneous CA Scaffold in Promoting the Surface Shape Recovery and Internal Osteogenesis of Alveolar Bone. *Biotechnol. J.* **2025**, *20*, e202400603. <https://doi.org/10.1002/biot.202400603>.

109. Krishnamoorthy, E.; Purusothaman, B.; Subramanian, B. Productizing Nano-Bioactive Glass-Based Bilayer Scaffolds: A Graft for Reconstruction of Mandibular and Femoral Bone Defects. *ACS Appl. Mater. Interfaces* **2024**, *16*, 25317–25332. <https://doi.org/10.1021/acsami.4c02689>.
110. Zhao, Q.; Yang, D.; Chen, S.; et al. Carbon nanotube bacterial cellulose polycaprolactone scaffolds for bone tissue engineering using top-heating fused deposition three-dimensional printing. *Int. J. Biol. Macromol.* **2025**, *318*, 144588. <https://doi.org/10.1016/j.ijbiomac.2025.144588>.
111. Farsinezhad, H.; Niknafs, M.; Samieifard, M.; et al. Enhanced hemostasis and alveolar bone regeneration induced by sandwich like egg shell membrane-laponite-chitosan nanocomposite after tooth extraction. *Int. J. Biol. Macromol.* **2025**, *330*, 147923. <https://doi.org/10.1016/j.ijbiomac.2025.147923>.
112. Vu, N.B.; Chuenchompoonut, V.; Jansisyant, P.; et al. Acemannan-induced tooth socket healing: A 12-month randomized controlled trial. *J. Dent. Sci.* **2021**, *16*, 643–653. <https://doi.org/10.1016/j.jds.2020.10.003>.
113. Machado, A.; Pereira, I.; Costa, F.; et al. Randomized clinical study of injectable dextrin-based hydrogel as a carrier of a synthetic bone substitute. *Clin. Oral Investig.* **2023**, *27*, 979–994. <https://doi.org/10.1007/s00784-023-04868-9>.
114. Wu, T.; Liu, Y.; Wang, S.; et al. Light-Switched Mesenchymal Stem Cells for In Situ Exosome Amplification in Craniofacial Bone Defect Reconstruction. *Adv. Sci.* **2026**, *13*, e75519. <https://doi.org/10.1002/advs.75519>.
115. Tavakoli, M.; Salehi, H.; Emadi, R.; et al. 3D printed polylactic acid-based nanocomposite scaffold stuffed with microporous simvastatin-loaded polyelectrolyte for craniofacial reconstruction. *Int. J. Biol. Macromol.* **2024**, *258*, 128917. <https://doi.org/10.1016/j.ijbiomac.2023.128917>.
116. Salehi, S.; Ghomi, H.; Hassanzadeh-Tabrizi, S.A.; et al. Antibacterial and osteogenic properties of chitosan-polyethylene glycol nanofibre-coated 3D printed scaffold with vancomycin and insulin-like growth factor-1 release for bone repair. *Int. J. Biol. Macromol.* **2025**, *298*, 139883. <https://doi.org/10.1016/j.ijbiomac.2025.139883>.
117. Huang, Y.; Zhang, Y.; Feng, Y.; et al. A DNA Tetrahedron Delivery Asiatic Acid to Reprogram Mitochondrial Metabolism for Promoting Bone Regeneration via STAT3 Phosphorylation. *Adv. Sci.* **2026**, *13*, e18796. <https://doi.org/10.1002/advs.202518796>.
118. Han, Y.; Wang, C.; Liu, M.; et al. EGCG-Loaded Zinc Ion-Cross-Linked Injectable Sodium Alginate Hydrogel for Extraction Socket Healing. *ACS Biomater. Sci. Eng.* **2025**, *11*, 7313–7328. <https://doi.org/10.1021/acsbiomaterials.5c00824>.
119. Zhao, X.Y.; Lei, S.; Yan, M.; et al. Polyhedral oligomeric silsesquioxane-functionalized carboxymethyl chitin microspheres via irradiation-induced grafting for hemostasis and tissue repair in post-extraction sockets. *Int. J. Biol. Macromol.* **2026**, *358*, 151727. <https://doi.org/10.1016/j.ijbiomac.2026.151727>.
120. Xu, C.; Li, W.; Mao, J.; et al. Using chondroitin sulfate lithium hydrogel for diabetic bone regeneration via regulation of macrophage polarization. *Carbohydr. Polym.* **2025**, *347*, 122787. <https://doi.org/10.1016/j.carbpol.2024.122787>.
121. He, S.; Zhao, H.; Chen, M.; et al. Bioglass-Integrated Dynamic Hydrogels Improve Matrix-Directed Repair of Cranial Defects through Cooperative Mechano-Biochemical Regulation. *Adv. Healthc. Mater.* **2025**, *14*, 2500134. <https://doi.org/10.1002/adhm.202500134>.
122. Zhan, H.; Shi, R.; Ni, H.; et al. Functional requirements for guided bone regeneration/guided tissue regeneration membrane design: Progress and challenges. *Periodontol. 2000* **2025**, *pr*, 70019. <https://doi.org/10.1111/prd.70019>.
123. Ren, Y.; Fan, L.; Alkildani, S.; et al. Barrier Membranes for Guided Bone Regeneration (GBR): A Focus on Recent Advances in Collagen Membranes. *Int. J. Mol. Sci.* **2022**, *23*, 14987. <https://doi.org/10.3390/ijms232314987>.
124. Hou, H.; Lanzi, A.M.; Feng, Y.; et al. Alginate Hydrogels with Tunable Degradation. *Macromol. Rapid Commun.* **2025**, *47*, e00348. <https://doi.org/10.1002/marc.202500348>.
125. Zhou, Y.; Li, M.; Zheng, H.; et al. A photothermal therapy-based composite hydrogel for sequential management of inflammation control and bone regeneration in severe periodontitis. *J. Mater. Chem. B* **2025**, *13*, 10225–10238. <https://doi.org/10.1039/d5tb01510c>.
126. Hu, Z.; Zhou, Y.; Wu, H.; et al. An injectable photopolymerizable chitosan hydrogel doped anti-inflammatory peptide for long-lasting periodontal pocket delivery and periodontitis therapy. *Int. J. Biol. Macromol.* **2023**, *252*, 126060. <https://doi.org/10.1016/j.ijbiomac.2023.126060>.
127. Liang, C.; Wu, S.; Huang, Z.; et al. Harnessing Oxidized Alginate Microgels for Rapid and Self-Assembling Dental Tissue Organogenesis In Vitro and In Vivo. *Small Sci.* **2025**, *5*, e202500053. <https://doi.org/10.1002/smssc.202500053>.
128. Nguyen, N.Q.T.; Luu, C.H.; Nguyen, N.D.H.; et al. Dual-functional injectable hydrogels as antimicrobial and angiogenic therapeutics for dental pulp regeneration. *J. Mater. Chem. B* **2025**, *13*, 6765–6783. <https://doi.org/10.1039/d5tb00559k>.
129. Moreira, M.S.; Sarra, G.; Carvalho, G.L.; et al. Physical and Biological Properties of a Chitosan Hydrogel Scaffold Associated to Photobiomodulation Therapy for Dental Pulp Regeneration: An In Vitro and In Vivo Study. *BioMed Res. Int.* **2021**, *2021*, 6684667. <https://doi.org/10.1155/2021/6684667>.
130. Ouyang, M.; Yu, X.; Zhong, J.; et al. Injectable sodium alginate/4-arm polyethylene glycol-lipoic acid double-network hydrogel loading Ca²⁺-tannic acid nanocomposite treats periodontitis via anti-bacteria, ROS scavenging and osteogenesis. *Int. J. Biol. Macromol.* **2025**, *307*, 141841. <https://doi.org/10.1016/j.ijbiomac.2025.141841>.

131. Wang, X.; Peng, Y.; Wu, Y.; et al. Chitosan/silk fibroin composite bilayer PCL nanofibrous mats for bone regeneration with enhanced antibacterial properties and improved osteogenic potential. *Int. J. Biol. Macromol.* **2023**, *230*, 123265. <https://doi.org/10.1016/j.ijbiomac.2023.123265>.
132. Wang, Y.; Qu, Y.; Liu, X.; et al. Dual-functional probiotic hydrogel with puerarin integration for microbiota-neuroimmune regulation in antibiotic-free periodontitis therapy. *Bioact. Mater.* **2025**, *53*, 72–83. <https://doi.org/10.1016/j.bioactmat.2025.07.004>.
133. Mousavi Nejad, Z.; Zamanian, A.; Saeidifar, M.; et al. 3D Bioprinting of Polycaprolactone-Based Scaffolds for Pulp-Dentin Regeneration: Investigation of Physicochemical and Biological Behavior. *Polymers* **2021**, *13*, 4442. <https://doi.org/10.3390/polym13244442>.
134. Leite, M.L.; Anselmi, C.; Soares, I.P.M.; et al. Calcium silicate-coated porous chitosan scaffold as a cell-free tissue engineering system for direct pulp capping. *Dent. Mater.* **2022**, *38*, 1763–1776. <https://doi.org/10.1016/j.dental.2022.09.014>.
135. Li, N.; Jiang, L.; Jin, H.; et al. An enzyme-responsive membrane for antibiotic drug release and local periodontal treatment. *Colloids Surfaces B Biointerfaces* **2019**, *183*, 110454. <https://doi.org/10.1016/j.colsurfb.2019.110454>.
136. Nnane, N.S.; Gaikwad, A.; Rahim, M.I.; et al. Synthesis of an Enzyme-Triggered Chitosan-Based Drug Delivery System for Peri-Implantitis Prevention. *Chem. – A Eur. J.* **2026**, *32*, e01800. <https://doi.org/10.1002/chem.202501800>.
137. Parisi, L.; Rivara, F.; Costa, C.A.; et al. Aptamers recognizing fibronectin confer improved bioactivity to biomaterials and promote new bone formation in a periodontal defect in rats. *Biomed. Mater.* **2020**, *16*, 015016. <https://doi.org/10.1088/1748-605x/abb6b2>.
138. Liu, X.; Li, X.; Yue, Y.; et al. Selection of a novel MSC-targeted aptamer Pt-1 and its functionalized hydrogel for tissue regeneration. *Mater. Today Bio* **2026**, *39*, 103410. <https://doi.org/10.1016/j.mtbio.2026.103410>.
139. Ning, X.; Zong, M.; Tong, J.; et al. Preliminary Study on Carboxymethyl Chitosan-Based Carbon Dots for Tracing and Promoting Osteogenic Differentiation. *ACS Biomater. Sci. Eng.* **2025**, *11*, 4087–4100. <https://doi.org/10.1021/acsbomaterials.5c00135>.
140. Elnawam, H.; Thabet, A.; Mobarak, A.; et al. Bovine pulp extracellular matrix hydrogel for regenerative endodontic applications: in vitro characterization and in vivo analysis in a necrotic tooth model. *Head Face Med.* **2024**, *20*, 61. <https://doi.org/10.1186/s13005-024-00460-y>.
141. Khalil, M.M.; Ibrahim, M.; Rawat, S.S.; et al. Comparative evaluation of 3D culture strategies for pulp-dentin models. *BMC Oral Health* **2026**, *26*, 242. <https://doi.org/10.1186/s12903-025-07561-3>.
142. Salar Amoli, M.; Anand, R.; EzEldeen, M.; et al. The development of a 3D printable chitosan-based copolymer with tunable properties for dentoalveolar regeneration. *Carbohydr. Polym.* **2022**, *289*, 119441. <https://doi.org/10.1016/j.carbpol.2022.119441>.
143. Miao, G.; Liang, L.; Li, W.; et al. 3D Bioprinting of a Bioactive Composite Scaffold for Cell Delivery in Periodontal Tissue Regeneration. *Biomolecules* **2023**, *13*, 1062. <https://doi.org/10.3390/biom13071062>.
144. Dai, Y.; Wang, P.; Mishra, A.; et al. 3D Bioprinting and Artificial Intelligence-Assisted Biofabrication of Personalized Oral Soft Tissue Constructs. *Adv. Healthc. Mater.* **2025**, *14*, 2402727. <https://doi.org/10.1002/adhm.202402727>.
145. Peluso, V.; De Santis, R.; Gloria, A.; et al. Design of 3D Additive Manufactured Hybrid Scaffolds for Periodontal Repair Strategies. *ACS Appl. Bio Mater.* **2025**, *8*, 6817–6829. <https://doi.org/10.1021/acsbm.5c00561>.
146. Wang, T.; Zhang, M.; Guo, J.; et al. Alginate/bacterial cellulose/GelMA scaffolds with aligned nanopatterns and hollow channel networks for vascularized bone repair. *Int. J. Biol. Macromol.* **2025**, *308*, 142578. <https://doi.org/10.1016/j.ijbiomac.2025.142578>.
147. Tu, X.; Guo, L.; Li, Y.; et al. 3D-printed gelatin/sodium alginate/58S bioactive glass scaffolds promote osteogenesis *in vitro* and *in vivo*. *J. Biomater. Appl.* **2023**, *37*, 1758–1766. <https://doi.org/10.1177/08853282231152128>.
148. Li, S.; Liu, Z.; Gao, X.; et al. Preparation and properties of a 3D printed nHA/PLA bone tissue engineering scaffold loaded with a β -CD-CHX combined dECM hydrogel. *RSC Adv.* **2024**, *14*, 9848–9859. <https://doi.org/10.1039/d4ra00261j>.
149. Ho, M.H.; Huang, K.Y.; Tu, C.C.; et al. Functionally graded membrane deposited with PDLLA nanofibers encapsulating doxycycline and enamel matrix derivatives-loaded chitosan nanospheres for alveolar ridge regeneration. *Int. J. Biol. Macromol.* **2022**, *203*, 333–341. <https://doi.org/10.1016/j.ijbiomac.2022.01.147>.
150. Peng, W.; Ren, S.; Zhang, Y.; et al. MgO Nanoparticles-Incorporated PCL/Gelatin-Derived Coaxial Electrospinning Nanocellulose Membranes for Periodontal Tissue Regeneration. *Front. Bioeng. Biotechnol.* **2021**, *9*, 668428. <https://doi.org/10.3389/fbioe.2021.668428>.
151. Huang, Q.; Han, L.; Wang, R.; et al. Electrospun Nanofibers Loaded with Concentrated Growth Factors and Nanohydroxyapatite for the Healing of Alveolar Bone in Tooth Extraction Wounds. *ACS Biomater. Sci. Eng.* **2025**, *11*, 5975–5990. <https://doi.org/10.1021/acsbomaterials.5c00159>.
152. Su, H.; Fujiwara, T.; Anderson, K.M.; et al. A comparison of two types of electrospun chitosan membranes and a collagen membrane *in vivo*. *Dent. Mater.* **2021**, *37*, 60–70. <https://doi.org/10.1016/j.dental.2020.10.011>.

153. Feng, Z.; Qiu, S.; Michálek, M.; et al. Anti-inflammatory and osteogenic nanofibrous scaffolds of bioactive glass/carboxymethyl chitosan-reinforced PCL short fibers for alveolar bone regeneration. *Int. J. Biol. Macromol.* **2025**, *323*, 147197. <https://doi.org/10.1016/j.ijbiomac.2025.147197>.
154. Helal, M.H.; Ali, A.N.; Hamdy, Y.; et al. β -tricalcium phosphate/gelatin composite scaffolds incorporated with gentamycin-loaded chitosan microspheres for periodontal regeneration in class II furcation defects in dogs. *Clin. Oral Investig.* **2025**, *29*, 540. <https://doi.org/10.1007/s00784-025-06582-0>.
155. Song, C.; Huang, D.; Zhao, C.; et al. Abalone-Inspired Adhesive and Photo-Responsive Microparticle Delivery Systems for Periodontal Drug Therapy. *Adv. Sci.* **2022**, *9*, 2202829. <https://doi.org/10.1002/advs.202202829>.
156. Liu, Z.; Zhang, H.; Gan, J.; et al. Black Phosphorus Tagged Responsive Strontium Hydrogel Particles for Bone Defect Repair. *Adv. Sci.* **2025**, *12*, 2408284. <https://doi.org/10.1002/advs.202408284>.
157. Zhou, E.; He, P.; Yang, Z.; et al. 3D-printed GelMA-Alginate microsphere scaffold with staged dual-growth factor release for enhanced bone regeneration. *Mater. Today Bio* **2025**, *35*, 102422. <https://doi.org/10.1016/j.mtbio.2025.102422>.
158. Chelu, M.; Popa, M.; Calderón Moreno, J.M. Next-Generation Natural Hydrogels in Oral Tissue Engineering. *Pharmaceutics* **2025**, *17*, 1256. <https://doi.org/10.3390/pharmaceutics17101256>.
159. Barreiro Carpio, M.; Thompson, P.M.; Moody, C.; et al. A versatile and efficient method to quantify purity and degree of substitution in alginate derivatives. *Carbohydr. Polym.* **2025**, *369*, 124299. <https://doi.org/10.1016/j.carbpol.2025.124299>.
160. Martel-Pelletier, J.; Farran, A.; Montell, E.; et al. Discrepancies in Composition and Biological Effects of Different Formulations of Chondroitin Sulfate. *Molecules* **2015**, *20*, 4277–4289. <https://doi.org/10.3390/molecules20034277>.
161. Xu, J.; Tang, W.; Che, S.; et al. From nature to clinic: Lessons from successfully marketed polysaccharide drugs. *Carbohydr. Polym.* **2026**, *381*, 125147. <https://doi.org/10.1016/j.carbpol.2026.125147>.
162. Qadir, B.H.; Mahmood, M.K.; Rasheed, T.A.; et al. Applications of chitosan in oral health and diseases. *Front. Oral Health* **2025**, *6*, 1632233. <https://doi.org/10.3389/froh.2025.1632233>.
163. Capuana, E.; Lopresti, F.; Carfi Pavia, F.; et al. Solution-Based Processing for Scaffold Fabrication in Tissue Engineering Applications: A Brief Review. *Polymers* **2021**, *13*, 2041. <https://doi.org/10.3390/polym13132041>.
164. Lin, A.; Yuan, S.; Liang, C.; et al. Scaffold-free cell sheet therapies: clinical advances, global approval landscapes, and strategic directions to address regenerative medicine barriers. *Stem Cell Res. Ther.* **2025**, *17*, 5. <https://doi.org/10.1186/s13287-025-04818-0>.
165. Han, P.; Liu, C.; Abdal-Hay, A.; et al. Proteome and microbiome profiles of polymicrobial salivary biofilms on 3D MEW fibrous scaffolds: biomimetic ECM-inspired structures. *J. Mater. Chem. B* **2025**, *13*, 13434–13445. <https://doi.org/10.1039/d5tb01410g>.
166. Utomo, R.N.C.; Palkowitz, A.L.; Gan, L.; et al. In vitro plaque formation model to unravel biofilm formation dynamics on implant abutment surfaces. *J. Oral Microbiol.* **2024**, *16*, 2424227. <https://doi.org/10.1080/20002297.2024.2424227>.
167. Helbig, R.; Hannig, M.; Basche, S.; et al. Bioadhesion on Textured Interfaces in the Human Oral Cavity—An In Situ Study. *Int. J. Mol. Sci.* **2022**, *23*, 1157. <https://doi.org/10.3390/ijms23031157>.
168. Asgary, S.; Shamszadeh, S. Immunomodulatory and angiogenic strategies in vital pulp therapy: a systematic review of scaffold-based, scaffold-free, and cell-laden interventions. *Clin. Oral Investig.* **2026**, *30*, 73. <https://doi.org/10.1007/s00784-025-06737-z>.
169. Shanbhag, S.; Stødle, I.H.; Lie, S.A.; et al. Histological Outcomes of Root Coverage Procedures: A Systematic Review With Meta-Analysis. *J. Periodontal Res.* **2026**, *61*, 9–29. <https://doi.org/10.1111/jre.70043>.
170. Chinta, M.L.; Gandam, P.K.; Parcha, S.R. Design and optimization of tamarind seed polysaccharide-based scaffold for tissue engineering applications using statistical modeling and machine learning, and its in-vitro validation. *Int. J. Biol. Macromol.* **2025**, *301*, 140411. <https://doi.org/10.1016/j.ijbiomac.2025.140411>.
171. Alqarni, M.; Al Harthi, S.M.; Alzubaidi, M.A.; et al. Model development using hybrid method for prediction of drug release from biomaterial matrix. *Chemom. Intell. Lab. Syst.* **2024**, *253*, 105216. <https://doi.org/10.1016/j.chemolab.2024.105216>.
172. Yin, X.; Hao, J.; Liu, S.; et al. Hybrid physics-informed and data-driven modeling of material–process–property relationships in extrusion-printed GelMA/alginate vascular scaffolds. *Addit. Manuf.* **2026**, *125*, 105251. <https://doi.org/10.1016/j.addma.2026.105251>.
173. Ng, W.L.; Goh, G.L.; Goh, G.D.; et al. Progress and Opportunities for Machine Learning in Materials and Processes of Additive Manufacturing. *Adv. Mater.* **2024**, *36*, 2310006. <https://doi.org/10.1002/adma.202310006>.
174. Liu, Y.; Xie, R.; Wang, L.; et al. Fully automatic AI segmentation of oral surgery-related tissues based on cone beam computed tomography images. *Int. J. Oral Sci.* **2024**, *16*, 34. <https://doi.org/10.1038/s41368-024-00294-z>.
175. Omigbodun, F.T.; Oladapo, B.I. AI-Optimized Lattice Structures for Biomechanics Scaffold Design. *Biomimetics* **2025**, *10*, 88. <https://doi.org/10.3390/biomimetics10020088>.
176. Chen, F.; Chen, H.; Hai, D.; et al. AI-assisted preoperative surgical planning for dental implant. *J. Transl. Med.* **2025**, *24*, 104. <https://doi.org/10.1186/s12967-025-07584-y>.