Functional Hydrogels for Intraoral Wound Care: Research Progress and Design Strategies

Zi Xin PAN[1,2], Wen Jie MA[1,2], Chao SI[1,2], Chun Ru KONG[1,2], Jia Kai QIAO[1,2], Xiao Duo TANG[1,2], Bei CHANG[1,2], Hong Chen SUN[1]

Oral soft tissue defects resulting from trauma, infections, tumour resection or congenital disorders present significant clinical challenges, impairing functions like mastication, speech and aesthetics. Current therapeutic approaches, including free gingival grafts (FGGs) and connective tissue grafts (CTGs), are associated with certain clinical limitations, such as donor site morbidity and structural fragility. Hydrogels are attractive biomaterials for oral soft tissue repair owing to their biocompatibility, tunable mechanics and extracellular matrix-mimicking properties. This review comprehensively explores hydrogel applications in oral wound healing, focusing on the histological structure of oral mucosa and unique challenges of the oral environment; design strategies using natural and synthetic polymers; advanced manufacturing strategies, such as 3D bioprinting, electrospinning and microfluidic organ-on-a-chip technology; and therapeutic applications in mucosa repair, gingival regeneration and periodontal therapy.

Keywords: *biomaterials, drug delivery, hydrogel, oral soft tissue regeneration, tissue engineering*

Chin J Dent Res 2026;29(2):91–118; doi: 10.3290/j.cjdr.b7044034

Oral soft tissue defects involve the loss or damage of soft tissues in the lips, cheeks, tongue, gums, palate and floor of the mouth. These defects arise from various causes, including congenital malformations, trauma, infections, tumour resection and radiation-induced injuries. More than 30% of the adult population is affected by oral lesions resulting from ulcers, physical trauma or dentofacial surgery, which can substantially reduce their quality of life.[1] Based on depth, oral wounds can be classified into four categories: superficial wounds, which are confined to the epithelial layer of the mucosa; partial-thickness wounds, which extend into the underlying lamina propria but do not penetrate the submucosa; deep wounds, which penetrate the mucosa and potentially affect the underlying muscles, glands or connective tissues; and penetrating wounds, which extend through the oral cavity into facial or neck regions.[2] In terms of duration, they may present as acute or chronic wounds.[3] These defects can result in significant functional impairments, including difficulties with mastication, swallowing, speech articulation and salivary control, as well as facial deformities and psychosocial challenges. Consequently, a comprehensive understanding of the classification, aetiology and reconstruction strategies for oral soft tissue defects is vital for improving patient quality of life and functional recovery.[4]

Oral soft tissue repair is critical for restoring function, aesthetics and periodontal health following trauma, disease or surgical resection. Recent advances in regenerative medicine and surgical techniques have

1 Hospital of Stomatology, Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling, Jilin University, Changchun, P.R. China
2 Hospital of Stomatology, Department of Pediatric Dentistry, Jilin University, Changchun, P.R. China

Corresponding authors: Drs Xiao Duo TANG and Bei CHANG, Department of Pediatric Dentistry, Jilin University, 763 Heguang Road, Changchun 130021, P.R. China. Tel: 86-0431-8557956. Email: xdtang@jlu.edu.cn; bchang@jlu.edu.cn.

Dr Hong Chen SUN, Hospital of Stomatology, Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling, Jilin University, 763 Heguang Road, Changchun 130021, P.R. China. Email: hcsun@jlu.edu.cn.

This work was supported by the Natural Science Foundation of China (82470941, 82101075, 82301044) and the Young Elite Scientists Sponsorship Program by CAST (YESS20210407, 2024QNRC001).

broadened the available options for managing gingival recession and enhancing soft tissue volume. Among these, free gingival graft (FGG), an autogenous graft harvested from the palate, is still considered the gold standard for managing gingival recession and enhancing keratinised tissue. Despite their predictable efficacy, FGGs are associated with drawbacks such as donor site morbidity and limited tissue availability.[5] For root coverage and ridge augmentation, subepithelial connective tissue graft (CTG) offers superior aesthetics compared to FGG; however, its primary limitation is the necessity of a second surgical site, resulting in greater postoperative pain and the risk of gingival flap shrinkage.[6] Initial strategies aimed to mitigate these limitations, such as cultured epithelial cell sheets, which facilitated the transplantation of intact epithelial or fibroblast layers and thus avoided the complications linked to scaffolds.[7] However, it was hindered by structural fragility and poor handling properties due to the absence of underlying connective tissue support.[8] Furthermore, the reliance on autogenous grafts not only exacerbates patient morbidity but also fails to meet the growing demand for off-the-shelf alternatives in regenerative dentistry.[7,9-11]

To advance oral soft tissue restoration, there is a pressing clinical need for the development of novel biomaterials. An ideal material must meet four key requirements. First, it must exhibit excellent biocompatibility and non-toxicity, supporting cellular activities and stable integration with host tissues. Second, its mechanical properties (e.g., elastic modulus and tensile strength) should closely match those of the target soft tissue in order to withstand physiological stresses and maintain normal function.[12] Furthermore, the material must retain structural stability in the dynamic oral environment, enduring persistent variations in moisture, pH, temperature and microbial flora.[13] Finally, if designed to be biodegradable, its degradation rate must be synchronised with the tissue regeneration process, thereby providing temporary mechanical support without compromising long-term restorative outcomes.

Hydrogels are a promising class of biomaterial that satisfies these criteria; however, a comprehensive review of their design strategies and clinical applications remains lacking. Although tissue engineering–based therapies for oral soft tissue regeneration are still in early development, they hold significant promise for future clinical implementation. This review explores the potential of hydrogels as scaffolds for dental soft tissue engineering, offering a novel analysis of their roles in intraoral regeneration. We begin by outlining the histological structure of oral soft tissues and the specific challenges posed by the highly dynamic intraoral environment. The second section focuses on the materials and fabrication techniques employed in hydrogel development, along with their targeted applications in oral soft tissue repair. Finally, we discuss current limitations in the field and suggest directions for future research. Departing from previous reviews that focused primarily on material types or general wound healing, this work systematically aligns advanced hydrogel design strategies with the structural and biological requirements of the oral cavity. Furthermore, it addresses current limitations and clinical translation challenges unique to oral applications, proposing forward-looking research directions and providing a comprehensive synthesis of the field.

Histological structure of oral soft tissue and restorative requirements

A thorough understanding of oral soft tissue architecture is fundamental for advancing restoration strategies. The oral mucosa, a specialised stratified epithelium lining the cavity, provides essential protection against mechanical, thermal and chemical insults. This structural adaptation is particularly evident in the gingiva, where its dense, collagen-rich lamina propria provides mechanical resilience while also serving as a barrier against microbial invasion. The oral environment is highly dynamic, characterised by constant saliva flow, tissue mobility and masticatory forces. These conditions create unique challenges for material retention and wound healing. These constraints necessitate the development of biomaterials with strong wet-adhesive capabilities, excellent biocompatibility and precisely controlled degradation profiles. Current research focuses on elucidating the mechanisms of mucosal healing and developing intelligent responsive materials.

Hierarchy of the oral mucosa and gingiva

The oral mucosa constitutes the main soft tissue structure within the oral cavity, encompassing both the gingiva and the lining membrane that overlies the alveolar bone, palate, tongue, oral floor and inner surfaces of the cheeks and lips. As a specialised interface, it provides a critical defensive barrier against mechanical, thermal and chemical insults resulting from mastication, speech and swallowing.[14]

To endure the persistent mechanical stresses associated with chewing and biting, the oral mucosa has evolved distinct histological adaptations. Structurally and functionally, the oral mucosa can be primarily

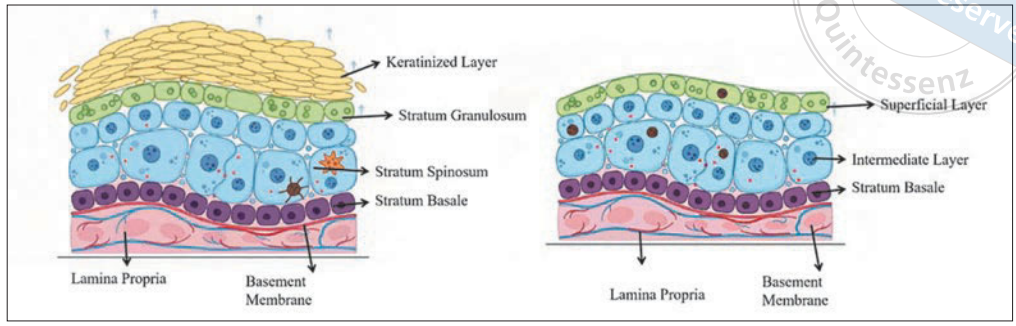

Fig 1 Histological structure diagram of gingiva and oral mucosa.

categorised into two types. The masticatory mucosa is characterised by a keratinised stratified squamous epithelium, which provides notable resistance to abrasion and shear forces. In contrast, the lining mucosa is covered by a non-keratinised stratified squamous epithelium, and its elastic properties facilitate flexible movement during speech and mastication.[15]

The oral epithelium and the underlying connective tissue of the lamina propria form a highly interdigitated interface, where ridges and projections greatly increase the contact surface area, thus improving mechanical attachment and overall structural integrity. Serving as the main supportive layer, the lamina propria consists of rich vascular networks, neural elements, and a robust extracellular matrix (ECM). Its cellular population is composed predominantly of fibroblasts, along with mesenchymal stem cells, macrophages, mast cells and various immune cell populations. Beyond structural support, the lamina propria also plays an essential role in immunoregulation and tissue repair through complex interactions among stromal cells, immune cells and the ECM. In the gingiva, fibroblasts maintain tissue homeostasis in the healthy state by regulating ECM homeostasis and inhibiting osteoclast differentiation. Excessive or abnormal activation of fibroblasts in periodontitis promotes chronic inflammation, bone destruction and disease progression. Under normal physiological conditions, oral mucosal fibroblasts maintain a quiescent state with minimal proliferative activity. However, during wound repair, these cells undergo activation and proliferation to facilitate ECM deposition and tissue regeneration. The oral mucosa receives its vascular supply primarily through submucosal arterial branches that anastomose to form an extensive capillary plexus immediately beneath the epithelial basement membrane.[16,17] This dense microvascular network ensures rapid nutrient exchange and oxygen delivery.

The gingiva represents a specialised masticatory mucosa characterised by keratinised epithelium that demonstrates firm attachment to both the underlying connective tissue and alveolar bone (Fig 1). Its lamina propria contains a dense collagen fibre network that confers exceptional mechanical resilience and structural integrity. Functionally, the gingiva serves to shield periodontal tissues from mechanical trauma and microbial infiltration and maintain the critical periodontal barrier.[18]

Characteristics and challenges of oral wound healing

Oral wound healing exhibits site-dependent variations due to differences in mucosal keratinisation. Lining mucosa heals rapidly via epithelial coverage without heavy reliance on matrix remodelling, whereas keratinised mucosa requires simultaneous epithelial and connective tissue regeneration, resulting in slower healing rates compared to lining mucosa. Besides, these regions are prone to impaired healing due to elevated mechanical tension during repair.[19]

The oral environment further complicates healing due to its dynamic humidity, salivary flow and masticatory forces, which disrupt biomaterial adhesion and retention. Continuous saliva exposure, dietary liquid intake and functional movements compromise material stability by reducing tensile strength and shortening interfacial contact duration.[20] Consequently, ideal biomaterials for oral soft tissue repair must combine wet adhesion, biocompatibility, biodegradability and mechanical resilience to withstand these challenges while promoting regeneration. Recent research aims to enhance repair strategies for oral wounds by overcoming these microenvironmental and biomechanical challenges.

Preparation and design of hydrogels

Hydrogels consist of 3D, hydrophilic polymer networks interconnected via chemical or physical crosslinks, enabling them to absorb hundreds or even thousands of

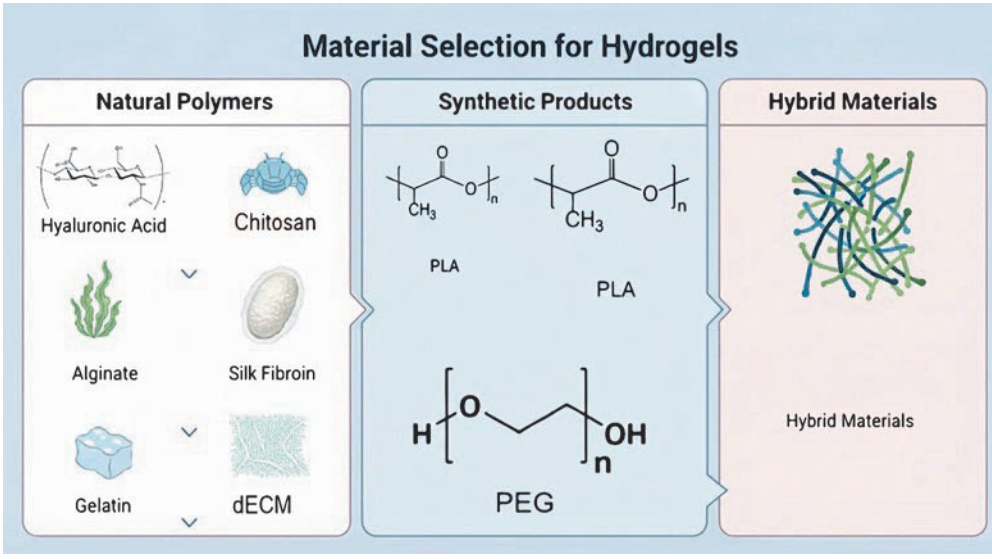

Fig 2 Overview of natural, synthetic and hybrid polymer materials commonly used for hydrogel fabrication in biomedical and tissue engineering applications.

times their dry mass in water without losing structural coherence. Due to their high water content and soft, tissue-like mechanical characteristics, they are exceptionally suited for biomedical use. Hydrogel properties such as swelling capacity, mechanical strength and degradation kinetics are essential for wound healing. These can be tuned by adjusting crosslinking density, polymer composition and responsiveness to environmental stimuli. Due to their biocompatibility, hydrogels serve as effective drug carriers, supportive tissue scaffolds and bioactive wound dressings. Natural hydrogels offer superior bioactivity and cell adhesion, while synthetic variants provide better mechanical control and reproducibility (Fig 2). Advanced fabrication techniques, such as 3D bioprinting and dynamic crosslinking, further enhance their functionality, enabling tailored structures with stimuli-responsive behaviour for specific biomedical needs.

Hydrogel material selection

Natural polymers

Natural polymer hydrogels consist of 3D, hydrophilic networks constructed from biomacromolecules, including proteins and polysaccharides. Due to their inherent biocompatibility, biodegradability and biofunctionality, natural polymers have emerged as essential building blocks for hydrogel fabrication in biomedical applications. Commonly utilised materials include chitosan, hyaluronic acid (HA), collagen, alginate and decellularised ECM, each of which offers unique physicochemical properties and tunability to meet diverse clinical requirements.

Chitosan

Chitosan, a cationic polysaccharide derived from chitin, is celebrated for its antimicrobial activity, mucoadhesiveness, low toxicity and pH-responsive behaviour. Under weak acidic conditions, certain amine groups can undergo protonation to form quaternary ammonium structures, thereby exhibiting antimicrobial efficacy.[21] Its protonated amino groups facilitate robust electrostatic adhesion to negatively charged mucosal surfaces, thereby improving retention within the oral cavity. This property also promotes binding to anionic bacterial cell membranes, resulting in membrane disruption, increased permeability and subsequent cell lysis.[22,23] Despite the many advantages of chitosan, its application is limited due to its pH-dependent solubility. Furthermore, poor water solubility and limited mechanical strength remain challenges prompting modifications such as glycol chitosan or carboxymethyl-hexanoyl chitosan to improve solubility and bioadhesion.[24,25] Chitosan-based hydrogels have demonstrated efficacy in periodontal drug delivery, such as thermosensitive systems for sustained release of antibiotics (e.g., metronidazole) and anti-inflammatory agents, showing reduced bacterial load and inflammation in preclinical models. Absorbable and suturable dense chitosan surgical films promote healing of palatal wounds in rats.[26,27] Injectable thermosensitive chitosan-poly (N-isopropylacrylamide)

hydrogel enhances antimicrobial efficacy and fibroblast proliferation and promotes repair of oral ulcers.[28] The dental dressing of chitosan significantly enhanced haemostasis and alveolar bone healing after tooth extraction. It is also effective in reducing inflammation, pain and swelling after third molar removal, particularly among patients undergoing antiplatelet therapy.[29,30]

HA

HA, a naturally occurring non-sulphated glycosaminoglycan, serves as a fundamental component of the ECM in oral tissues. Recognised for its high hydrophilicity, moisture-retention capacity, viscoelastic behaviour and excellent biocompatibility, HA significantly contributes to the regulation of wound healing processes in the oral cavity.[31,32] Studies suggest that HA supports scarless regeneration by inhibiting TGF-β1 expression, thereby reducing excessive collagen synthesis.[33,34] The biological functions of HA are critically determined by its molecular size. High-molecular-weight HA (> 5 MDa) exhibits immunosuppressive effects and inhibits blood vessel formation; in contrast, its lower-molecular-weight (6 to 20 kDa) counterpart stimulates pro-inflammatory responses and angiogenesis.[35]

HA-based hydrogels have emerged as prominent biomaterials in oral tissue engineering applications. Clinically, HA hydrogels accelerate oral ulcer healing; for example, 0.2% HA gel reduces ulcer number, size, pain and healing time.[36] Drug-loaded HA microneedle patches can penetrate tongue mucosa within 3 minutes, releasing therapeutics and demonstrating high therapeutic potential.[37] However, the therapeutic efficacy of HA in alveolar ridge preservation remains clinically contentious,[38] with randomised controlled trials reporting inconsistent outcomes, including significant horizontal ridge resorption in some studies. Furthermore, HA-based biomaterials necessitate substantial optimisation of their viscoelastic properties and structural stability to meet clinical demands.[39] HyaDENT BG (Regedent, Zurich, Switzerland) exhibits clinically beneficial sustained-release properties, as demonstrated by Asparuhova et al.[40] In vitro studies confirm that it significantly boosts the expansion of osteoprogenitor cells and enhances the proliferation, migration and wound healing capacity of gingival fibroblasts.[41] Clinical trials reveal that when combined with THE Graft (Purgo Biologics, Seongnam, South Korea), HyaDENT BG leads to significant enhancements in clinical attachment levels and reduction in probing depth within intrabony defects, although its outcomes remain slightly inferior to those achieved with Emdogain (Straumann, Basel, Switzerland).[42] The HA-based product Gengigel (Ricerfarma, Milan, Italy) (containing 0.2% to 0.8% sodium hyaluronate and xylitol) exhibits dual antibacterial and anti-inflammatory properties. Clinical data demonstrate that Gengigel, when used adjunctively with bone grafts, significantly improves periodontal regeneration in class II furcation defects, yielding superior clinical attachment gain compared to controls.[43,44]

In biomaterial engineering, UV-curable HA hydrogels (e.g., CNB-HA) demonstrate rapid elastic adhesive formation within 5 seconds through thiol-nitroso photopolymerisation under 395 nm irradiation. These hydrogels achieve superior tissue adhesion strength (40 kPa) compared to conventional fibrin glue (~15 kPa) while maintaining structural stability in moist oral environments for > 24 hours.[45] However, their clinical utility is constrained by UV-dependent curing mechanisms and limited accessibility to light-restricted anatomical sites (e.g., deep periodontal pockets). Emerging alternatives include dual-amide-functionalised zwitterionic polymers, which leverage robust hydrogen bonding networks for effective wet adhesion while simultaneously enhancing cellular proliferation and neovascularisation. This dual functionality positions them as promising candidates for next-generation oral adhesive biomaterials.[46]

Gelatin

Gelatin, a derivative of collagen, is readily biodegradable under physiological conditions and generates metabolic byproducts with high biocompatibility.[47,48] Thus, it can be used to make hydrogels with high biocompatibility and low immunogenicity.[49] Gelatin-based hydrogels have poor mechanical strength because of the absence of stable triple helices in collagen. Therefore, gelatin is often combined with structural polymers to enhance bioactivity.[50,51] In periodontal regenerative therapy, gelatin methacrylate (GelMA), a derivative obtained by functionalising gelatin with methacrylic anhydride, serves as a photo-responsive hydrogel platform. Its methacrylate groups enable precise light-initiated crosslinking, yielding significantly improved mechanical properties while maintaining favourable biological characteristics.[52,53] To enhance its functional performance, GelMA has been chemically modified through incorporation of quaternary ammonium groups to impart potent antibacterial properties and copolymerisation with methacrylic poly-phosphoester to improve elastomeric behaviour while maintaining biocompatibility.[54-56] Enzymatic crosslinking via micro-

bial transglutaminase significantly enhances the mechanical properties of gelatin hydrogels, achieving a yield strength of 61 kPa. These engineered matrices closely resemble pre-mineralised bone architecture and have been shown to promote osteogenic differentiation of bone marrow stem cells (BMSCs) in vitro.[57]

For intraoral wound care, collagen-based materials are favoured for their biocompatibility and structural mimicry of the ECM. Collagen membranes adhere to oral mucosal defects, promote angiogenesis and reduce inflammation, though challenges persist, such as high cost and antigenicity.[58-61] Recent innovations in collagen-based biomaterials include laser tissue soldering for sutureless stabilisation of periodontal membranes[62] and ternary collagen-glycosaminoglycan-chitosan scaffolds that successfully replicate the stratified architecture of native oral mucosa.[63] Furthermore, bioinspired gelatin-polydopamine-nanoclay composite hydrogels demonstrate exceptional wet tissue adhesion (38.72 ± 10.94 kPa) and significantly accelerate healing in preclinical oral ulcer models.[64,65]

Alginate

Alginate is a natural high-molecular-weight polysaccharide, often used as a key structural additive to significantly enhance the flexibility of composite materials. It is composed of alternating blocks of guluronic and mannuronic acids. This biopolymer forms 3D hydrogel networks through ionic crosslinking mediated by divalent cations, such as Ca^{2+}, resulting in a distinctive "egg-box" microstructure. The resulting porous hydrogel matrix provides an optimal microenvironment for cellular activities including adhesion, migration and proliferation.[66] Alginate has emerged as the gold standard impression material in clinical dentistry owing to its favourable biocompatibility and ease of use, and significant research efforts have been dedicated to developing alginate-based hydrogels for use in periodontal treatments. Composite formulations incorporating elements such as silver have been developed to enhance mechanical performance for targeted periodontal drug delivery compared with single-component alginate hydrogels.[67,68] Alginate hydrogels can be chemically functionalised to significantly improve their physicochemical properties. For instance, the covalent conjugation of cell-adhesive peptides such as arginine-glycine-aspartic acid-serine (RGDS) to alginate, through carboxyl group activation, has been shown to markedly enhance the cell-adhesive capacity of the resulting hydrogels.[69] These RGD-functionalised alginate hydrogels have also been demonstrated to promote the reparative functions of human mesenchymal stem cells (hMSCs). Further, photocrosslinkable alginate derivatives have been developed by introducing methacrylate groups at the hydroxyl sites, enabling shape plasticity and tunable mechanical properties, akin to those of synthetic polymers such as GelMA.[70] A notable example is the OSA-DA-PAM hydrogel, synthesised from dopamine-modified oxidised sodium alginate. This material exhibits exceptional mechanical robustness, intrinsic self-healing capability, strong tissue adhesion and excellent biocompatibility, along with the ability to sustain the release of epidermal growth factors (EGFs). These advanced features position it as a highly promising candidate for next-generation wound dressings.[21]

Decellularised ECM

Decellularised ECM (dECM) is derived by removing cellular components via physical, chemical or enzymatic treatments, retaining the natural ECM structure and bioactive molecules that support cell migration, proliferation and differentiation. Its lack of cellular antigens minimises immune rejection risks. dECM has emerged as a versatile bioink for 3D bioprinting applications. Kim et al[71] fabricated vascularized skin grafts using porcine dECM bioink with keratinocytes, fibroblasts and endothelial progenitor cells. Kim et al[71] and Pourchet et al[72] developed gelatin-alginate-fibrinogen dECM bioink to print 5-mm-thick skin mimicking natural epidermis. Beyond printing, dECM enhances vascularisation and integration. Heller et al[73] created pre-vascularised oral mucosa equivalents that rapidly anastomosed with host vasculature post-transplantation. For antimicrobial and wound healing, dECM has been combined with synthetic materials to improve functionality. Afghah et al[74] incorporated silver nanoparticles into dECM-PCL scaffolds to boost antimicrobial activity and skin regeneration. Ilhan et al[75] used plant extract–modified dECM scaffolds to accelerate diabetic ulcer healing and combat infections.

Despite its potential, dECM suffers from batch variability, inconsistent composition across sources (porcine, bovine, human), and inadequate mechanical strength, often requiring synthetic reinforcement. Future efforts should be made to standardise preparation, optimise mechanics and advance clinical applications in gingival and oral tissue engineering.

Other materials

In addition to the materials mentioned above, silk fibroin has attracted growing interest as a leading biomaterial

candidate for load-bearing tissue repair, primarily due to its tunable degradation kinetics. The material's characteristic β-sheet crystalline structure imparts remarkable elastic resilience to formed hydrogels, while degradation rates (ranging from weeks to months) can be precisely modulated through crystallinity control.[76,77]

Collagen, which constitutes up to 30% of total body protein, serves as the primary structural component of the ECM. Its characteristic triple-helical conformation presents multiple cell-adhesive domains (e.g., RGD sequences) that mediate cellular attachment and directional migration. While collagen hydrogels demonstrate enzyme-specific degradability (primarily via matrix metalloproteinase-1/collagenase), their limited mechanical strength (typically < 1 kPa) necessitates reinforcement with synthetic polymers like polyethylene glycol (PEG) to achieve clinically relevant stability.[78]

Despite the excellent biocompatibility and bioactivity of natural polymer-based hydrogels, three key limitations hinder their clinical translation for oral applications: insufficient wet adhesion strength (< 10 kPa) in saliva-rich environments, mechanical property mismatch with native oral tissues and uncontrolled degradation kinetics. Emerging strategies to address these challenges include hybrid systems or functional modifications to optimise performance in the complex oral microenvironment.

Synthetic hydrogels

Synthetic hydrogels are chemically engineered, 3D polymeric networks formed via covalent bonding or physical crosslinking of hydrophilic polymer chains.[78] Compared to natural hydrogels, synthetic variants offer several distinct advantages: simplified and reproducible fabrication processes that facilitate large-scale production, precisely tunable physicochemical properties and controllable degradation kinetics, enhanced structural and functional stability under physiological conditions and superior mechanical strength, making them suitable for load-bearing applications.[79] These properties make synthetic hydrogels highly attractive for biomedical applications requiring material durability, long-term stability and design flexibility.

Polyvinyl alcohol

Polyvinyl alcohol (PVA) hydrogel exhibits excellent water solubility, hydrophilicity, biodegradability and low cost, along with the ability to create a moist wound environment.[80] However, PVA materials have bioinert properties, poor exudate absorption capacity and insufficient elasticity. Blending or modifying PVA with other bioactive substances can improve its performance. After modification with dopamine (DOPA), PVA can be used to prepare materials with enhanced mucosal adhesion.[65] Scaffold materials made of PVA allow connective tissue and bone to grow into them due to their porous and biocompatible structure. Notably, Sinclair-Hall[81] investigated the effects of PVA sponge implants in treating alveolar bone defects in dogs over 3 to 74 weeks. More recent studies further confirm the potential of PVA-based scaffolds in tissue engineering and wound healing applications.[80] The PVA sponge delayed early bone repair but enhanced later ossification and calcification, which is beneficial for hard tissue recontouring. PVA can serve as an inert scaffold for cell encapsulation and storage. Building on this, by leveraging the stability of boronate ester bonds under physiological pH and their dissociation upon glucose addition, combining PVA with thermoresponsive polymers, a dual-responsive smart system capable of reacting to both temperature and glucose has been developed. This technology has been successfully applied in areas such as stem cell encapsulation and cryopreservation.[82]

Polylactic acid (PLA)

Polylactic acid (PLA) is an eco-friendly and biodegradable polyester,[83] suitable for processing techniques such as fused deposition modelling (FDM).[84] It releases lactic acid via hydrolytic degradation in vivo, which acts as a signalling molecule for wound healing.[85,86] Based on this mechanism, PLA-based biomaterials play important roles in tissue repair, collagen deposition, angiogenesis and infection prevention.[87] PLA also serves as an ideal carrier for encapsulating bioactive compounds.[88]

Chen et al[89] engineered thermo-mechanically enhanced nanocomposite scaffolds by incorporating graphene oxide into a polyurethane (TPU)/PLA matrix. In a separate development, Go et al[90] designed an innovative star-shaped PLA-heparin construct that exhibited superior biocompatibility, as evidenced by reduced platelet adhesion and protein adsorption, along with enhanced fibroblast spreading compared to heparin-free controls.

PEG

PEG, a synthetic polymer with tunable physicochemical properties, has emerged as a cornerstone material in biomedical engineering. This synthetic polymer demonstrates remarkable biocompatibility and biodegradability profiles, making it an ideal candidate

for applications ranging from controlled drug delivery systems to 3D tissue scaffolds. Notably, its intrinsic high water solubility and unique capacity for molecular weight customisation enable precise modulation of hydrogel mechanical strength and degradation kinetics, critical parameters in replicating native tissue microenvironments. Its ease of chemical modification further enhances its adaptability, enabling the design of functionalised hydrogels tailored to specific therapeutic needs. As a methacrylate-functional derivative of PEG, polyethylene glycol dimethacrylate exhibits unique photo-crosslinkable characters that enable rapid hydrogel formation under UV irradiation. When combined with lithium phenyl-2,4,6-trimethylbenzoyphosphinate (LAP), this monomer undergoes chain-growth polymerisation to form a covalent network, achieving gelation times as short as 5 seconds under optimised light intensity (50 mW/cm^2).[91] Moreover, residual monomer toxicity from unreacted N-isopropylacrylamide (NIPPAm) requires rigorous purification protocols, with high-performance liquid chromatography (HPLC) analysis confirming monomer clearance below 0.1% (w/w) for biomedical applications.[92] In periodontal disease contexts, the pH (4.5 to 5.5) and matrix metalloproteins 8 (MMP-8) levels of the gingival sulcus fluid are affected (more than threefold increase compared to healthy tissues). Based on this rationale, Li et al[93] engineered an innovative pH-responsive hydrogel system using PEG as a backbone that is capable of responding to acidic environments (pH ≤ 6.0). Guo et al[94] synthesised MMP-8-responsive hydrogels based on PEG diacrylate with cysteine-capped peptide crosslinkers, which can be cleaved by MMP-8 to control drug release. Application of liquid PEG in extraction sockets results in in situ crosslinking to form a hydrogel within 90 seconds. The molecular network of PEG guides tissue response by permitting nutrient penetration while inhibiting soft tissue cell migration, thereby significantly preserving alveolar ridge width.[95]

Stimuli-responsive polymers

Stimuli-responsive polymers are a specialised class of synthetic materials designed to undergo environmentally triggered structural rearrangements when exposed to defined external stimuli, including variations in temperature, pH, light, enzyme activity or biomolecular concentrations. Their transformations are marked by high specificity, predictability and adjustable properties, which underpins their broad utility in applications such as controlled drug release, tissue scaffolding and biosensor development. A hallmark feature of these materials is their dual-phase responsiveness, with their nonlinear kinetic behaviour (unlike linear polymer systems, these materials exhibit threshold-dependent responses) and dynamic reversibility, achieved through reversible covalent bonds (e.g., disulphide bridges with 103 s-1 exchange rates) or non-covalent interactions that enable multiple activation/deactivation cycles.

For instance, PEG itself does not possess typical stimuli responsiveness. However, it can be endowed with stimuli-responsive capabilities through modification or compounding. It exhibits excellent biocompatibility, and its degradation products are non-toxic, harmless and easily metabolised in the human body. Moreover, poly(N-isopropylacrylamide) (PNIPAM) exhibits a temperature-dependent phase change, transitioning from a solution to a gel as temperature increases, which has been extensively studied to date. Its lower critical solution temperature (LCST) is adjacent to physiological temperature conditions.[96] This property makes it suitable for injectable hydrogel design.[97] In addition, PNIPAM-based hydrogels can be used in cell-sheet technology: intact cell sheets can be recovered nondestructively by cooling the hydrogel below LCST to dissolve it. However, the low mechanical strength of pure PNIPAM often requires copolymerisation with methacrylate-based monomers (e.g., HEMA) or the introduction of dynamic covalent crosslinks (e.g., bisulfide bonds) to improve stability, but they may also affect the thermal response properties of PNIPAM. It is worth noting that although PNIPAM demonstrates favourable biocompatibility with minimal immunogenic response in biological systems.[98] However, N-isopropylpropionamide is cytotoxic and neurotoxic, and therefore requires complete removal of the residual monomer after polymerisation.[88] Zheng et al[99] fabricated a thermally responsive hydrogel system composed of PDLLA-PEG-PDLLA reinforced with catechol-functionalised quaternised chitosan (QCS-C). The incorporation of QCS-C not only significantly reduced the LCST of the hydrogel but also markedly enhanced its tissue adhesion strength.

A series of innovative injectable hydrogels have emerged for targeted periodontal therapy, combining thermoresponsiveness with multifunctional drug delivery. Almoshari et al[100] engineered a thermoresponsive hydrogel by conjugating PNIPAM with osteophilic pyrophosphate. This modification enhanced the hydrogel's affinity for hydroxyapatite, achieving a binding appeal of 3.2 ± 0.5 μm as measured by isothermal titration calorimetry.[100] The system effectively protects alveolar bone and periodontal ligaments while concurrently mitigating inflammatory responses in periodontal applications.[100] Wang et al[101] developed an injectable polyisocyanopeptide hydrogel loaded with

Table 1 Common physical crosslinking methods and their characteristics.

Method	Crosslinking mechanism	Key characteristics	Representative systems
Ionic interactions	Ionic bridges formed between multivalent cations and anionic polymer chains	Rapid gelation under ambient temperature and physiological pH; reversible crosslinks; limited mechanical robustness	Ionically crosslinked chitosan hydrogels for drug delivery;[116] chitosan/PSBMA ionic–covalent double-network hydrogels with high mechanical strength and self-recovery capability[117]
Crystallisation	Formation of crystalline domains via ordered chain alignment, typically induced by freeze–thaw cycles	Reversible and biocompatible; thermosensitive behaviour; mechanical properties highly dependent on molecular weight, polymer concentration, and freezing conditions	PVA/alginate blends with tunable mechanical strength and drug release profiles;[118] high-concentration dextran crystallisation-based hydrogels[119]
Hydrogen bonding	Dynamic secondary interactions between hydrogen atoms and electronegative atoms (O, N)	pH and temperature-responsive; often self-healable; moderate mechanical strength; suitable for injectable or printable systems	NAGA-based bioinks for 3D printing applications;[120] freeze–thaw induced PVA–Phytagel hydrogels[121,122]

doxycycline and the lipoxin A4, which significantly reduced the subgingival bacterial burden. This work presents an innovative approach to engineering smart hydrogels integrating biomimetic mechanical properties with programmable drug release capabilities, showing promising applicability for precision periodontitis treatment.[101]

Hybrid materials (natural/synthetic composites)

Hybrid biomaterials combine the mechanical strength and tunability of synthetic polymers with the biocompatibility and bioactivity of natural polymers, addressing key limitations of each.[102,103] While synthetic materials offer excellent structural stability and controlled drug delivery, their slow degradation can hinder tissue regeneration. Conversely, natural polymers promote cell adhesion and haemostasis but often lack sufficient mechanical robustness. By integrating these components, hybrid hydrogels achieve synergistic effects, namely enhanced mechanical performance, improved bioactivity and tailored degradation.[104]

This design philosophy finds exemplary implementation in bacterial cellulose (BC)-based systems. With its superior properties compared to plant cellulose, including high purity, crystallinity (60% to 80%), tensile strength (200 to 300 MPa) and water retention capacity,[105] BC serves as an ideal matrix for oral applications requiring sustained moisture retention and mucosal adhesion. Recent advancements below demonstrate its unique applications. Singh et al[106] developed a light-curable BC-poly(amido-amine)-g-diazepane composite hydrogel that forms elastic membranes conforming to irregular wounds. Other hybrid biomaterials have also been designed in clinical fields. For example, for enhanced clinical utility, sprayable hydrogels like pectin-lignan formulations demonstrate strong mucosal adhesion, resisting phosphate-buffered saline (PBS) rinsing after application in rat models.[19] Zhang et al[107] developed a Schiff base-crosslinked chitosan-polydextran hydrogel integrated with silver nanoparticles. This composite system effectively modulated the oral microbiota and potentiated antitumour immunity in models of oral squamous cell carcinoma.[107] In haemostasis, phenylboronic acid-alginate quaternised chitosan-catechol powders developed by Du et al[108] rapidly absorb blood and form stable hydrogel barriers upon hydration. Meanwhile, the calcium alginate/fucoidan hydrogel fabricated by Dou et al[109] maintains robust wet adhesion even when subjected to rinsing. The crosslinking of calcium ions with alginate results in the formation of a wet-adhesive hydrogel that exhibits high resistance to rinsing with water. Utilising the antibacterial capacity of quaternary ammonium salts, Jiao et al[110] and Zhou et al[111] developed dental restorative materials endowed with antimicrobial properties. Quaternised chitosan has antimicrobial efficacy against caries-inducing pathogens such as *Streptococcus mutans*, comparable to that of chlorhexidine. The enhanced biofilm radioprotection and bacterial viability inhibition were attributed to the synergistic action of hydrophobic alkyl chains and hydrophilic quaternary ammonium moieties. Furthermore, modifications with glycol chitosan and carboxymethyl hexanoyl chitosan were shown to improve water solubility and biocompatibility, paving the way for the application of chitosan-based hydrogels in periodontal drug delivery.[112]

Table 2 Familiar chemical crosslinking methods and their characteristics.

Method	Reaction mechanism	Key characteristics	Representative systems/examples
Free radical polymerisation	Radicals generated by light, heat or redox initiators trigger vinyl monomer polymerisation	Enables in situ gelation; potential cytotoxicity from radicals or residual initiators; widely applied in commercial hydrogels	Vinyl-based hydrogels initiated by persulfate/TEMED;[124] UV-polymerized ulvan methacrylate hydrogels;[125] allyl cellulose-based ionic hydrogels[126]
Schiff base reaction	Condensation between aldehyde and amine or hydrazide groups forming reversible imine (C=N) bonds	Catalyst-free; pH-responsive; suitable for bioactive molecule delivery; glutaraldehyde may induce cytotoxicity	Chitosan–aldehyde HA hydrogels for controlled release;[127] glutaraldehyde-crosslinked gelatin systems;[128] aldehyde-functionalised HA–antibody films[129]
Enzymatic crosslinking	Enzyme-catalysed covalent bond formation between specific functional groups	Mild reaction conditions (physiological pH and temperature); avoids toxic crosslinkers; suitable for cell and protein encapsulation	Transglutaminase-catalysed PEG–poly (lysine) hydrogels with tunable degradation;[130,131] Ca^{2+}-dependent transglutaminase systems enabling temperature-triggered gelation[132]
Click chemistry	Highly selective and efficient coupling reactions under mild conditions	Excellent biocompatibility and modularity; allows dynamic bond formation; catalyst removal may be required in some systems	CuAAC systems (fast reaction but potential copper cytotoxicity);[133] metal-free SPAAC reactions; catalyst-free Diels–Alder and IEDDA reactions suitable for physiological environments[134]

Preparation techniques

Physical crosslinking method

Physical crosslinking forms polymer network structures mainly through non-covalent interactions. Physical crosslinking does not require crosslinking agents, so the toxicity is greatly reduced. Physical crosslinking prepares hydrogels under mild reaction conditions with little cellular damage,[113,114] but the hydrogels typically exhibit limited mechanical strength, while the dynamic nature of their crosslinking often compromises structural integrity.[115] Some common physical crosslinking methods and their characteristics are outlined in Table 1.

Chemical crosslinking

Chemical crosslinking forms hydrogel networks through strong covalent bonds, typically requiring crosslinking agents, which can raise biocompatibility concerns. While this method produces hydrogels with superior mechanical strength and high structural stability, the often-harsh reaction conditions may compromise cell viability when used in biomedical applications.[123] Some familiar chemical crosslinking methods and their characteristics are presented in Table 2.

Emerging technologies

There are four major emerging technologies in biomedical and tissue engineering: electrostatic spinning, 3D bioprinting, microfluidic organ-on-chip systems and scaffold-free tissue engineering (Fig 3).

Electrostatic spinning

The electrostatic spinning technique can mimic the collagen/elastin fibre structure of the natural ECM for cellular interactions by modulating fibre diameter (50 to 500 nm).[135] Multilayered electrospun scaffolds mimic the layered structure of gingival tissues (epithelial layer, lamina propria, basement membrane) and promote vascularisation.[136] Functional enhancements are achieved through strategic material engineering. For example, GelMA-based electrospun fibres loaded with azithromycin can control drug release and fight infection.[137] Polycaprolactone/collagen multilayer scaffolds showed angiogenic capacity in in vivo experiments.[138]

The diameter of electrospun fibres critically affects cell migration and phenotype, e.g., human umbilical vein endothelial cells (HUVECs) have higher infiltration and survival on 4.83-μm fibres.[139] Conversely, smooth muscle cells (VSMCs) migrate more easily on 7- to 10-μm fibres.[140] The porosity (> 30%) and pore size (100 to 700 μm) of electrospun scaffolds are critical parameters for vascularisation.[141,142] However, single-layer electrospun membranes are difficult to use for constructing thick tissues and need to be combined with multilayer design or 3D printing. Further validation of efficacy in large animal models is required.[136] Chen et al[143] developed carboxymethyl chitosan-based hydrogel-Janus nanofiber scaffolds with unidirectional biofluid storage-drainage for accelerating full-thickness wound healing. The hydrogel

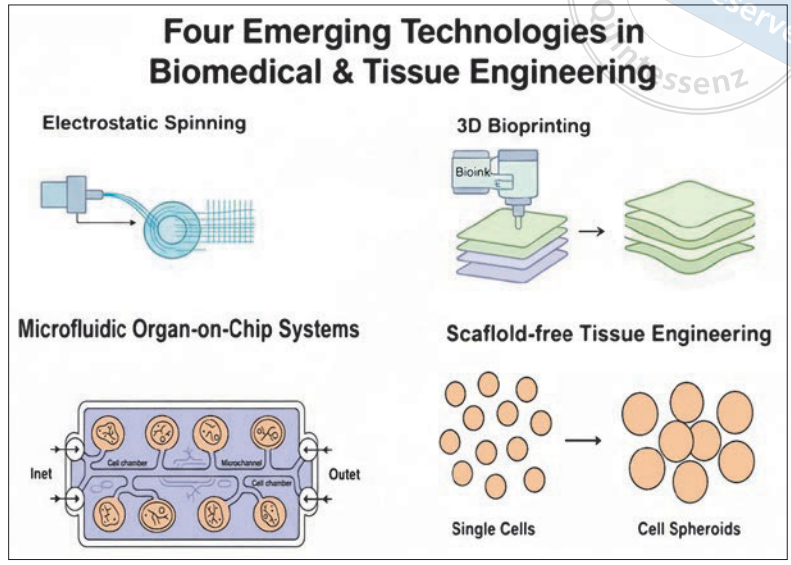

Fig 3 Four major emerging technologies in biomedical and tissue engineering: electrostatic spinning, 3D bioprinting, microfluidic organ-on-chip systems and scaffold-free tissue engineering.

showed antibacterial activity against Escherichia coli and Staphylococcus aureus, supported L929 fibroblast proliferation without evident cytotoxicity and significantly accelerated wound closure, granulation tissue formation, collagen deposition and neovascularisation in a rat full-thickness skin defect model.

3D bioprinting

3D bioprinting enables precise arrangement of cells, biomaterials and signalling factors through layer-by-layer assembly technology, which is able to mimic the anatomical and functional properties (e.g., mechanical strength and porosity) of natural gingival tissues, offering the possibility of personalised regenerative therapy.[144] Hydrogels of collagen,[145] fibrin,[146] gelatin[147] and methacrylated polymers are widely used for their biocompatibility and bionic ECM properties. Nutrient delivery and host vascular integration are enhanced by co-printing endothelial and mesenchymal cells to form a functional microvascular network or by incorporating microfluidic organ chips to mimic tissue fluid flow.[148-150]

In oral soft tissue regeneration, gelatin-based bioinks play a critical role as cell carriers. For instance, gelatin-fibrinogen-collagen type I-elastin bioinks encapsulating neonatal human dermal fibroblasts have been used to engineer dermis-like structures, demonstrating barrier functionality through electrical impedance testing.[151] This aligns with studies on gingival fibroblast heterogeneity, which indirectly supports gelatin's utility in 3D cultures for epithelial morphogenesis and immune response modulation.[152-155]

In skin tissue engineering, the use of decellularised matrix bioinks or polycaprolactone (PCL) hydrogels loaded with silver particles can enhance antimicrobial properties and barrier function, and ideally, the rate of degradation of the graft material should match the time required for gingival tissue regeneration.[74,156,157] The ideal graft would both prevent the gingival epithelium from growing into the defect and promote the formation of new ligament tissue, a process that takes 4 to 6 weeks. Choosing the right material is currently a challenge. A recent study by Ma et al[158] developed a photosensitive composite hydrogel composed of 5% GelMA and 0.5% HA methacrylate (HAMA), utilising epidermal stem cells and skin-derived precursor cells as seed cells. Employing a 3D bioprinting technique, a grid-structured scaffold was fabricated to enable precise co-printing of cells and hydrogels. The resulting hydrogel demonstrated an optimal pore size range (5 to 30 μm), robust mechanical integrity and excellent biocompatibility. When the bioprinted artificial skin was transplanted into a full-thickness skin defect model in nude mice, complete wound healing was observed after 4 weeks. Notably, the regenerated tissue included key skin appendages such as the epidermis, dermis, hair follicles, blood vessels and sebaceous glands, closely replicating the structural complexity of native skin. While these findings are promising for skin tissue engineering, the applicability of such bioprinted constructs in the oral environment requires further investigation.[158]

Microfluidic organ-on-chip systems

Beyond biofabrication techniques, microfluidic organ-on-chip platforms enable precise regulation of fluid dynamics, nutrient delivery and metabolic waste removal, effectively reproducing the vascular perfusion and interstitial fluid exchange observed in native tissues. With their zoned culture capability and dynamic fluid control, organ-on-chip platforms enable the precise spatiotemporal delivery of microorganisms, microbial products or pharmaceutical compounds to gingival cells. This biomimetic strategy supports cellular development within microengineered architectures that better replicate in vivo microenvironments.

Microfluidic technology has emerged as a transformative tool for recapitulating gingival microenvironment dynamics. Makkar et al[145] developed a microfluidic device they termed a "gingival crevice-on-a-chip." This platform allowed for sustained host-microbe coculture, mimicry of microbial clearance mechanisms, and modulation of innate immune responses.[145] Rahimi[159] used a similar horizontally stacked three-channel design to grow oral mucosal structures on a microchip, thereby elucidating host-material and host-microbe interactions. In this design, the lack of an air-liquid interface resulted in an immature epithelial barrier.[159] Whole-layer gingival equivalents in a microfluidic chip (gingiva-on-chip) achieved superior epithelial morphogenesis, maturation and barrier function compared to static cultures through a vertical stacking design and dynamic culturing at the air-liquid interface. When simulating the mechanical effects of mouthrinse, researchers found that flow conditions exacerbated cytotoxicity of oral care preparations on tissues.[10] Microfluidics and 3D bioprinting can precisely control the spatial arrangement of cells/ECM and enable perfusion culture of vascularised tissues to advance the development of personalised gingival constructs.[160-163] Microfluidics significantly improves the physiological relevance of gingival tissue models by mimicking physiological flow, mechanical stress and dynamic microenvironments, providing a research platform closer to in vivo for regenerative medicine and drug testing. Machla et al[164] employed a stereolithography-based additive manufacturing approach using BioMed Clear V1 resin (Formlabs, Somerville, MA, USA) for the main body and Elastic 50A resin (Formlabs) for the sealing ring, resulting in an open double-chamber structure. The upper chamber was seeded with TR146 epithelial cell lines, while the lower chamber housed either human gingival fibroblasts or a collagen/fibrin hydrogel, designed to mimic the lamina propria. Following 3 weeks of dynamic culture, a well-organised multilayered epithelium and a viable fibroblast-laden lamina propria analogue were successfully developed. The resulting tissue construct closely resembled the structural characteristics of native oral mucosa, offering a promising in vitro model for oral tissue regeneration and testing.[164]

Scaffold-free tissue engineering

Scaffold-free tissue engineering is a regenerative strategy that relies on cellular self-assembly rather than exogenous scaffolds to form functional tissues. This approach avoids the issues associated with traditional scaffolds, such as immune reactions and mismatched degradation rates, while better replicating natural cell-cell interactions.[165] Cell sheet engineering utilises temperature-responsive polymers to cultivate cells into intact ECM-rich sheets that can be layered to create 3D tissues. For example, human dental pulp stem cell (hDPSC) sheets have been used to generate vascularised pulp-like tissues for dental pulp regeneration and promote periodontal ligament and alveolar bone repair.[166-168] Although this technique preserves native ECM and enhances cell survival, its manipulation is technically complex, particularly in confined spaces like root canals.[169] Cellular spheroids employ low-adhesion cultures, microfluidics or magnetic levitation to enable cell self-assembly into 3D microtissues. Co-cultured hDPSC and HUVEC spheroids enhance vascularisation and pulp regeneration, while hDPSC spheroids also improve osteogenic differentiation and periodontal repair.[170,171] However, spheroid size inconsistency and suboptimal culture conditions remain challenges. Despite their promise in dental regeneration, scaffold-free methods still face hurdles in cell survival, vascularisation and nerve integration.

The primary scaffold-free methods for constructing cellular spheroids include the liquid overlay method and the hanging drop method. In the liquid overlay method, the bottom of the culture vessel is coated with non-adhesive materials such as agarose, poly-HEMA or HA to prevent cell attachment and promote spontaneous aggregation into spheroids. However, this method lacks cell–ECM interactions and the spheroid size is limited.

The hanging drop method involves placing droplets of cell suspension on the inner side of a culture plate lid, where cells aggregate at the bottom of the droplet due to gravity, forming spheroids. This technique allows for precise size control (by adjusting the initial cell

number), generates uniformly shaped spheroids and is well-suited for high-throughput screening. However, it is labour-intensive, making culture-medium exchange difficult while lacking ECM support.

The stirring method/rotating culture systems utilise spinner flasks, rotating vessels or bioreactors to dynamically suspend cells, promoting spheroid formation. This method is suitable for large-scale spheroid production.[172]

A water-swellable hydrogel serves as a culture substrate, supporting the formation of a confluent cell sheet over a 14-day period. The hydrogel with the adherent cell sheet is then inverted and placed into a new culture plate. By reducing the culture temperature from 37°C to approximately 15°C for around 40 minutes, the hydrogel undergoes enhanced hydrophilicity, leading to the spontaneous detachment of the entire cell sheet from the hydrogel surface. Following removal of the hydrogel, the cell sheet adheres to the new culture substrate. This method preserves cell–cell and cell–ECM connections, eliminates the need for enzymatic digestion and avoids associated cellular damage.[173]

Hydrogel design and applications for oral soft tissue repair

The successful application of hydrogels in the dynamic oral environment requires a design strategy that addresses two fundamental challenges: achieving stable adhesion under wet conditions and fulfilling the specific biological needs of different tissues. This section first outlines the critical design principles for overcoming the adhesion challenge. It then introduces the role of hydrogels as programmable delivery platforms, a core functionality that enables their therapeutic action. Finally, it reviews how these foundational designs are applied across key clinical scenarios in oral soft tissue repair.

Foundational design strategy: achieving robust wet adhesion

The primary challenge for any intraoral biomaterial is achieving stable adhesion in a constantly wet, mobile and mechanically active environment. While saliva contains proteins and growth factors beneficial for healing,[174] its flushing effect can rapidly displace unsecured dressings. Therefore, enhancing adhesion to moist surfaces is a top priority. Current strategies are largely bioinspired, exploiting specific chemical and physical interactions to create strong interfacial bonds (Fig 4).

Catechol-based adhesion

Marine mussels possess the ability to firmly attach to wet surfaces even in environments with strong waves and turbulent currents, thus inspiring the development of numerous oral-related materials. Mussels secrete mussel adhesive proteins (MAPs) from their feet. These proteins are rich in glycine and 3, 4-dihydroxy-L-phenylalanine (L-DOPA), and the catechol groups in the side chains of L-DOPA are primarily responsible for the adhesive properties of mussels.

The mussel-inspired bionic adhesive Janus hydrogel achieves adhesion mainly through polydopamine (PDA) generated by the oxidation of dopamine.[64] The hydrogel achieves non-covalent and covalent interactions with various functional groups on the tissue surface through the catechol groups in PDA. These interactions include hydrogen bonds, Schiff base reactions and binding to functional groups such as amino, sulfhydryl and carboxyl groups. Additionally, PDA adhesives can undergo further reactions with amine and thiol groups through Michael addition reactions. Apart from dopamine, its derivatives, including DOPA, norepinephrine, gallic acid and tannic acid, can also be used to modify polymers via self-polymerisation techniques.[175,176] Modifying dopamine and its derivatives using the coupling chemistry of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and N-hydroxysuccinimide facilitates the efficient formation of amide bonds between -NH_2 and -COOH groups under acidic conditions. As most natural polymers are rich in amino and carboxyl groups, dopamine and related compounds can readily attach to them.[177-179] Schiff base chemistry provides another effective approach for synthesising catechol- or gallol-functionalised polymers. This method involves the reaction between amino and aldehyde groups under mild conditions to form C=N double bonds.[180,181]

Catechol groups are highly versatile and capable of undergoing physical and covalent crosslinking with different functional groups. For example, their hydroxyl groups can interact electrostatically with metal oxides and form hydrogen bonds with hydrophilic surfaces. Moreover, their benzene rings can promote cation-π interactions, hydrophobic interactions and π–π stacking with adherends exhibiting diverse interfacial characteristics. When catechol is oxidised to quinone, the resulting products can form covalent bonds with amines and thiols via Michael addition, while also establishing strong coordination complexes with metal oxides.[182]

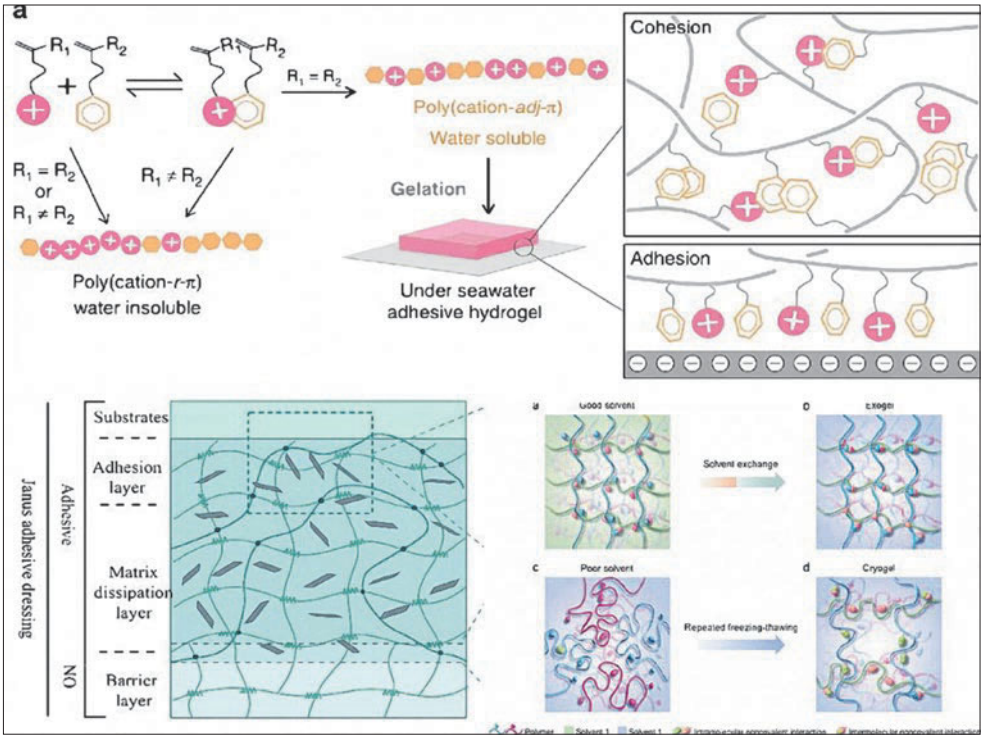

Fig 4a to c Several different adhesion mechanisms. The hydrogel is based on a cation-π complex-aided free radical polymerisation strategy to synthesise poly (cation-adj-π) with adjacent cationic–aromatic sequences. The resulting supramolecular hydrogel exhibits electrostatic adhesion in seawater (a). The adhesive layer adheres to the oral mucosal surface, while the barrier layer prevents mutual adhesion between dressings and forms a barrier against external foreign matter (b). Exogels were formed via solvent exchange-induced polymer crosslinking, while cryogels were prepared through repeated freeze–thaw cycles. The resulting PVA hydrogels exhibit strong underwater adhesion (c).

Hydrogen bonding-mediated adhesion

Hydrogen bonding interactions possess relatively low binding energies, typically ranging from 0.5 to 1.8 kcal mol^{-1}. Under moist conditions, hydrogen bonds tend to form preferentially between water molecules and either the substrate or the adhesive rather than between the adhesive and the substrate surface itself, resulting in diminished adhesion energy. Among various candidates, PVA stands out as one of the most competitive materials for hydrogen bond-mediated adhesion due to its high density of hydroxyl groups. In dimethyl sulfoxide (DMSO), PVA exhibits high fluidity, promoting effective interfacial interactions. Upon replacing DMSO with water, strong intrachain hydrogen bonding is induced, leading to the formation of tough PVA hydrogels, while residual hydroxyl groups on PVA chains establish hydrogen bonds with adjacent substrates.[183]

To enhance the wet adhesion capacity via hydrogen bonding, Cui et al[184] developed a Janus hydrogel with a gradient distribution of polyelectrolyte complexes, transitioning from a fully neutralised carboxyl-rich surface to one with fewer carboxyl groups. Consequently, the hydrogel presents asymmetrical properties: one side offers strong adhesion to wet tissues while the other exhibits non-adhesive characteristics to prevent undesired tissue adhesion. Experiments confirmed that this hydrogel could achieve rapid and strong adhesion to wet biological tissues while effectively inhibiting postoperative tissue adhesion on the opposite surface.

Electrostatic interaction-based adhesion

In wet environments, conventional hydrogels that rely on electrostatic interactions often struggle to adhere to biological surfaces because both hydrogels and many biological tissues typically carry net negative charges,[185] resulting in electrostatic repulsion at the interface.[186,187]

A recent study reported a class of polymer hydrogels whose copolymers feature adjacent cationic–aromatic sequences via sequence-controlled copolymerisation. These structures are synthesised through a cation-π-complexation-assisted free radical polymerisation strategy. The resulting hydrogels demonstrate fast, strong and reversible adhesion even in high ionic strength saline environments, where conventional electrostatic interactions are typically screened. Remarkably, despite the presence of such electrostatic screening, the designed hydrogels maintain robust adhesion to negatively charged surfaces, offering a promising approach for underwater and saline condition applications. These interactions enable the hydrogel to firmly adhere to the surface of biological tissues in a moist environment. The interlayer structure of nano-clay can

Table 3 Different materials and their biological functions.

Material	Biological functions
Amniotic membrane	Serves as a bioscaffold for postoperative mucosal defects, promoting epithelialisation and pain relief; applied in cleft palate repair and salivary gland regeneration[203-206]
Salamander skin secretion	Induces angiogenesis and accelerates palatal mucosal healing in rat models[207,208]
Curcumin	Attenuates inflammation and enhances collagen deposition through inhibition of the NF-κB signalling pathway[209]
Anthocyanin niosomes	Enhance mucosal permeability and reduce inflammation associated with traumatic oral ulcers[192,210]
Histones and growth factors in saliva	Accelerate cell migration during mucosal wound healing[212]

Table 4 Different hydrogel type materials and their properties.

Hydrogel type	Functional component	Mechanism of action	Oral application and outcome
Chitosan-based hydrogel	Tretinoin + catechol modification	Covalent binding to mucosal proteins via catechol groups; hydrogen bonding and electrostatic interactions enable wet adhesion	Promoted oral ulcer healing with prolonged drug release and stable adhesion in humid oral conditions[214]
UV-curable CNB-HA hydrogel	Photo-reactive aldehyde groups	Aldehyde groups bind to tissue amines via Schiff	Retained under salivary washout for 24 h; suitable for oral mucosal defect repair without affecting oral function[45]
Polydopamine nanoparticles in hydrogel matrix	PDA NPs	ROS scavenging; anti-inflammatory	Reduced mucosal oxidative stress and inflammatory infiltration in periodontitis model[215]
Acidic hydrogel dressing	pH-modulating agents	Local pH regulation of wound environment	Promoted wound healing via optimised acidic microenvironment[213]

restrict the oxidation degree of dopamine, preserve the number of unoxidised catechol groups and thereby maintain a stronger adhesive capacity.

Enabling technology: hydrogels as programmable delivery platforms

Beyond adhesion, the transformation of hydrogels from passive dressings into active therapeutic devices fundamentally depends on their functionality as advanced delivery platforms. The controlled spatiotemporal release of bioactive agents, including drugs, growth factors and cells, enables precise intervention in the complex processes of oral wound healing and regeneration. Conventional delivery systems face limitations for intraoral use, such as rapid degradation of active compounds, uncontrolled release, and potential local toxicity.[188,189] Addressing these requires systems designed for sustained, low-dose and localised delivery.

The necessity for such sophisticated carriers is illustrated by specific agents. Curcumin, despite its potential, has poor solubility, low stability and dose-dependent toxicity, necessitating specialised systems like mucoadhesive formulations (MFCs) for oral mucositis to prolong contact and control release.[190] Similarly, anthocyanins degrade easily in saliva and require nanocarrier encapsulation to improve stability and mucosal permeability.[191,192]

Hydrogels, with their crosslinked hydrophilic polymer networks, present an ideal foundation for these delivery systems due to their high biocompatibility, porous structure and ability to maintain a moist wound environment.[193,194] Natural polymers are particularly promising. Gelatin-based hydrogels offer excellent biocompatibility and a porous structure for encapsulation, with advanced variants enabling stimuli-responsive release.[195] Sericin can be modified into sericin methacryloyl (SerMA) hydrogels, where crosslinking density dictates release rates for tunable delivery.[196] Chitosan-based hydrogels are notable for their injectability and pH/temperature responsiveness, allowing precise delivery of diverse agents for applications like bone regeneration.[197,198] Furthermore, chitosan can be ionically crosslinked to form hydrogels suitable for drug delivery.[116] Hydrogel-based drug carriers have proven effective in managing chronic wounds, including diabetic ulcers and burns, by promoting re-epithelialisation, reducing fibrosis and stimulating angiogenesis.[199]

Hydrogel applications in oral soft tissue

Building upon the fundamental adhesion strategies and delivery platform technology outlined in the preceding sections, the targeted application of functional hydrogels addresses the distinct requirements of various oral soft tissue defects. This section describes how integrat-

ed hydrogel design is tailored to meet the challenges posed by three key clinical areas (Table 4).

Repair of oral mucosal wounds

Oral mucosal wounds, resulting from trauma, ulceration or surgery, require a healing environment that promotes rapid re-epithelialisation. Hydrogels designed for this application provide a protective barrier, maintain moisture and adhere securely to the moist, mobile mucosa. Critically, their therapeutic function is augmented by their role as delivery systems for bioactive compounds that modulate the healing process.

Oral mucosal wound healing proceeds through four stages: haemostasis, inflammation, proliferation and remodelling.[200] Compared with skin, oral mucosa exhibits a milder inflammatory response and a higher TGF-β3/β1 ratio,[201] which contributes to reduced scar formation; disruption of tissue homeostasis leads to delayed or impaired healing.[202] Hydrogel-based delivery systems can incorporate various agents to support this process. For instance, naturally derived bioactive agents provide essential biological cues. An amniotic membrane serves as a bioscaffold to cover postoperative mucosal defects, promoting epithelialisation, reducing pain[203,204] and finding application in cleft palate repair and salivary gland regeneration.[205,206] Salamander skin secretion contains a variety of growth factors and exhibits excellent antibacterial, antioxidant, wound healing promoting and haemostatic properties. In both normal and diabetic rat models of palatal defects, salamander skin secretion–derived powder promotes angiogenesis, attenuates the immune response and accelerates wound healing.[207,208] Natural plant extracts, known for being low-cost and accessible with remarkable antibacterial and antioxidant properties, can accelerate healing through immunomodulatory and anti-inflammatory effects. Curcumin attenuates inflammation and promotes collagen deposition by inhibiting the NF-κB pathway,[209] while anthocyanin niosomes improve mucosal permeability and reduce inflammation in traumatic ulcers.[192, 210] The chitosan-based thermosensitive hydrogel demonstrates dual functionality, offering antibacterial effects and enhancing gingival fibroblast proliferation via electrostatic interactions.[27,28] HA mimics the ECM environment, reduces collagen overdeposition and accelerates lingual mucosal re-epithelialisation.[36,211] Furthermore, histones and growth factors (e.g., vascular endothelial growth factor [VEGF]) present in saliva are known to accelerate cell migration.[212] Collectively, these studies demonstrate that a wide range of naturally derived bioactive agents can be effectively incorporated into hydrogel-based delivery systems to promote oral mucosal wound healing (Table 3). While natural agents provide essential biological cues, synthetic materials enable the rational design of hydrogel systems with programmable mechanics, degradation and drug release behaviours. For example, antimicrobial hydrogels can inhibit biofilm formation, and acidic dressings can modulate wound pH to promote healing.[213] Synthetic design also allows for enhanced wet adhesion. Ryu et al[214] developed a chitosan-based hydrogel loaded with tretinoin, where catechol modification enhanced adhesion. The catechol moiety covalently binds to mucosal proteins to prolong drug release, and the hydrogel stabilises adhesion in a humid environment through hydrogen bonding and electrostatic interactions, significantly accelerating ulcer healing. Zhang et al[45] designed a UV-curable hydrogel (CNB-HA) that forms strong adhesion via a photolytic reaction generating aldehyde groups, which bind to tissue amino groups. This hydrogel retains adhesion for over 24 hours despite salivary washout and oral movements, gels within 5 seconds, is degradable and does not affect oral function, making it suitable for mucosal defect repair. Additionally, Bao et al[215] reported that polydopamine nanoparticles (PDA NPs) attenuate oxidative stress-induced mucosal injury by scavenging ROS, and in a periodontitis model, they significantly reduced inflammatory cell infiltration.

Regeneration of gingival tissues

The engineering of functional gingival tissues in vitro presents significant challenges, necessitating sophisticated 3D microenvironments that extend beyond the capabilities of conventional monolayer cultures or decellularised biomaterials. Biofabrication has therefore emerged as a particularly promising approach within tissue engineering, employing a suite of advanced techniques to precisely construct complex, living tissue structures.[216] The success of such endeavours hinges on several critical design factors. First, scaffolds must be fabricated from porous biomaterials that closely mimic the native ECM to facilitate essential cellular activities such as attachment, migration and nutrient diffusion; the pore architecture, including its size and interconnectivity, critically influences subsequent vascularisation and tissue integration. Second, the mechanical properties of the engineered construct should match those of natural gingival tissue to ensure it can withstand physiological masticatory forces. Third, the material must possess appropriate permeability to allow for efficient oxygen and nutrient transport as well as the removal of metabolic

waste. Finally, the biodegradation rate of the scaffold must be carefully synchronised with the pace of new tissue regeneration to provide temporary support without impeding long-term healing.[217]

Current strategies in gingival tissue engineering utilise a diverse array of biomaterials, each offering distinct advantages. Acellular dermal matrix, for instance, serves as a well-established alternative to autogenous CTGs. Its application has been shown to effectively increase gingival thickness and keratinised tissue width,[218] reduce postoperative inflammation[219] and accelerate processes of epithelialisation and angiogenesis,[220,221] although its long-term stability in clinical settings continues to be a subject of discussion.[6,222] Collagen membranes represent another cornerstone biomaterial that is widely used to support post-surgical repair. They provide essential structural support, help in reducing pain and the risk of infection[223] and create a conducive environment for the regeneration of both soft and hard tissues.[224] For the repair of buccal mucosa, scaffolds derived from sericin protein have demonstrated efficacy by minimising wound contraction and actively promoting the growth of new epithelium.[225] Furthermore, commercially available formulations like Gengigel, which is based on a high-molecular-weight HA hydrogel (1000 to 1890 kDa) supplemented with xylitol, a compound known to inhibit plaque and promote remineralisation, have shown measurable efficacy in the management of gingivitis and as an adjunct to non-surgical periodontal therapy.[226,227]

Management of periodontitis and periodontal regeneration

Periodontitis is a chronic inflammatory disease affecting the periodontal tissues, characterised by dysbiotic microbial biofilms and an exaggerated host immune response, which together drive progressive periodontal destruction. The pathophysiology of periodontitis stems from a disrupted equilibrium in host–microbe interactions. Although bacterial biofilms initiate periodontal inflammation,[228,229] excessive and dysregulated host immune responses are recognised as the primary drivers of tissue breakdown.[230,231]

At the cellular level, epithelial cells in both healthy and inflamed gingival tissues can be classified into basal cells (KRT15$^+$), spinous cells (KRT76$^+$) and superficial cells (SPRR3$^+$). Notably, the proportion of basal epithelial cells is significantly increased under inflammatory conditions.[155] In addition, periodontitis is associated with a marked infiltration of immune cells, including plasma cells (IGHA1$^+$), T cells (CD3D$^+$) and monocytes (CD11b$^+$). Among these, plasma cells contribute to alveolar bone destruction through high expression of CXCL12.[232] The key mediators of periodontal bone resorption include proinflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-17 (IL-17), alongside the activation of the receptor activator of nuclear factor κB ligand (RANKL) signalling pathway.[233,234] Furthermore, systemic diseases can exacerbate the progression of periodontitis by modulating metabolic and immune pathways, thereby amplifying local inflammatory responses.[235]

Given this pathophysiology, anti-inflammatory, immunomodulatory and antioxidant strategies constitute major therapeutic directions for hydrogels used in periodontal restoration. pH-responsive hydrogels encapsulating dexamethasone demonstrate efficacy by selectively targeting acidic inflammatory microenvironments (pH ≤ 6.0) and suppressing the production of TNF-α and IL-6, thereby reducing bone resorption.[236] A simvastatin-loaded Pluronic F127 temperature-sensitive hydrogel has been shown to reduce alveolar bone loss in a rat periodontitis model by modulating inflammation and bone metabolism. Hydrogels incorporating plant extracts also offer a promising avenue for assisting periodontal regeneration.[93] For instance, a glycan-based hydrogel loaded with the flavonoid naringenin reduced inflammatory infiltration and bone loss through its anti-inflammatory effects in a mouse periodontitis model.[237] Similarly, a self-repairing hydrogel loaded with ginsenoside Rg1 and glaucogenin promoted anti-inflammatory effects and bone regeneration in a rat periodontitis model.[238] Xu et al[239] developed chitosan/sodium β-glycerophosphate/gelatin temperature-sensitive hydrogels loaded with aspirin and erythropoietin, which inhibited inflammation and promoted bone regeneration in a rat periodontitis model. In another approach, He et al[57] developed transglutaminase-crosslinked gelatin hydrogels loaded with immunomodulatory cytokines to repair alveolar bone defects. To address the characteristic high ROS microenvironment in periodontitis, Zhao et al[240] designed an injectable ROS-responsive hydrogel co-loaded with metformin and doxycycline. This hydrogel demonstrated significant antibacterial efficacy in vitro, along with attenuated inflammatory responses and reduced alveolar bone loss in a diabetic rat model.[240] Furthermore, the hydrogel developed by Saita et al[241] effectively suppressed osteoclast differentiation from precursor cells and impeded *Porphyromonas gingivalis*-induced alveolar bone resorption in a rat periodontitis model.It is important to note that these findings are

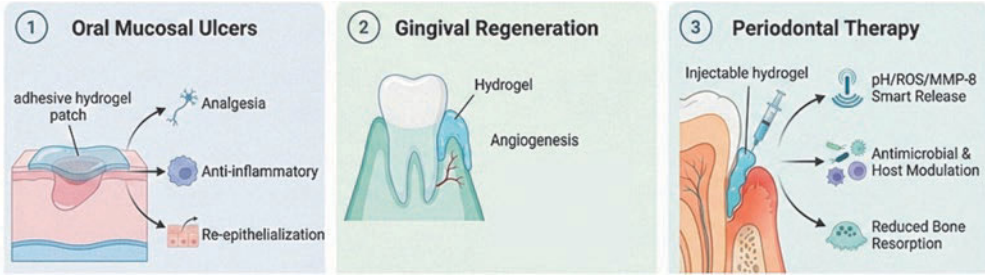

Fig 5 Application scenarios and therapeutic outcomes of hydrogel-based systems in oral soft tissue repair.

derived primarily from rat models. Inherent differences exist in both pathophysiological mechanisms and clinical manifestations between these animal models and human periodontitis. Therefore, the translation of the aforementioned therapeutic strategies and conclusions to clinical applications requires further validation (Fig 5).

Clinical translational challenges and solutions

At present, hydrogel-based restorative materials for oral applications face several key limitations that hinder their clinical translation. A primary issue is the short tissue retention time; existing dressings often exhibit limited adhesion in the moist oral environment, typically remaining in place for only 2 to 8 hours before being dislodged by saliva or mastication.[242] Furthermore, achieving sufficient tissue compatibility is challenging due to the significant variation in mechanical properties across different oral tissues, which necessitates tailored designs; for instance, keratinised mucosa possesses low elasticity whereas lining mucosa is more extensible. The complexity and high cost associated with multifunctional modifications further impede the development of clinically viable dressings. Regarding antimicrobial strategies, while the use of narrow-spectrum antibiotics can delay resistance, the complexity of the oral microbiota frequently demands materials with broad-spectrum activity.[20] Another common problem is the initial burst release of drugs from hydrogels upon implantation, which risks local toxicity and shortens the effective therapeutic period.[243]

Beyond these material-centric challenges, achieving predictably complete tissue regeneration remains a significant hurdle. Even established materials such as Emdogain, platelet-rich fibrin (PRF) and bone grafts often fail to achieve complete closure of defects, particularly in complex scenarios like Class III furcation defects.[244,245] Their limitations may include poor space maintaining capability, rapid degradation or insufficient antimicrobial activity.[246-248] For example, the fluid consistency of Emdogain can lead to membrane collapse, thereby compromising the outcome of bone regeneration procedures.[249,250] The regeneration of complex defects, including Class III furcations or single-walled intrabony defects, remains particularly challenging. Even in more favourable defects such as Class II furcations or two- to three-walled intrabony defects, rates of complete clinical closure are often low. Additionally, methodological flaws in clinical study design, such as inadequate randomisation protocols in split-mouth studies or a lack of histological evidence, may introduce bias and limit the interpretability of research findings.[245,251,252] Finally, effective biofilm control is critical during the regenerative process, yet current biomaterials frequently offer limited inherent antimicrobial efficacy.[253]

To address these persistent limitations, several advanced design strategies with promising translational potential have emerged.[254] One innovative approach involves the incorporation of dynamic covalent bonds, such as boronate esters. These bonds can impart self-healing properties to hydrogels and create robust, long-lasting adhesion capable of withstanding the challenging moist conditions of the oral cavity.[255] Another promising strategy is the design of multilayered or gradient hydrogels that mimic the inherent biomechanical anisotropy and heterogeneity of oral tissues. In such systems, a mechanically stiffer outer layer can enhance adhesion and provide protection, while a softer, more porous inner layer facilitates cellular infiltration and nutrient diffusion. This hierarchical structure promotes better integration with host tissues and helps address issues related to mechanical mismatch.[256]

Furthermore, technologies such as light-activated polymerisation enable rapid in situ gelation directly at the wound site. This ensures intimate tissue coverage and prolongs material retention. Hydrogels like GelMA, especially when functionalised with antimicrobial peptides, have demonstrated the potential for sustained antibacterial action and controlled drug release.[257] Lastly, the integration of micro- or nano-encapsu-

lation systems within hydrogel matrices, combined with engineered gradient diffusion layers, allows for sophisticated spatiotemporal control over therapeutic delivery.[258] Such designs are particularly effective in mitigating the issue of burst release by enabling multi-stage, prolonged release of antibiotics, growth factors or anti-inflammatory agents over periods ranging from days to weeks. Collectively, these innovations represent viable and scalable pathways towards the successful clinical implementation of next-generation hydrogel therapies for oral tissue repair.

Future directions

To advance the development of bioadhesive materials, future research should focus on enhancing adhesion performance and stability through biomimetic strategies. For instance, catechol chemistry inspired by mussel foot proteins and electrostatic interactions such as polyelectrolyte complexation could be further optimised to improve interfacial bonding strength and durability in physiological environments.[259] Additionally, dynamic covalent chemistry can endow materials with reversible adhesion capabilities, whose tunable stability allows for adaptation to dynamic tissue microenvironments. The development of self-stabilising elastomers represents another critical direction, as such systems hold promise for bridging the gap between temporary wound closure and long-term tissue regeneration.[260]

Smart responsive materials constitute a transformative frontier. Integrating pH- or temperature-responsive polymers into material systems enables real-time monitoring and adaptive therapeutic delivery.[261] Combining these features with bioactive components such as growth factors, stem cells or platelets can synergistically accelerate the tissue repair process while minimising off-target effects.[262-265]

Future antimicrobial materials should aim to target bacterial cell membranes while avoiding damage to intracellular organelles, thereby balancing antibacterial efficacy with the mitigation of resistance development.[20] Combination therapies show significant potential, such as the synergistic use of Emdogain with Bio-Oss bone grafts for space maintenance[266] or the combination of PRF with bone grafts to enhance regeneration.[267] Furthermore, novel materials including hydrogels that promote angiogenesis and cell proliferation,[268] bone putty with improved handling and stability, and host modulators possessing anti-inflammatory and osteogenic properties are also gaining attention.[269,270] Given that periodontal disease originates from microbial dysbiosis, integrating probiotics and prebiotics into hydrogel delivery systems to restore microbial balance represents a promising strategy.[271-273]

Regarding clinical translation, future studies must strike a balance between personalisation and practicality. Advanced designs, such as metal-organic framework-modified proteins, can enhance mechanical robustness and enable spatiotemporally controlled drug release.[274] Simultaneously, simplifying fabrication processes is crucial for reducing production costs, improving scalability and facilitating widespread clinical adoption.[275]

Finally, clinical studies should adhere to CONSORT reporting guidelines, extend follow-up durations and incorporate more histopathological evidence.[276] In periodontal research, refining the classification of periodontal defects is essential to improve the comparability of study outcomes.[277]

Conclusions

Oral soft tissue defects pose significant clinical challenges due to their complex aetiology, functional impairments and negative impact on patients' quality of life. Traditional repair strategies, such as autografts and synthetic membranes, are limited by donor site morbidity, poor adhesion and inadequate mechanical properties. Hydrogels, with their tunable physicochemical properties, biocompatibility and ability to mimic the native ECM, have emerged as promising alternatives for oral soft tissue regeneration.

This review has highlighted the diverse materials used in hydrogel design, including natural polymers (e.g., chitosan, HA, gelatin) and synthetic polymers (e.g., PVA, PEG, PLA), as well as innovative preparation techniques such as physical/chemical crosslinking, 3D bioprinting, and microfluidics. Hydrogels functionalised with bioactive agents (e.g., drugs, growth factors, antimicrobials) demonstrate enhanced wound healing, anti-inflammatory effects and antimicrobial activity. Their applications span oral mucosa repair, gingival regeneration and periodontal therapy, effectively addressing the unique demands of the oral environment, such as the need for wet adhesion and resistance to dynamic stresses (Fig 6).

Despite considerable progress, challenges remain, including short intraoral retention time, initial burst drug release and scalability for clinical translation. Future research directions should focus on developing smart-responsive hydrogels (e.g., pH- or temperature-sensitive), creating hybrid systems that combine natural and synthetic materials and exploring microbiome-modulating strategies to optimise tissue regen-

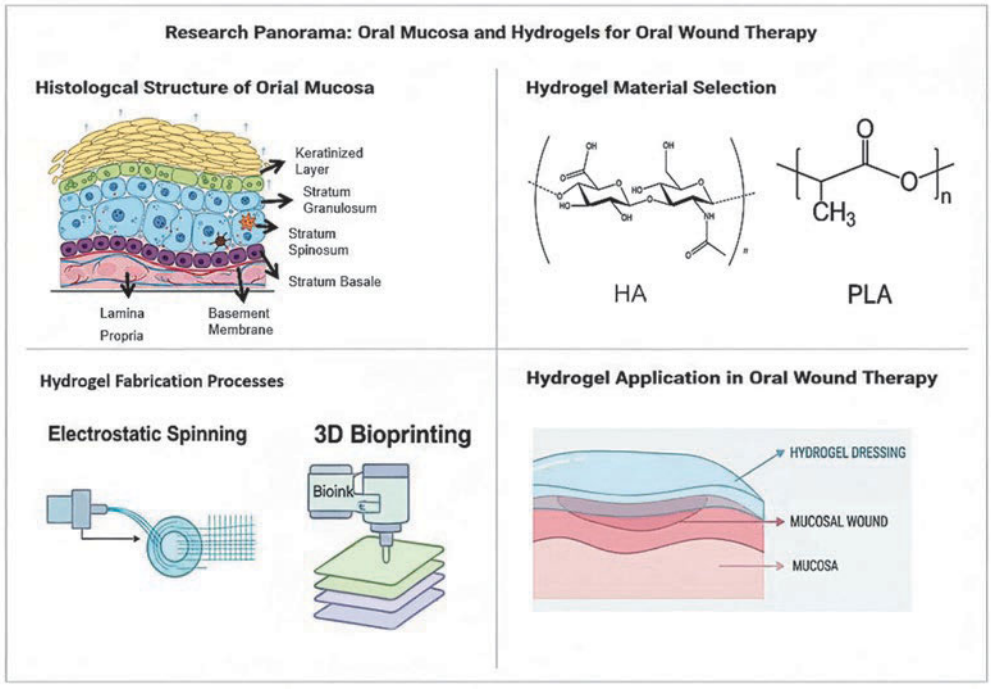

Fig 6 Overview of oral mucosa and hydrogels for oral wound therapy.

eration. By advancing hydrogel technology, specifically by improving adhesion strength, mechanical resilience and personalised therapeutic delivery, it will be possible to bridge the gap between laboratory innovation and clinical practice, ultimately improving outcomes for patients with oral soft tissue defects.

In summary, hydrogels represent a transformative approach to oral soft tissue repair, offering a versatile platform to address unmet clinical needs. Continued interdisciplinary collaboration will be essential to refine these biomaterials and realise their full potential in regenerative dentistry. Future efforts should prioritise enhancing the intelligent responsiveness, safety and biocompatibility of hydrogels, as well as accelerating their clinical translation, to achieve the ultimate goal of alleviating patient suffering and promoting optimal healing.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Acknowledgements

Part of the language polishing in this manuscript was assisted by ChatGPT.

Author contribution

Dr Zi Xin PAN contributed to the literature search and original draft preparation; Dr Wen Jie MA contributed to the manuscript revision; Dr Chao SI contributed to image collection for analysis; Dr Chun Ru KONG contributed to the literature search and analysis; Dr Jia Kai QIAO contributed to the data interpretation and validation; Drs Xiao Duo TANG and Bei CHANG contributed to the conceptualisation and supervision; Dr Hong Chen SUN contributed to the final revision of the manuscript.

(Received Sep 09, 2025; accepted Jan 14, 2026)

References

1. Sun J, Chen T, Zhao B, et al. Acceleration of oral wound healing under diabetes mellitus conditions using bioadhesive hydrogel. ACS Appl Mater Interfaces 2023;15:416–431.
2. Abazari M, Ghaffari A, Rashidzadeh H, Badeleh SM, Maleki Y. A systematic review on classification, identification, and healing process of burn wound healing. Int J Low Extrem Wounds 2022;21:18–30.
3. Sharma A, Sharma D, Zhao F. Updates on recent clinical assessment of commercial chronic wound care products. Adv Healthc Mater 2023;12:e2300556.
4. Gao D, Wang Z, Wu Z, et al. 3D-printing of solvent exchange deposition modeling (SEDM) for a bilayered flexible skin substitute of poly (lactide-co-glycolide) with bioorthogonally engineered EGF. Mater Sci Eng C Mater Biol Appl 2020;112:110942.

5. Zucchelli G, Tavellii L, McGuire MK, et al. Autogenous soft tissue grafting for periodontal and peri-implant plastic surgical reconstruction. J Periodontol 2020;91:9–16.
6. Barootchi S, Tavelli L, Di Gianfilippo R, et al. Acellular dermal matrix for root coverage procedures: 9-year assessment of treated isolated gingival recessions and their adjacent untreated sites. J Periodontol 2021;92:254–262.
7. Moharamzadeh K, Colley H, Murdoch C, et al. Tissue-engineered oral mucosa. J Dent Res 2012;91:642–650.
8. Lauer G. Autografting of feeder-cell free cultured gingival epithelium. Method and clinical application. J Craniomaxillofac Surg 1994;22:18–22.
9. Moharamzadeh K, Brook IM, Van Noort R, Scutt AM, Thornhill MH. Tissue-engineered oral mucosa: A review of the scientific literature. J Dent Res 2007;86:115–124.
10. Muniraj G, Tan RHS, Dai Y, Wu R, Alberti M, Sriram G. Microphysiological modeling of gingival tissues and host-material interactions using gingiva-on-chip. Adv Healthc Mater 2023;12:e2301472.
11. Huang C, Sanaei F, Verdurmen WPR, Yang F, Ji W, Walboomers XF. The application of organs-on-a-chip in dental, oral, and craniofacial research. J Dent Res 2023;102:364–375.
12. Ding Y, Zhu Z, Zhang X, Wang J. Novel functional dressing materials for intraoral wound care. Adv Healthc Mater 2024;13:2400912.
13. Wu J, Pan Z, Zhao ZY, et al. Anti-swelling, robust, and adhesive extracellular matrix-mimicking hydrogel used as intraoral dressing. Adv Mater 2022;34:e2200115.
14. Nanci A. Ten Cate's Oral Histology: Development, Structure, and Function. St. Louis: Elsevier, 2017.
15. Squier CA, Kremer MJ. Biology of oral mucosa and esophagus. J Natl Cancer Inst Monogr 2001;29:7–15.
16. Avery JK, Chiego DJ. Essentials of Oral Histology and Embryology. St. Louis: Mosby, 2006.
17. Wong JW, Gallant-Behm C, Wiebe C, et al. Wound healing in oral mucosa results in reduced scar formation as compared with skin: Evidence from the red Duroc pig model and humans. Wound Repair Regen 2009;17:717–729.
18. Hollins C. Basic Guide to Anatomy and Physiology for Dental Care Professionals. Chichester: Wiley-Blackwell, 2012.
19. Choi JJE, Zwirner J, Ramani RS, et al. Mechanical properties of human oral mucosa tissues are site dependent: A combined biomechanical, histological and ultrastructural approach. Clin Exp Dent Res 2020;6:602–611.
20. Jia B, Zhang B, Li J, et al. Emerging polymeric materials for treatment of oral diseases: Design strategy towards a unique oral environment. Chem Soc Rev 2024;53:3273–3301.
21. Chen T, Chen YJ, Rehman HU, et al. Ultratough, self-healing, and tissue-adhesive hydrogel for wound dressing. ACS Appl Mater Interfaces 2018;10:33523–33531.
22. Rashki S, Asgarpour K, Tarrahimofrad H, et al. Chitosan-based nanoparticles against bacterial infections. Carbohydr Polym 2021;251:117108.
23. Matica MA, Aachmann FL, Tondervik A, Sletta H, Ostafe V. Chitosan as a wound dressing starting material: Antimicrobial properties and mode of action. Int J Mol Sci 2019;20:5889.
24. Yap LS, Yang MC. Thermo-reversible injectable hydrogel composing of pluronic F127 and carboxymethyl hexanoyl chitosan for cell-encapsulation. Colloids Surf B Biointerfaces 2020;185:110606.
25. Lin F, Jia HR, Wu FG. Glycol chitosan: A water-soluble polymer for cell imaging and drug delivery. Molecules 2019;24:4371.
26. Nordback PH, Miettinen S, Kääriäinen M, et al. Chitosan membranes in a rat model of full-thickness cutaneous wounds:healing and IL-4 levels. J Wound Care 2015;24:245–251.
27. Dooley TP, Ellis AL, Belousova M, Petersen D, DeCarlo AA. Dense chitosan surgical membranes produced by a coincident compression-dehydration process. J Biomater Sci Polym Ed 2013;24:621–643.
28. Luo Z, Xue K, Zhang X, et al. Thermogelling chitosan-based polymers for the treatment of oral mucosa ulcers. Biomater Sci 2020;8:1364–1379.
29. Pippi R, Santoro M, Cafolla A. The use of a chitosan-derived hemostatic agent for postextraction bleeding control in patients on antiplatelet treatment. J Oral Maxillofac Surg 2017;75:1118–1123.
30. de Jesus G, Marques L, Vale N, Mendes RA. The effects of chitosan on the healing process of oral mucosa: An observational cohort feasibility split-mouth study. Nanomaterials (Basel) 2023;13:706.
31. Vigani B, Rossi S, Sandri G, Bonferoni MC, Caramella CM, Ferrari F. Hyaluronic acid and chitosan-based nanosystems: A new dressing generation for wound care. Expert Opin Drug Deliv 2019;16:715–740.
32. Aya KL, Stern R. Hyaluronan in wound healing: Rediscovering a major player. Wound Repair Regen 2014;22:579–593.
33. Kaul A, Short WD, Keswani SG, Wang X. Immunologic roles of hyaluronan in dermal wound healing. Biomolecules 2021;11:1234.
34. Albeiroti S, Soroosh A, de la Motte CA. Hyaluronan's role in fibrosis: A pathogenic factor or a passive player? Biomed Res Int 2015;2015:790203.
35. Bayer IS. Hyaluronic acid and controlled release: A review. Molecules 2020;25:2543.
36. Lee JH, Lee KE, Nam OH, et al. Orodispersible hyaluronic acid film delivery for oral wound healing in rats. J Dent Sci 2022;17:1595–1603.
37. Guo X, Zhu T, Yu X, et al. Betamethasone-loaded dissolvable microneedle patch for oral ulcer treatment. Colloids Surf B Biointerfaces 2023;222:113100.
38. Celien E, Julie A, Maarten G, Jan C. A randomized controlled trial evaluating hyaluronic acid gel as wound healing agent in alveolar ridge preservation. J Clin Periodontol 2022;49:280–291.
39. Graca MFP, Miguel SP, Cabral CSD, Correia IJ. Hyaluronic acid-based wound dressings: A review. Carbohydr Polym 2020;241:116364.
40. Asparuhova MB, Kiryak D, Eliezer M, Mihov D, Sculean A. Activity of two hyaluronan preparations on primary human oral fibroblasts. J Periodontal Res 2019;54:33–45.
41. Asparuhova MB, Chappuis V, Stahli A, Buser D, Sculean A. Role of hyaluronan in regulating self-renewal and osteogenic differentiation of mesenchymal stromal cells and pre-osteoblasts. Clin Oral Investig 2020;24:3923–3937.
42. Pilloni A, Zeza B, Kuis D, et al. Treatment of residual periodontal pockets using a hyaluronic acid-based gel: A 12 month multicenter randomized triple-blinded clinical trial. Antibiotics (Basel) 2021;10:924.
43. Mamajiwala AS, Sethi KS, Raut CP, Karde PA, Mamajiwala BS. Clinical and radiographic evaluation of 0.8% hyaluronic acid as an adjunct to open flap debridement in the treatment of periodontal intrabony defects: Randomized controlled clinical trial. Clin Oral Investig 2021;25:5257–5271.

44. Gupta S, Kediege SD, Gupta A, Jain K. Evaluation of Gengigel application in the management of furcation with coronally advanced flap through surgical re-entry-A split mouth clinical study. J Clin Diagn Res 2017;11:ZC27–ZC32.
45. Zhang W, Bao B, Jiang F, et al. Promoting oral mucosal wound healing with a hydrogel adhesive based on a photo-triggered S-nitrosylation coupling reaction. Adv Mater 2021;33:e2105667.
46. Dai X, Zhang Y, Gao L, et al. A mechanically strong, highly stable, thermoplastic, and self-healable supramolecular polymer hydrogel. Adv Mater 2015;27:3566–3571.
47. Jaipan P, Nguyen A, Narayan RJ. Gelatin-based hydrogels for biomedical applications. Mrs Communications 2017;7: 497–507.
48. Tondera C, Hauser S, Krueger-Genge A, et al. Gelatin-based hydrogel degradation and tissue interaction in vivo: Insights from multimodal preclinical imaging in immunocompetent nude mice. Theranostics 2016;6:2114–2128.
49. Rose JB, Pacelli S, El Haj AJ, et al. Gelatin-based materials in ocular tissue engineering. Materials (Basel) 2014;7:3106–3135.
50. Shi W, Sun M, Hu X, et al. Structurally and functionally optimized silk-fibroin-gelatin scaffold using 3D printing to repair cartilage injury in vitro and in vivo. Adv Mater 2017;29:1700999.
51. Angele P, Mueller R, Schumann D, et al. Characterization of esterified hyaluronan-gelatin polymer composites suitable for chondrogenic differentiation of mesenchymal stem cells. J Biomed Mater Res A 2009;91:416–427.
52. Santos MS, Dos Santos AB, Carvalho MS. New insights in hydrogels for periodontal regeneration. J Funct Biomater. 2023;14:545.
53. Liu Y, Chan-Park MB. A biomimetic hydrogel based on methacrylated dextran-graft-lysine and gelatin for 3D smooth muscle cell culture. Biomaterials 2010;31:1158–1170.
54. Vargas-Alfredo N, Munar-Bestard M, Ramis JM, Monjo M. Synthesis and modification of gelatin methacryloyl (GelMA) with antibacterial quaternary groups and its potential for periodontal applications. Gels 2022;10:630.
55. Li N, Xie L, Wu Y, et al. Dexamethasone-loaded zeolitic imidazolate frameworks nanocomposite hydrogel with antibacterial and anti-inflammatory effects for periodontitis treatment. Mater Today Bio 2022;16:100360.
56. Liu L, Guo S, Shi W, et al. Bone marrow mesenchymal stem cell-derived small extracellular vesicles promote periodontal regeneration. Tissue Eng Part A 2021;27:962–976.
57. He XT, Li X, Xia Y, et al. Building capacity for macrophage modulation and stem cell recruitment in high-stiffness hydrogels for complex periodontal regeneration: Experimental studies in vitro and in rats. Acta Biomater 2019;88:162–180.
58. Gardikiotis I, Cojocaru FD, Mihai CT, Balan V, Dodi G. Borrowing the features of biopolymers for emerging wound healing dressings: A review. Int J Mol Sci 2022;23:8778.
59. Peng W, Li D, Dai K, et al. Recent progress of collagen, chitosan, alginate and other hydrogels in skin repair and wound dressing applications. Int J Biol Macromol 2022;208:400–408.
60. Pallaske F, Pallaske A, Herklotz K, Boese-Landgraf J. The significance of collagen dressings in wound management: A review. J Wound Care 2018;27:692–702.
61. Lee CH, Singla A, Lee Y. Biomedical applications of collagen. Int J Pharm 2001;221:1–22.
62. Birkelbach MA, Smeets R, Fiedler I, et al. In vitro feasibility analysis of a new sutureless wound-closure system based on a temperature-regulated laser and a transparent collagen membrane for laser tissue soldering (LTS). Int J Mol Sci 2020;21:7104.
63. Kinikoglu B, Auxenfans C, Pierrillas P, et al. Reconstruction of a full-thickness collagen-based human oral mucosal equivalent. Biomaterials 2009;30:6418–6425.
64. An H, Gu Z, Zhou L, et al. Janus mucosal dressing with a tough and adhesive hydrogel based on synergistic effects of gelatin, polydopamine, and nano-clay. Acta Biomater 2022;149: 126–138.
65. Hu S, Pei X, Duan L, et al. A mussel-inspired film for adhesion to wet buccal tissue and efficient buccal drug delivery. Nat Commun 2021;12:1689.
66. Lee KY, Mooney DJ. Alginate: Properties and biomedical applications. Prog Polym Sci 2012;37:106–126.
67. Lengert EV, Savkina AA, Ermakov AV, et al. Influence of the new formulation based on silver alginate microcapsules loaded with tannic acid on the microcirculation of the experimental periodontitis in rats. Mater Sci Eng C Mater Biol Appl 2021;126:112144.
68. Xu J, Gou L, Zhang P, Li H, Qiu S. Platelet-rich plasma and regenerative dentistry. Aust Dent J 2020;65:131–142.
69. Kang SW, Cha BH, Park H, Park KS, Lee KY, Lee SH. The effect of conjugating RGD into 3D alginate hydrogels on adipogenic differentiation of human adipose-derived stromal cells. Macromol Biosci 2011;11:673–679.
70. Hunt NC, Hallam D, Karimi A, et al. 3D culture of human pluripotent stem cells in RGD-alginate hydrogel improves retinal tissue development. Acta Biomater 2017;49:329–343.
71. Kim BS, Kwon YW, Kong JS, et al. 3D cell printing of in vitro stabilized skin model and in vivo pre-vascularized skin patch using tissue-specific extracellular matrix bioink: A step towards advanced skin tissue engineering. Biomaterials 2018;168:38–53.
72. Pourchet LJ, Thepot A, Albouy M, et al. Human skin 3D bioprinting using scaffold-free approach. Adv Healthcare Mater 2017;6:1601062.
73. Heller M, Frerick-Ochs EV, Bauer HK, et al. Tissue engineered pre-vascularized buccal mucosa equivalents utilizing a primary triculture of epithelial cells, endothelial cells and fibroblasts. Biomaterials 2016;77:207–215.
74. Afghah F, Ullah M, Zanjani JSM, et al. 3D printing of silver-doped polycaprolactone-poly(propylene succinate) composite scaffolds for skin tissue engineering. Biomed Mater 2020;15:035015.
75. Ilhan E, Cesur S, Guler E, et al. Development of Satureja cuneifolia loaded sodium alginate/polyethylene glycol scaffolds produced by 3D-printing technology as a diabetic wound dressing material. Int J Biol Macromol 2020;161:1040–1054.
76. Numata K, Kaplan DL. Silk-based delivery systems of bioactive molecules. Adv Drug Delivery Rev 2010;62:1497–1508.
77. Pritchard EM, Kaplan DL. Silk fibroin biomaterials for controlled release drug delivery. Expert Opin Drug Delivery 2011;8:797–811.
78. Slaughter BV, Khurshid SS, Fisher OZ, Khademhosseini A, Peppas NA. Hydrogels in regenerative medicine. Adv Mater 2009;21:3307–3329.
79. Mogosanu GD, Grumezescu AM. Natural and synthetic polymers for wounds and burns dressing. Int J Pharm 2014;463:127–136.
80. Jin SG. Production and application of biomaterials based on polyvinyl alcohol (PVA) as wound dressing. Chem Asian J 2022;17:e202200595.
81. Sinclair-Hall AH. Repair of bony and dentinal defects following implantation of polyvinyl alcohol sponge. J Dent Res 1964;43:476–494.

82. Konno T, Ishihara K. Temporal and spatially controllable cell encapsulation using a water-soluble phospholipid polymer with phenylboronic acid moiety. Biomaterials 2007;28: 1770–1777.
83. Hamad K, Kaseem M, Yang HW, Deri F, Ko YG. Properties and medical applications of polylactic acid: A review. eXPRESS Polym Lett 2015;9:435–455.
84. Pu'ad NASM, Haq RHA, Noh HM, Abdullah HZ, Idris MI, Lee TC. Review on the fabrication of fused deposition modelling (FDM) composite filament for biomedical applications. Mater Today Proc 2020;29:1–5.
85. Wu DT, Munguia-Lopez JG, Cho YW, et al. Polymeric scaffolds for dental, oral, and craniofacial regenerative medicine. Molecules 2021;26:7043.
86. Puiggali-Jou A, Ordono J, del Valle LJ, Perez-Amodio S, Engel E, Aleman C. Tuning multilayered polymeric self-standing films for controlled release of L-lactate by electrical stimulation. J Control Release 2021;330:669–683.
87. Chen HL, Chung JWY, Yan VCM, Wong TKS. Polylactic acid-based biomaterials in wound healing: A systematic review. Adv Skin Wound Care 2023;36:1–8.
88. Hajikhani M, Emam-Djomeh Z, Askari G. Fabrication and characterization of mucoadhesive bioplastic patch via coaxial polylactic acid (PLA) based electrospun nanofibers with antimicrobial and wound healing application. Int J Biol Macromol 2021;172:143–153.
89. Chen Q, Mangadlao JD, Wallat J, De Leon A, Pokorski JK, Advincula RC. 3D printing biocompatible polyurethane/poly(lactic acid)/graphene oxide nanocomposites: Anisotropic properties. ACS Appl Mater Interfaces 2017;9:4015–4023.
90. Go DH, Joung YK, Park SY, Park YD, Park KD. Heparin-conjugated star-shaped PLA for improved biocompatibility. J Biomed Mater Res Part A 2008;86:842–848.
91. Lin CC, Anseth KS. PEG Hydrogels for the controlled release of biomolecules in regenerative medicine. Pharm Res 2009;26:631–643.
92. Vihola H, Laukkanen A, Valtola L, Tenhu H, Hirvonen J. Cytotoxicity of thermosensitive polymers poly (N-isopropylacrylamide), poly (N-vinylcaprolactam) and amphiphilically modified poly (N-vinylcaprolactam). Biomaterials 2005;26:3055–3064.
93. Li ZM, Li G, Xu JJ, et al. Hydrogel transformed from nanoparticles for prevention of tissue injury and treatment of inflammatory diseases. Adv Mater 2022;34:2107119.
94. Guo J, Sun H, Lei W, et al. MMP-8-responsive polyethylene glycol hydrogel for intraoral drug delivery. J Dent Res 2019;98:564–571.
95. Santana R, Gyurko R, Kanasi E, Xu WP, Dibart S. Synthetic polymeric barrier membrane associated with blood coagulum, human allograft, or bovine bone substitute for ridge preservation: A randomized, controlled, clinical and histological trial. Int J Oral Maxillofac Surg 2019;48:675–683.
96. Haq MA, Su Y, Wang D. Mechanical properties of PNIPAM based hydrogels: A review. Mater Sci Eng C Mater Biol Appl 2017;70:842–855.
97. Chen Y, Gao Y, da Silva LP, et al. A thermo-/pH-responsive hydrogel (PNIPAM-PDMA-PAA) with diverse nanostructures and gel behaviors as a general drug carrier for drug release. Polym Chem 2018;9:4063–4072.
98. Thorpe AA, Freeman C, Farthing P, et al. In vivo safety and efficacy testing of a thermally triggered injectable hydrogel scaffold for bone regeneration and augmentation in a rat model. Oncotarget 2018;9:18277–18295.
99. Zheng Z, Bian S, Li Z, et al. Catechol modified quaternized chitosan enhanced wet adhesive and antibacterial properties of injectable thermo-sensitive hydrogel for wound healing. Carbohydr Polym 2020;249:116826.
100. Almoshari Y, Ren RG, Zhang HP, et al. GSK3 inhibitor-loaded osteotropic Pluronic hydrogel effectively mitigates periodontal tissue damage associated with experimental periodontitis. Biomaterials 2020;261:120293.
101. Wang B, Booij-Vrieling HE, Bronkhorst EM, et al. Antimicrobial and anti-inflammatory thermo-reversible hydrogel for periodontal delivery. Acta Biomater 2020;116:259–267.
102. Paradowska-Stolarz A, Wieckiewicz M, Owczarek A, Wezgowiec J. Natural polymers for the maintenance of oral health: Review of recent advances and perspectives. Int J Mol Sci 2021;22:10337.
103. Liu Z, Ma X, Liu J, Zhang H, Fu D. Advances in the application of natural/synthetic hybrid hydrogels in tissue engineering and delivery systems: A comprehensive review. Int J Pharm 2025;672:125323.
104. Cheah CW, Al-Namnam NM, Lau MN, et al. Synthetic material for bone, periodontal, and dental tissue regeneration: Where are we now, and where are we heading next? Materials 2021;14:6123.
105. Trovatti E, Silva NHCS, Duarte IF, et al. Biocellulose membranes as supports for dermal release of lidocaine. Biomacromolecules 2011;12:4162–4168.
106. Singh J, Steele TWJ, Lim S. Fibrillated bacterial cellulose liquid carbene bioadhesives for mimicking and bonding oral cavity surfaces. J Mater Chem B 2022;10:2570–2583.
107. Zheng DW, Deng WW, Song WF, et al. Biomaterial-mediated modulation of oral microbiota synergizes with PD-1 blockade in mice with oral squamous cell carcinoma. Nat Biomed Eng 2022;6:32–43.
108. Du Y, Chen X, Li L, et al. Benzeneboronic-alginate/quaternized chitosan-catechol powder with rapid self-gelation, wet adhesion, biodegradation and antibacterial activity for non-compressible hemorrhage control. Carbohydr Polym 2023;318:121049.
109. Dou X, Li G, Wang S, et al. Probiotic-loaded calcium alginate/fucoidan hydrogels for promoting oral ulcer healing. Int J Biol Macromol 2023;244:125273.
110. Jiao Y, Niu LN, Ma S, Li J, Tay FR, Chen JH. Quaternary ammonium-based biomedical materials: State-of-the-art, toxicological aspects and antimicrobial resistance. Prog Polym Sci 2017;71:53–90.
111. Zhou ZX, Hu W, Zhao Z, Fu H. Photochemically driven polymeric biocompatible and antimicrobial thiol-acrylate nanocomposite suitable for dental restoration. ACS Appl Mater Interfaces 2022;14:46313–46323.
112. Chen YH, Chung YC, Wang IJ, Young TH. Control of cell attachment on pH-responsive chitosan surface by precise adjustment of medium pH. Biomaterials 2012;33:1336–1342.
113. Yang Q, Lai SK. Anti-PEG immunity: Emergence, characteristics, and unaddressed questions. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2015;7:655–677.
114. Mackova H, Plichta Z, Hlidkova H, et al. Reductively degradable poly (2-hydroxyethyl methacrylate) hydrogels with oriented porosity for tissue engineering applications. ACS Appl Mater Interfaces 2017;9:10544–10553.
115. Liu Z, Tang M, Zhao J, Chai R, Kang J. Looking into the future: Toward advanced 3D biomaterials for stem-cell-based regenerative medicine. Adv Mater 2018;30:e1705388.
116. Janes KA, Fresneau MP, Marazuela A, Fabra A, Alonso MJ. Chitosan nanoparticles as delivery systems for doxorubicin. J Control Release 2001;73:255–267.

117. Zhang J, Shen B, Chen L, Chen L, Mo J, Feng J. Antibacterial and antifouling hybrid ionic-covalent hydrogels with tunable mechanical properties. ACS Appl Mater Interfaces 2019;11:31594–31604.
118. Takamura A, Ishii F, Hidaka H. Drug release from poly (vinyl alcohol) gel prepared by freeze-thaw procedure. J Control Release 1992;20:21–27.
119. Stenekes RJH, Talsma H, Hennink WE. Formation of dextran hydrogels by crystallization. Biomaterials 2001;22:1891–1898.
120. Wang HB, Zhu H, Fu WG, et al. A high strength self-healable antibacterial and anti-inflammatory supramolecular polymer hydrogel. Macromol Rapid Commun 2017;38:1600695.
121. Tan ZC, Parisi C, Di Silvio L, Dini D, Forte AE. Cryogenic 3D printing of super soft hydrogels. Sci Rep 2017;7:16293.
122. Akiyama Y, Shinose M, Watanabe H, Yamada S, Kanda Y. Cryoprotectant-free cryopreservation of mammalian cells by superflash freezing. PNAS 2019;116:7738–7743.
123. GhavamiNejad A, Ashammakhi N, Wu XY, Khademhosseini A. Crosslinking strategies for 3D bioprinting of polymeric hydrogels. Small 2020;16:e2002931.
124. Michalek J, Hobzova R, Pradny M, Duskova M. Hydrogels Contact Lenses. Boca Raton: CRC Press, 2010.
125. Morelli A, Chiellini F. Ulvan as a new type of biomaterial from renewable resources: Functionalization and hydrogel preparation. Macromol Chem Phys 2010;211:821–832.
126. Tong R, Chen G, Pan D, et al. Highly stretchable and compressible cellulose ionic hydrogels for flexible strain sensors. Biomacromolecules 2019;20:2096–2104.
127. Tan H, DeFail AJ, Rubin JP, Chu CR, Marra KG. Novel multiarm PEG-based hydrogels for tissue engineering. J Biomed Mater Res A 2010;92:979–987.
128. Yamamoto M, Tabata Y, Hong L, Miyamoto S, Hashimoto N, Ikada Y. Bone regeneration by transforming growth factor β1 released from a biodegradable hydrogel. J Control Release 2000;64:133–142.
129. Luo Y, Kirker KR, Prestwich GD. Cross-linked hyaluronic acid hydrogel films: New biomaterials for drug delivery. J Control Release 2000;69:169–184.
130. Sperinde JJ, Griffith LG. Control and prediction of gelation kinetics in enzymatically cross-linked poly(ethylene glycol) hydrogels. Macromolecules 2000;33:5476–5480.
131. Sperinde JJ, Griffith LG. Synthesis and characterization of enzymatically-cross-linked poly (ethylene glycol) hydrogels. Macromolecules 1997;30:5255–5264.
132. Westhaus E, Messersmith PB. Triggered release of calcium from lipid vesicles: A bioinspired strategy for rapid gelation of polysaccharide and protein hydrogels. Biomaterials 2001;22:453–462.
133. DeForest CA, Polizzotti BD, Anseth KS. Sequential click reactions for synthesizing and patterning three-dimensional cell microenvironments. Nat Mater 2009;8:659–664.
134. Murphy SV, Skardal A, Atala A. Evaluation of hydrogels for bio-printing applications. J Biomed Mater Res A 2013;101: 272–284.
135. Rahimnejad M, Rasouli F, Jahangiri S, et al. Engineered biomimetic membranes for organ-on-a-chip. ACS Biomater Sci Eng 2022;8:5038–5059.
136. Abedi N, Rajabi N, Kharaziha M, Nejatidanesh F, Tayebi L. Layered scaffolds in periodontal regeneration. J Oral Biol Craniofac Res 2022;12:782–797.
137. Ayoub AA, Mahmoud AH, Ribeiro JS, et al. Electrospun azithromycin-laden gelatin methacryloyl fibers for endodontic infection control. Int J Mol Sci 2022;23:13761.
138. Hong S, Jung BY, Hwang C. Multilayered engineered tissue sheets for vascularized tissue regeneration. Tissue Eng Regener Med 2017;14:371–381.
139. Reid JA, McDonald A, Callanan A. Modulating electrospun polycaprolactone scaffold morphology and composition to alter endothelial cell proliferation and angiogenic gene response. PLoS One 2020;15:e0240332.
140. Han DG, Ahn CB, Lee JH, et al. Optimization of electrospun poly (caprolactone) fiber diameter for vascular scaffolds to maximize smooth muscle cell infiltration and phenotype modulation. Polymers 2019;11:643.
141. Loh QL, Choong C. Three-dimensional scaffolds for tissue engineering applications: Role of porosity and pore size. Tissue Eng Part B Rev 2013;19:485–502.
142. Mastrullo V, Cathery W, Velliou E, Madeddu P, Campagnolo P. Angiogenesis in tissue engineering: As nature intended? Front Bioeng Biotechnol 2020;8:188.
143. Chen X, Huang H, Song X, et al. Carboxymethyl chitosan-based hydrogel-Janus nanofiber scaffolds with unidirectional storage-drainage of biofluid for accelerating full-thickness wound healing. Carbohydr Polym 2024;331:121870.
144. Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol 2014;32:773–785.
145. Makkar H, Zhou Y, Tan KS, Lim CT, Sriram G. Modeling crevicular fluid flow and host-oral microbiome interactions in a gingival crevice-on-chip. Adv Healthcare Mater 2023;12:e2202376.
146. Atkuru S, Muniraj G, Sudhaharan T, Chiam KH, Wright GD, Sriram G. Cellular ageing of oral fibroblasts differentially modulates extracellular matrix organization. J Periodontal Res 2021;56:108–120.
147. Kim JJ, Hou L, Huang NF. Vascularization of three-dimensional engineered tissues for regenerative medicine applications. Acta Biomater 2016;41:17–26.
148. Cabral KA, Srivastava V, Graham AJ, et al. Programming the self-organization of endothelial cells into perfusable microvasculature. Tissue Eng Part A 2023;29:80–92.
149. Sriram G, Handral HK, Gan SU, Islam I, Rufaihah AJ, Cao T. Fabrication of vascularized tissue constructs under chemically defined culture conditions. Biofabrication 2020;12:045013.
150. Ronaldson-Bouchard K, Teles D, Yeager K, et al. A multi-organ chip with matured tissue niches linked by vascular flow. Nat Biomed Eng 2022;6:351–371.
151. Derr K, Zou J, Luo K, et al. Fully three-dimensional bioprinted skin equivalent constructs with validated morphology and barrier function. Tissue Eng Part C Methods 2019;25:334–343.
152. Lu EM, Hobbs C, Ghuman M, Hughes FJ. Development of an in vitro model of the dentogingival junction using 3D organotypic constructs. J Periodontal Res 2021;56:147–153.
153. Lu EM, Hobbs C, Dyer C, Ghuman M, Hughes FJ. Differential regulation of epithelial growth by gingival and periodontal fibroblasts in vitro. J Periodontal Res 2020;55:859–867.
154. Makkar H, Atkuru S, Tang YL, et al. Differential immune responses of 3D gingival and periodontal connective tissue equivalents to microbial colonization. J Tissue Eng 2022;13:20417314221111650.
155. Williams DW, Greenwell-Wild T, Brenchley L, et al. Human oral mucosa cell atlas reveals a stromal-neutrophil axis regulating tissue immunity. Cell 2021;184:4090–4106.
156. Ma J, Qin C, Wu J, et al. 3D printing of strontium silicate microcylinder-containing multicellular biomaterial inks for vascularized skin regeneration. Adv Healthc Mater 2021;10:2100452.

157. Baltazar T, Merola J, Catarino C, et al. Three dimensional bioprinting of a vascularized and perfusable skin graft using human keratinocytes, fibroblasts, pericytes, and endothelial cells. Tissue Eng Part A 2020;26:227–238.
158. Ma X, Zhu X, Lv S, et al. 3D bioprinting of prefabricated artificial skin with multicomponent hydrogel for skin and hair follicle regeneration. Theranostics 2025;15:2933–2950.
159. Rahimi C, Rahimi B, Padova D, et al. Oral mucosa-on-a-chip to assess layer-specific responses to bacteria and dental materials. Biomicrofluidics 2018;12:054106.
160. Mathes SH, Wohlwend L, Uebersax L, et al. A bioreactor test system to mimic the biological and mechanical environment of oral soft tissues and to evaluate substitutes for connective tissue grafts. Biotechnol Bioeng 2010;107:1029–1039.
161. Bao K, Papadimitropoulos A, Akguel B, Belibasakis GN, Bostanci N. Establishment of an oral infection model resembling the periodontal pocket in a perfusion bioreactor system. Virulence 2015;6:265–273.
162. Adelfio M, Bonzanni M, Callen GE, Hasturk H, Ghezzi CE. A physiologically relevant culture platform for long-term studies of in vitro gingival tissue. Acta Biomater 2023;167:321–334.
163. Ravichandran A, Liu Y, Teoh SH. Review:bioreactor design towards generation of relevant engineered tissues: Focus on clinical translation. J Tissue Eng Regener Med 2018;12: E7–E22.
164. Machla F, Monou PK, Artemiou P, et al. Design, additive manufacturing, and characterization of an organ-on-chip microfluidic device for oral mucosa analogue growth. J Mech Behav Biomed Mater 2025;163:106877.
165. Banerjee K, Radhakrishnan J, Ayyadurai N, Ganesan P, Kamini NR. Advances in neoteric modular tissue engineering strategies for regenerative dentistry. J Sci Adv Mater Devices 2022;7:110479.
166. Nakao Y, Fukuda T, Zhang QZ, et al. Exosomes from TNF-α-treated human gingiva-derived MSCs enhance M2 macrophage polarization and inhibit periodontal bone loss. Acta Biomater 2021;99:135–149.
167. Sheikh Z, Hamdan N, Ikeda Y, Grynpas M, Ganss B, Glogauer M. Natural graft tissues and synthetic biomaterials for periodontal and alveolar bone reconstructive applications: A review. Biomater Res 2017;21:9.
168. Iwata T, Yamato M, Ishikawa I, Ando T, Okano T. Tissue engineering in periodontal tissue. Anat Rec (Hoboken) 2014;297: 16–25.
169. Zhu B, Liu WJ, Zhang H, et al. Tissue-specific composite cell aggregates drive periodontium tissue regeneration by reconstructing a regenerative microenvironment. J Tissue Eng Regener Med 2017;11:e2298–e2311.
170. Dissanayaka WL, Zhang CF. Scaffold-based and scaffold-free strategies in dental pulp regeneration. J Endod 2020;46: 1275–1282.
171. Ovsianikov A, Khademhosseini A, Mironov V. The synergy of scaffold-based and scaffold-free tissue engineering strategies. Trends Biotechnol 2018;36:348–358.
172. Yadav P, Singh S, Jaiswal S, Kumar R. Synthetic and natural polymer hydrogels: A review of 3D spheroids and drug delivery. Int J Biol Macromol 2024;280:136126.
173. Garcia-Sobrino R, Casado-Losada I, Caltagirone C, et al. Osteoblastic cell sheet engineering using P (VCL-HEMA)-based thermosensitive hydrogels doped with pVCL@Icariin nanoparticles obtained with supercritical CO2-SAS. Pharmaceutics 2024;16:1037.
174. Neves CR, Buskermolen J, Roffel S, et al. Human saliva stimulates skin and oral wound healing in vitro. J Tissue Eng Regener Med 2019;13:1079–1092.
175. Lee HA, Park E, Lee H. Polydopamine and its derivative surface chemistry in material science: A focused review for studies at KAIST. Adv Mater 2020;32:2001865.
176. Musial C, Kuban-Jankowska A, Gorska-Ponikowska M. Beneficial properties of green tea catechins. Int J Mol Sci 2020;21:1744.
177. Lee Y, Sugihara K, Gillilland MG, Jon S, Kamada N, Moon JJ. Hyaluronic acid-bilirubin nanomedicine for targeted modulation of dysregulated intestinal barrier, microbiome and immune responses in colitis. Nat Mater 2020;19:37–45.
178. Nguyen LTB, Hsu CC, Ye H, Cui ZF. Development of an in situ injectable hydrogel containing hyaluronic acid for neural regeneration. Biomed Mater 2020;15:055004.
179. Huang SS, Liu HL, Liao KD, Hu QQ, Guo R, Deng KX. Functionalized GO nanovehicles with nitric oxide release and photothermal activity-based hydrogels for bacteria-infected wound healing. ACS Appl Mater Interfaces 2020;12:29371–29384.
180. Talebian S, Mehrali M, Taebnia N, et al. Self-healing hydrogels: The next paradigm shift in tissue engineering? Adv Sci 2019;6:1801664.
181. Mohamed MA, Fallahi A, El-Sokkary AMA, et al. Stimuli-responsive hydrogels for manipulation of cell microenvironment: From chemistry to biofabrication technology. Prog Polym Sci 2019;92:1–28.
182. Saiz-Poseu J, Mancebo-Aracil J, Nador F, Busqué F, Ruiz-Molina D. The chemistry behind catechol-based adhesion. Angew Chem Int Ed 2019;58:696–714.
183. Xu LJ, Gao S, Guo QR, Wang C, Qiao Y, Qiu D. A solvent-exchange strategy to regulate noncovalent interactions for strong and antiswelling hydrogels. Adv Mater 2020;32:e2004579.
184. Cui CY, Wu TL, Chen XY, et al. A Janus hydrogel wet adhesive for internal tissue repair and anti-postoperative adhesion. Adv Funct Mater 2020;30:e2005689.
185. Hillel A, Shah P, Elisseeff J. Hydrogels in cell encapsulation and tissue engineering. In: Jenkins M (ed),. Biomedical Polymers. Cambridge: Woodhead Publishing/Elsevier; 2007:57-82.
186. Zhang YS, Khademhosseini A. Advances in engineering hydrogels. Science 2017;356:eaaf3627.
187. Kim DW, Baik S, Min H, et al. Highly permeable skin patch with conductive hierarchical architectures inspired by amphibians and octopi for omnidirectionally enhanced wet adhesion. Adv Funct Mater 2019;29:1808900.
188. Accioni F, Rassu G, Begines B, et al. Novel utilization of therapeutic coatings based on infiltrated encapsulated rose Bengal microspheres in porous titanium for implant applications. Pharmaceutics 2022;14:1244.
189. Accioni F, Vazquez J, Merinero M, Begines B, Alcudia A. Latest trends in surface modification for dental implantology: Innovative developments and analytical applications. Pharmaceutics 2022;14:455.
190. Schmidt TR, Curra M, Wagner VP, et al. Mucoadhesive formulation containing Curcuma longa L. reduces oral mucositis induced by 5-fluorouracil in hamsters. Phytother Res 2019;33:881–890.
191. Damrongrungruang T, Paphangkorakit J, Limsitthichaikoon S, et al. Anthocyanin complex niosome gel accelerates oral wound healing: In vitro and clinical studies. Nanomedicine 2021;37:102423.
192. Priprem A, Damrongrungruang T, Limsitthichaikoon S, et al. Topical niosome gel containing an anthocyanin complex: A potential oral wound healing in rats. Aaps Pharmscitech 2018;19:1681–1692.
193. Bashir S, Hina M, Iqbal J, et al. Fundamental concepts of hydrogels: Synthesis, properties, and their applications. Polymers 2020;12:2702.

194. Dabiri G, Damstetter E, Phillips T. Choosing a wound dressing based on common wound characteristics. Adv Wound Care (New Rochelle) 2016;5:32–41.
195. Cao LL, Zhao ZJ, Wang XY, Huang XL, Li JJ, Wei YP. Tough, antifreezing, and conductive hydrogel based on gelatin and oxidized dextran. Adv Mater Technol 2022;7:2200252.
196. Qi C, Liu J, Jin Y, et al. Photo-crosslinkable, injectable sericin hydrogel as 3D biomimetic extracellular matrix for minimally invasive repairing cartilage. Biomaterials 2018;160:55–70.
197. Satyamurthy P, Jain P, Balasubramanya RH, Vigneshwaran N. Preparation and characterization of cellulose nanowhiskers from cotton fibres by controlled microbial hydrolysis. Carbohydr Polym 2011;83:122–129.
198. Lavanya K, Chandran SV, Balagangadharan K, Selvamurugan N. Temperature- and pH-responsive chitosan-based injectable hydrogels for bone tissue engineering. Mater Sci Eng C Mater Biol Appl 2020;111:110862.
199. Oryan A, Jalili M, Kamali A, Nikahval B. The concurrent use of probiotic microorganism and collagen hydrogel/scaffold enhances burn wound healing: An in vivo evaluation. Burns 2018;44:1775–1786.
200. Shi C, Wang C, Liu H, et al. Selection of appropriate wound dressing for various wounds. Front Bioeng Biotechnol 2020;8:556763.
201. Schrementi ME, Ferreira AM, Zender C, DiPietro LA. Site-specific production of TGF-β in oral mucosal and cutaneous wounds. Wound Repair Regener 2008;16:80–86.
202. Smith PC, Martinez C, Martinez J, McCulloch CA. Role of fibroblast populations in periodontal wound healing and tissue remodeling. Front Physiol 2019;10:270.
203. Velez I, Parker WB, Siegel MA, Hernandez M. Cryopreserved amniotic membrane for modulation of periodontal soft tissue healing: A pilot study. J Periodontol 2010;81:1797–1804.
204. Kar IB, Singh AK, Mohapatra PC, Mohanty PK, Misra S. Repair of oral mucosal defects with cryopreserved human amniotic membrane grafts: Prospective clinical study. Int J Oral Maxillofac Surg 2014;43:1339–1344.
205. Li W, Fu Y, Jiang B, et al. Polymer-integrated amnion scaffold significantly improves cleft palate repair. Acta Biomater 2019;92:104–114.
206. Hsiao YC, Lee HW, Chen YT, Young TH, Yang TL. The impact of compositional topography of amniotic membrane scaffold on tissue morphogenesis of salivary gland. Biomaterials 2011;32:4424–4432.
207. Liu X, Mao X, Ye G, et al. Bioinspired Andrias davidianus-derived wound dressings for localized drug-elution. Bioact Mater 2022;15:482–494.
208. Zhang X, Jiang L, Li X, et al. A bioinspired hemostatic powder derived from the skin secretion of Andrias davidianus for rapid hemostasis and intraoral wound healing. Small 2022;18:2101699.
209. Lim YS, Kwon SK, Park JH, Cho CG, Park SW, Kim WK. Enhanced mucosal healing with curcumin in animal oral ulcer model. Laryngoscope 2016;126:E68–E73.
210. Limsitthichaikoon S, Khampaenjiraroch B, Damrongrungruang T, Limphirat W, Thapphasaraphong S, Priprem A. Topical oral wound healing potential of anthocyanin complex:animal and clinical studies. Ther Deliv 2018;9:359–374.
211. Lee JH, Jung JY, Bang D. The efficacy of topical 0.2% hyaluronic acid gel on recurrent oral ulcers: Comparison between recurrent aphthous ulcers and the oral ulcers of Behcet's disease. J Eur Acad Dermatol Venereol 2008;22:590–595.
212. Oudhoff MJ, van den Keijbus PAM, Kroeze KL, et al. Histatins enhance wound closure with oral and non-oral cells. J Dent Res 2009;88:846–850.
213. Piva RH, Rocha MC, Piva DH, Imasato H, Malavazi I, Rodrigues-Filho UP. Acidic dressing based on agarose/Cs2.5H0.5PW12O40 nanocomposite for infection control in wound care. ACS Appl Mater Interfaces 2018;10:30963–30972.
214. Ryu JH, Choi JS, Park E, et al. Chitosan oral patches inspired by mussel adhesion. J Control Release 2020;317:57–66.
215. Bao X, Zhao J, Sun J, Hu M, Yang X. Polydopamine nanoparticles as efficient scavengers for reactive oxygen species in periodontal disease. ACS Nano 2018;12:8882–8892.
216. Abpeikar Z, Alizadeh AA, Ahmadyousefi Y, Najafi AA, Safaei M. Engineered cells along with smart scaffolds: Critical factors for improving tissue engineering approaches. Regen Med 2022;17:855–876.
217. Rahimnejad M, Makkar H, Dal-Fabbro R, Malda J, Sriram G, Bottino MC. Biofabrication strategies for oral soft tissue regeneration. Adv Healthc Mater 2024;13:e2304537.
218. Schlee M, Ghanaati S, Willershausen I, Stimmlmayr M, Sculean A, Sader RA. Bovine pericardium-based non-cross-linked collagen matrix for successful root coverage: A clinical study in humans. Head Face Med 2012;8:6.
219. Moraschini V, Calasans-Maia MD, Dias AT, et al. Effectiveness of connective tissue graft substitutes for the treatment of gingival recessions compared with coronally advanced flap: A network meta-analysis. Clin Oral Investig 2020;24:3395–3406.
220. Nunez J, Caffesse R, Vignoletti F, Guerra F, San Roman F, Sanz M. Clinical and histological evaluation of an acellular dermal matrix allograft in combination with the coronally advanced flap in the treatment of miller class I recession defects: An experimental study in the mini-pig. J Clin Periodontol 2009;36:523–531.
221. Shi LJ, Wang Y, Yang C, Jiang WW. Application of acellular dermal matrix in reconstruction of oral mucosal defects in 36 cases. J Oral Maxillofac Surg 2012;70:E586–E591.
222. Tang J, Han Y, Zhang F, Ge Z, Liu X, Lu Q. Buccal mucosa repair with electrospun silk fibroin matrix in a rat model. Int J Artif Organs 2015;38:105–112.
223. Rastogi S, Modi M, Sathian B. The efficacy of collagen membrane as a biodegradable wound dressing material for surgical defects of oral mucosa: A prospective dtudy. J Oral Maxillofac Surg 2009;67:1600–1606.
224. Kilinc A, Ataol M. How effective is collagen resorbable membrane placement after partially impacted mandibular third molar surgery on postoperative morbidity? A prospective randomized comparative study. BMC Oral Health 2017;17:126.
225. Ge Z, Yang Q, Xiang X, Liu KZ. Assessment of silk fibroin for the repair of buccal mucosa in a rat model. Int J Oral Maxillofac Surg 2012;41:673–680.
226. Chircov C, Grumezescu AM, Bejenaru LE. Hyaluronic acid-based scaffolds for tissue engineering. Rom J Morphol Embryol 2018;59:71–76.
227. Gasmi Benahmed A, Gasmi A, Arshad M, et al. Health benefits of xylitol. Appl Microbiol Biotechnol 2020;104:7225–7237.
228. Darveau RP. Periodontitis: A polymicrobial disruption of host homeostasis. Nat Rev Microbiol 2010;8:481–490.
229. Lourenço TGB, Heller D, Silva-Boghossian CM, Cotton SL, Paster BJ, Colombo APV. Microbial signature profiles of periodontally healthy and diseased patients. J Clin Periodontol 2014;41:1027–1036.
230. Ryder MI. Comparison of neutrophil functions in aggressive and chronic periodontitis. Periodontology 2000 2010;53:124–137.
231. Pan WY, Wang QX, Chen QM. The cytokine network involved in the host immune response to periodontitis. Int J Oral Sci 2019;11:30.

232. Shen Z, Zhang R, Huang Y, et al. The spatial transcriptomic landscape of human gingiva in health and periodontitis. Sci China Life Sci 2023;67:720–732.
233. Khader SA, Gaffen SL, Kolls JK. Th17 cells at the crossroads of innate and adaptive immunity against infectious diseases at the mucosa. Mucosal Immunol 2009;2:403–411.
234. Chakravarti A, Raquil MA, Tessier P, Poubelle PE. Surface RANKL of Toll-like receptor 4-stimulated human neutrophils activates osteoclastic bone resorption. Blood 2009;114: 1633–1644.
235. Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: A review. Diabetologia 2001;44:129–146.
236. Chen NR, Ren RG, Wei X, et al. Thermoresponsive hydrogel-based local delivery of simvastatin for the treatment of periodontitis. Mol Pharmaceutics 2021;18:1992–2003.
237. Chang PC, Chao YC, Hsiao MH, et al. Inhibition of periodontitis induction using a stimuli-responsive hydrogel carrying naringin. J Periodontol 2017;88:190–196.
238. Guo HL, Huang S, Yang XF, et al. Injectable and self-healing hydrogels with double-dynamic bond tunable mechanical, gel-sol transition and drug delivery properties for promoting periodontium regeneration in periodontitis. ACS Appl Mater Interfaces 2021;13:61100–61114.
239. Xu XW, Gu ZY, Chen X, et al. An injectable and thermosensitive hydrogel: Promoting periodontal regeneration by controlled-release of aspirin and erythropoietin. Acta Biomater 2019;86:235–246.
240. Zhao XD, Yang YX, Yu J, et al. Injectable hydrogels with high drug loading through B-N coordination and ROS-triggered drug release for efficient treatment of chronic periodontitis in diabetic rats. Biomaterials 2022;282:121387.
241. Saita M, Kaneko J, Sato T, et al. Novel antioxidative nanotherapeutics in a rat periodontitis model: Reactive oxygen species scavenging by redox injectable gel suppresses alveolar bone resorption. Biomaterials 2016;76:292-301.
242. Narayanan A, Dhinojwala A, Joy A. Design principles for creating synthetic underwater adhesives. Chem Soc Rev 2021;50:13321–13345.
243. Yin Y, Yang S, Ai D, et al. Rational design of bioactive hydrogels toward periodontal delivery :From pathophysiology to therapeutic applications. Adv Funct Mater 2023;33:2301062.
244 Ramseier CA, Rasperini G, Batia S, Giannobile WV. Advanced reconstructive technologies for periodontal tissue repair. Periodontology 2000 2012;59:185–202.
245. Jepsen S, Gennai S, Hirschfeld J, Kalemaj Z, Buti J, Graziani F. Regenerative surgical treatment of furcation defects: A systematic review and Bayesian network meta-analysis of randomized clinical trials. J Clin Periodontol 2020;47:352–374.
246. Bartold PM, Gronthos S, Ivanovski S, Fisher A, Hutmacher DW. Tissue engineered periodontal products. J Periodontal Res 2016;51:1–15.
247. Wang HL, Boyapati L. "PASS" principles for predictable bone regeneration. Implant Dent 2006;15:8–17.
248. Ovrebo O, Perale G, Wojciechowski JP, et al. Design and clinical application of injectable hydrogels for musculoskeletal therapy. Bioeng Transl Med 2022;7:e10295.
249. Turkal HA, Demirer S, Dolgun A, Keceli HG. Evaluation of the adjunctive effect of platelet-rich fibrin to enamel matrix derivative in the treatment of intrabony defects. Six-month results of a randomized, split-mouth, controlled clinical study. J Clin Periodontol 2016;43:955–964.
250. Miron RJ, Sculean A, Cochran DL, et al. Twenty years of enamel matrix derivative: The past, the present and the future. J Clin Periodontol 2016;43:668–683.
251. Cirelli JA, Fiorini T, Cunha Moreira CH, de Molon RS, Dutra TP, Sallum EA. Periodontal regeneration: Is it still a goal in clinical periodontology? Braz Oral Res 2021;35:e097.
252. Laugisch O, Cosgarea R, Nikou G, et al. Histologic evidence of periodontal regeneration in furcation defects: A systematic review. Clin Oral Investig 2019;23:2861–2906.
253. Shrivastava D, Natoli V, Srivastava KC, et al. Novel approach to dental biofilm management through guided biofilm therapy (GBT): A review. Microorganisms 2021;9:1966.
254. Yang H, Zeng T, Jiang T, et al. Recent progress on functional hydrogels as biomaterial for biomedicine. Results Chem 2025;16:102464.
255. Liu Y, Meng H, Konst S, Sarmiento R, Rajachar R, Lee BP. Injectable dopamine-modified poly (ethylene glycol) nanocomposite hydrogel with enhanced adhesive property and bioactivity. ACS Appl Mater Interfaces 2014;6:16982–16992.
256. Wang Y, Qin X, Feng Y, et al. Dual-gradient silk-based hydrogel for spatially targeted delivery and osteochondral regeneration. Adv Mater 2025;37:e2420394.
257. Yue K, Trujillo-de Santiago G, Alvarez MM, Tamayol A, Annabi N, Khademhosseini A. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. Biomaterials 2015;73:254–271.
258. Li J MD. Designing hydrogels for controlled drug delivery. Nat Rev Mater 2016;1:16071.
259. Cui CY, Liu WG. Recent advances in wet adhesives: Adhesion mechanism, design principle and applications. Prog Polym Sci 2021;116:101388.
260. Cui C, Mei L, Wang D, Jia P, Zhou Q, Liu W. A self-stabilized and water-responsive deliverable coenzyme-based polymer binary elastomer adhesive patch for treating oral ulcer. Nat Commun 2023;14:7707.
261. Korupalli C, Li H, Nguyen N, et al. Conductive materials for healing wounds: Their incorporation in electroactive wound dressings, characterization, and perspectives. Adv Healthcare Mater 2021;10:e2001384.
262. Ben Amara H, Thoma DS, Schwarz F, Song HY, Capetillo J, Koo KT. Healing kinetics of oral soft tissue wounds treated with recombinant epidermal growth factor: Translation from a canine model. J Clin Periodontol 2019;46:105–117.
263. Schenck K, Schreurs O, Hayashi K, Helgeland K. The role of nerve growth factor (NGF) and its precursor forms in oral wound healing. Int J Mol Sci 2017;18:386.
264. Albanese A, Licata ME, Polizzi B, Campisi G. Platelet-rich plasma (PRP) in dental and oral surgery:from the wound healing to bone regeneration. Immun Ageing 2013;10:23.
265. Femminella B, Iaconi MC, Di Tullio M, et al. Clinical comparison of platelet-rich gibrin and a gelatin dponge in the management of palatal wounds after epithelialized free gingival graft harvest: A randomized clinical trial. J Periodontol 2016;87:103–113.
266. Matarasso M, Iorio-Siciliano V, Blasi A, Ramaglia L, Salvi GE, Sculean A. Enamel matrix derivative and bone grafts for periodontal regeneration of intrabony defects. A systematic review and meta-analysis. Clin Oral Investig 2015;19:1581–1593.
267. Lekovic V, Milinkovic I, Aleksic Z, et al. Platelet-rich fibrin and bovine porous bone mineral vs. platelet-rich fibrin in the treatment of intrabony periodontal defects. J Periodontal Res 2012;47:409–417.

268. Kitamura M, Akamatsu M, Kawanami M, et al. Randomized placebo-controlled and controlled non-inferiority phase III trials comparing trafermin, a recombinant human fibroblast growth factor 2, and enamel matrix derivative in periodontal regeneration in intrabony defects. J Bone Miner Res 2016;31:806–814.
269. Donos N, Calciolari E, Brusselaers N, Goldoni M, Bostanci N, Belibasakis GN. The adjunctive use of host modulators in non-surgical periodontal therapy. A systematic review of randomized, placebo-controlled clinical studies. J Clin Periodontol 2020;47:199–238.
270. Aimetti M, Baima G, Aliyeva N, et al. Influence of locally delivered doxycycline on the clinical and molecular inflammatory status of intrabony defects prior to periodontal regeneration: A double-blind randomized controlled trial. J Periodontal Res 2023;58:1096–1104.
271. Hardan L, Bourgi R, Cuevas-Suárez CE, et al. The use of probiotics as adjuvant therapy of periodontal treatment: A systematic review and meta-analysis of clinical trials. Pharmaceutics 2022;14:1017.
272. Moraes RM, Schlagenhauf U, Anbinder AL. Outside the limits of bacterial viability: Postbiotics in the management of periodontitis. Biochem Pharmacol 2022;201:115072.
273. Nguyen T, Brody H, Lin GH, et al. Probiotics, including nisin-based probiotics, improve clinical and microbial outcomes relevant to oral and systemic diseases. Periodontol 2000 2020;82:173–185.
274. Zhu Z, Liu Y, Chen J, et al. Structural-functional pluralistic modification of silk fibroin via MOF bridging for advanced wound care. Adv Sci 2022;9:e2204553.
275. Sionkowska A. Current research on the blends of natural and synthetic polymers as new biomaterials: Review. Prog Polym Sci 2011;36:1254–1276.
276. Cuschieri S. The CONSORT statement. Saudi J Anaesth 2019;13:S27–S30.
277. Caton JG. Overview of clinical trials on periodontal regeneration. Ann Periodontol 1997;2:215–222.