Review

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Antimicrobial, remineralization, and infiltration: advanced strategies for interrupting dental caries

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Abstract: Dental caries, driven by plaque biofilm, poses a major oral health challenge due to imbalance in mineralization and demineralization. The primary objective in caries management is to maintain biofilm homeostasis while facilitating the repair and regeneration of dental hard tissues, thus restoring both structural integrity and functionality of affected teeth. Though antimicrobial and remineralization approaches haven shown promise, their standalone utilization without concurrent bacterial control or rebalancing lacks an integrated strategy to effectively arrest caries progression. Furthermore, according to the principles of minimally invasive dentistry, treatment materials should exhibit high permeability to ensure optimal sealing of demineralized tooth surfaces. The concept of interrupting dental caries (IDC) has emerged as a holistic approach, drawing upon extensive research encompassing three pivotal techniques: antibacterial strategies, remineralization therapies, and infiltration mechanisms, all of which are indispensable components in combating the progression of dental caries. In this review, we provide a comprehensive overview of the mechanisms and applications of antibacterial, remineralization, and infiltration technologies within the context of caries management. Additionally, we summarize advanced materials that align with the IDC concept, aiming to offer valuable insights for designing next-generation materials adept at preventing or halting caries progression efficiently.

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Introduction

Dental caries, a widespread oral disease, presents a major public health concern globally. Though epidemiological data indicates a decrease in the lifetime prevalence of dental caries over the past four decades, it still afflicts over two billion individuals [1, 2]. Current conventional treatment approaches predominantly involve invasive measures, such as resin filling, which inevitably compromises the integrity of healthy dental hard tissue during cavity preparation. Moreover, the interfaces between the restoration and the tooth exist in a complex dynamic equilibrium with various chemicals and minerals present in both the relatively porous hard tissues of the tooth and saliva [3]. The development of dental plaque at the tooth-restoration interface frequently disturbs the aforementioned delicate equilibrium, leading to the onset of secondary caries, which account for 36.5 % of restorative treatment failures [4]. Furthermore, existing therapeutic methods for dental caries predominantly center on restorative techniques following the development of defects. This approach diverges from the clinical care ethos of minimizing therapeutic interventions [5, 6], neglecting to adequately address prevention and mitigation of the underlying causes. The occurrence of dental caries is ascribed to the colonization of cariogenic microorganisms within biofilms, particularly highlighting *Streptococcus mutans*. These microorganisms metabolize dietary carbohydrates, yielding acids that disturb the intricate equilibrium between demineralization and remineralization processes in dental hard tissues, and ultimately culminating in structural tooth deterioration [7]. Given the multifactorial etiology, the employment of antimicrobial agents stands as a pivotal strategy in both the prophylaxis and management of dental caries [8]. Additionally, to counteract the imbalance between demineralization and remineralization, treatment materials must prioritize the optimization of tooth tissue remineralization [9]. This approach effectively seals the lesion area, thereby preventing caries progression through non-invasive or minimally invasive means.

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The concept of "interrupting dental caries" (IDC) aims to restore the equilibrium of caries progression by utilizing materials and technologies that integrate remineralization capabilities alongside antibacterial efficacy and permeability [9]. An example aligned with the IDC vision is silver diamine fluoride, a compound combining fluorine and silver ions [10]. Nevertheless, when confronted with situations involving saliva deficient in mineral ion content, fluoride alone might not prompt swift or noticeable remineralization. Additionally, contentious issues regarding adverse effects associated with silver ions include tooth discoloration, oral soft tissue irritation, and cytotoxicity [11, 12]. Therefore, agents within the IDC concept should possess the following capabilities: 1) robust and reliable antibacterial efficacy; 2) efficient delivery of substantial amounts of calcium and phosphate for lesion remineralization; 3) superior permeability to effectively seal enamel voids and dentin tubules. This review presents a comprehensive overview of recent advancements in caries management, encompassing antimicrobial therapies, remineralization strategies, and minimally invasive infiltration treatment (Figure 1). The mechanisms and agents employed in these approaches are thoroughly discussed. Subsequently, the agents are highlighted and discussed in accordance with the IDC concept, and are then categorized into two groups: composite materials and synthetic materials. Lastly, we outline past challenges encountered as well as future prospects for interventions in caries management. We aim to provide valuable insights into potential next-generation caries management agents that can effectively interrupt disease progression.

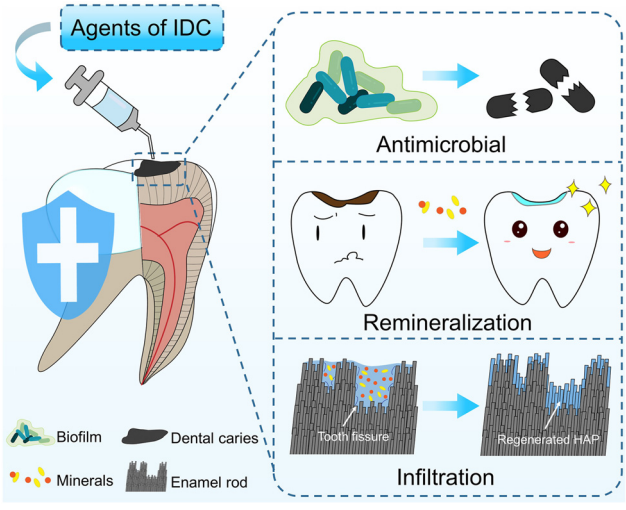

Figure 1: Schematic representation of the caries management mechanism under the IDC concept, supported by antimicrobial, remineralization, and infiltration technologies.

Dental biofilms: biological mediators of dental caries

It is widely acknowledged that the etiology of dental caries involves four primary factors: dental plaque, host factors, dietary habits, and time. Dental plaque refers to a bacterial biofilm that adheres to tooth surfaces and establishes a stable microenvironment within the oral cavity in its healthy state [13]. The transition of bacteria into acid-producing and acid-resistant strains disrupts the micro-ecological balance of biofilms, thereby precipitating the onset of dental caries [14]. Consequently, the contemporary approach to caries prevention and control not only targets the inhibition of early colonization by cariogenic bacteria but also endeavors to optimize the restoration of a healthy biofilm composition and sustain dynamic equilibrium [15].

Dental biofilms in dental caries

Cariogenic bacteria primarily comprise Gram-positive species, notably including Lactobacillus spp., Actinobacillus spp., and Streptococcus spp. *Lactobacillus acidophilus*, a normal genus in the oral cavity, contributes to dental caries due to its ability to produce lactic acid through fermentation [16]. Actinobacillus spp., such as viscous Actinobacillus and Actinobacillus endothelialis, metabolize glucose to generate lactic acid-based acids, which are associated with the development of root caries [17]. Among these, *S. mutans*, a pathogenic bacterium within the Streptococcus spp., is widely recognized as one of the most significant species associated with dental caries [18, 19]. Though the dominance of *S. mutans* as the primary oral bacteria has not always been confirmed, it is widely recognized as a significant cariogenic species due to its aciduric and acid production properties, along with its capacity for matrix synthesis. In the presence of dietary sucrose, it regulates the formation of dental biofilms efficiently [20].

Bacteria inhabiting biofilms often display distinctive phenotypic characteristics compared to their planktonic counterparts (Figure 2) [21]. One of the most crucial among these features is an enhanced resistance to antimicrobial agents, primarily attributed to the accumulation of extracellular polymeric substances (EPS) surrounding the bacterial cells, which constitute a major component of the biofilm structure [22]. EPS is biopolymers derived from microbial sources, serving as a three-dimensional framework for biofilm development and contributing to the establishment of diverse spatial, metabolic, and micro environmental conditions. Additionally, it enhances bacterial resilience against

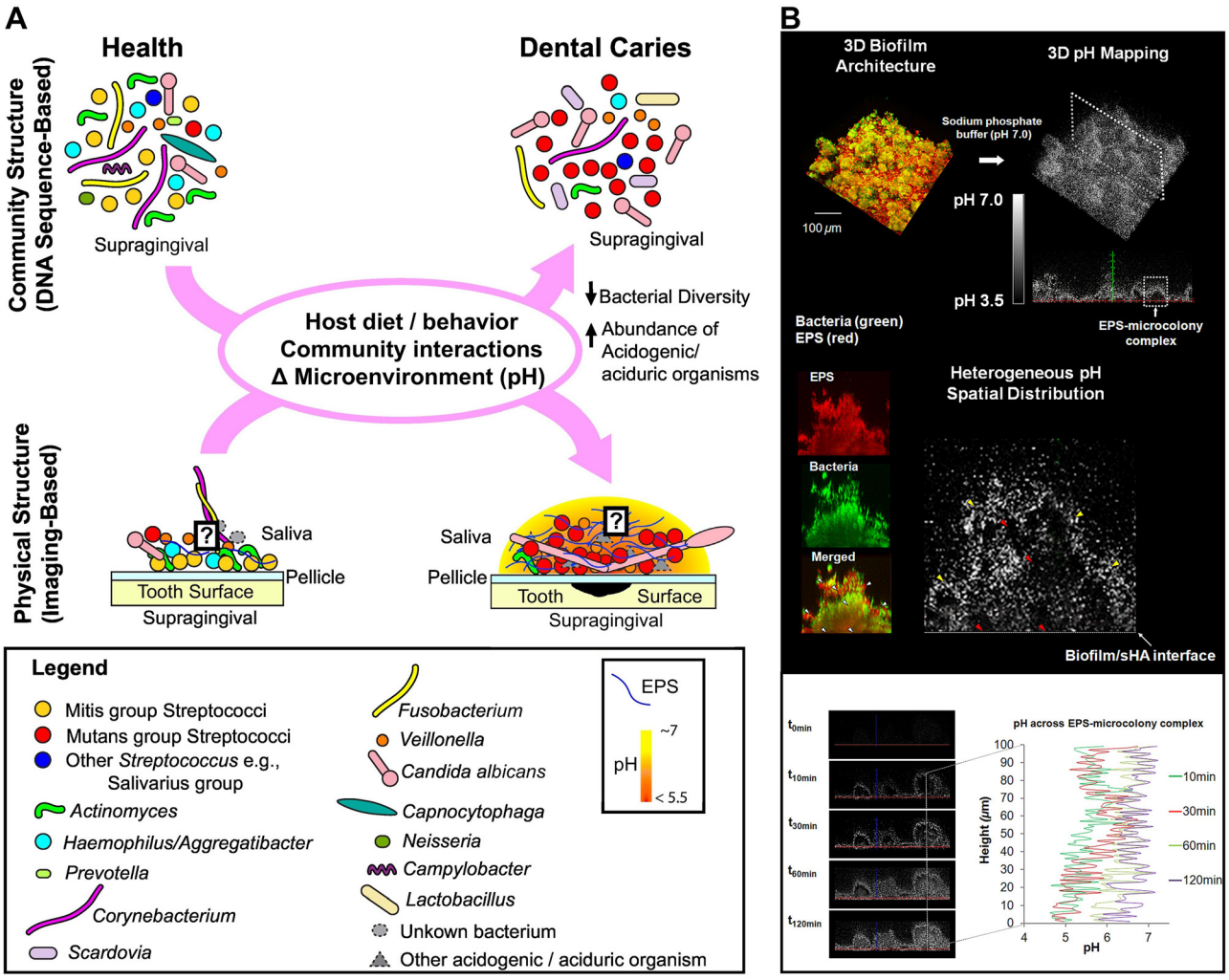

Figure 2: Structural patterning (image source: Valm et al. [14] with permission) (A) and three-dimensional *in situ* pH mapping (image source: Xiao et al. [21] with permission) (B) of biofilms.

environmental stressors while hindering metabolite diffusion. The primary cariogenic virulence factor of *S. mutans* lies in its capacity to synthesize EPS [23]. Therefore, disruption of EPS may serve as a potential strategy to hinder the colonization of *S. mutans* and restore the dynamic equilibrium of healthy biofilms.

Advances in agents targeting *S. mutans* biofilms

EPS formation provides a platform for adhesion of *S. mutans* to tooth surfaces, mechanical stability, and an acidic microenvironment. Biofilms acquire emergent properties through the structural and biochemical composition of the matrix, including surface adhesion, chemical and spatial heterogeneities, competitive and synergistic interactions, as well as enhanced resistance to microbial agents (Figure 3) [24]. The development of antimicrobial strategies targeting EPS can be achieved through diverse methodologies [25]. The glucan matrix is the main component of EPS in caries biofilms [26]. The bacterium *S. mutans* produces glucosyltransferases (Gtfs) that can break down sucrose from food and, after releasing its fructose component, catalyze the formation of extracellular polysaccharides primarily linked by α-1,3 linked glucose and α-1,6 linked glucose [27, 28]. Consequently, inhibiting Gtfs activity can hinder bacterial adhesion. Furthermore, direct bactericidal approaches are available, such as disrupting the integrity of the phospholipid bilayer in the bacterial membrane [29] or interfering with bacterial protein synthesis. In addition to enhancing antimicrobial efficacy against biofilms, advanced drug delivery methods can efficiently transport antimicrobial drugs to deeper layers within the biofilm, thus further

augmenting antimicrobial effectiveness. For example, small nanoparticles generally exhibit strong biofilm permeability due to their minimal diffusion retardance [30]; cationic nanoparticles demonstrate enhanced penetration and retention through electrostatic interactions with negatively charged bacteria cells [30]; and conjugating drugs with polyethylene glycol enhance drug dispersion and mucus-penetrating properties [31]. Meanwhile, considering the intricate nature of the oral cavity, targeting specific pathogenic microenvironments (or niches) by employing agents that are triggered by low pH or bacterial products can present an appealing strategy against cariogenic biofilms [32]. Researchers are actively investigating the microenvironment of biofilms and the physiological processes of *S. mutans* within these biofilms, which has led to the development of various agents for caries prevention, as elaborated below.

The synthetic agents

Currently, commonly utilized synthetic agents include fluoride, chloride, and heavy metal agents. Fluoride can effectively inhibit acid production by *S. mutans* through direct targeting of enolase enzyme to impede the glycolytic pathway (Figure 4A) [33], while simultaneously enhancing enamel resistance against acidic solutions through the formation of fluorapatite [34]. Abundant evidence-based resources of high quality are readily available to support the utilization of fluoride toothpaste in caries prevention [35]. Well-controlled clinical trials consistently demonstrate significant reductions in caries incidence, up to 30 %, with the use of fluoride toothpastes such as Cheerio gel, Colgate sensitive, Close up deep action, Senquel-F, and Sensodent-KF [34]. The utilization of commercially available

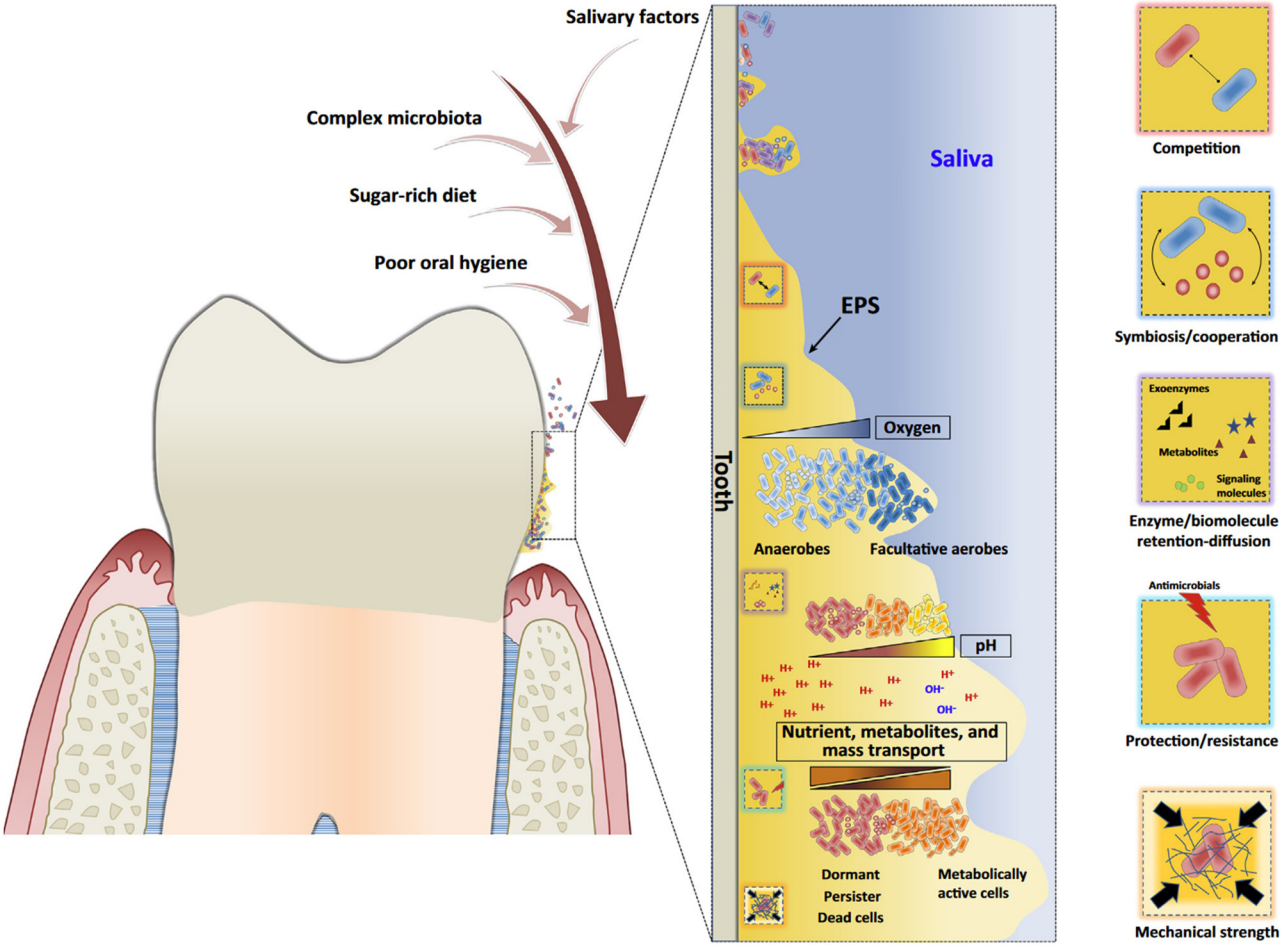

Figure 3: A high-sugar diet provides the oral cavity with a substrate for synthesizing extracellular polysaccharides, significantly alters the biological and physical characteristics of the biofilm. Exopolysaccharides create a polymeric matrix that embeds microorganisms on tooth surfaces, enhancing microbial adhesion-cohesion and accumulation. The metabolic processes of embedded organisms, along with the diffusion-modifying properties of the matrix, generate various chemical microenvironments such as localized pH and oxygen gradients. Additionally, the matrix can capture or sequester a wide range of chemicals, including nutrients, metabolites, and quorum sensing molecules (image source: Bowen et al. [24] with permission).

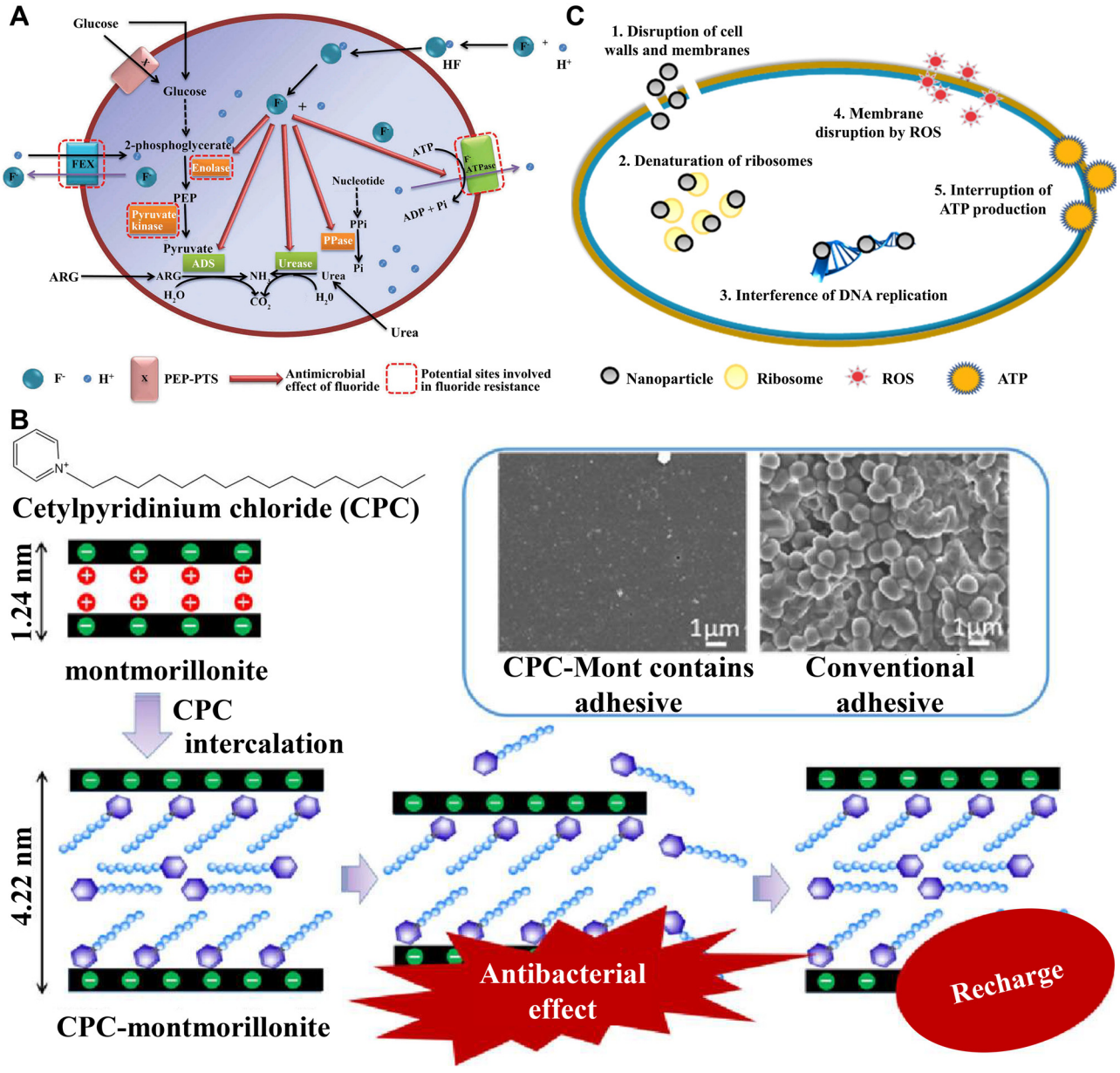

Figure 4: Antimicrobial mechanisms of chemical agents. (A) Mechanisms underlying the antimicrobial effects of fluoride and potential sites implicated in fluoride resistance (image source: Liao et al. [33] with permission). (B) Schematics illustrating the CPC-mont antibacterial technology (image source: Matsuo et al. [39] with permission). (C) The antibacterial mechanism of metal nanoparticles (image source: Chen et al. [42] with permission).

fluoride-containing varnish and toothpaste has become widespread [36]. Though the use of fluoride additives for the societal improvement and personal consumption has been prevalent, their effectiveness needs to be evaluated in light of the varying levels of fluoridated water consumed across different regions. Consequently, recommended dosage regimens vary regionally [36]. It should be noted that fluoride intake is a critical factor in the development of fluorosis. Therefore, it is important to remain cognizant of its potential negative effects. It is well-established that exposure to fluoride during post-secretory or early maturation period of enamel development increases the risk of fluorosis [36]. Reducing the fluoride content in water supplies is a viable strategy to mitigate the risk of dental fluorosis while maintaining nearly optimal caries prevention. Several countries have already implemented this measure. For example, in 2007–2008, Ireland and Canada reduced the target fluoride concentration from 0.9/1.0 to 0.7 ppm F. Currently, the United States Public Health Service recommends 0.7 ppm as the optimal fluoride concentration, which is at the lower end

of the previous range of 0.7–1.2 ppm F [36]. The levels of fluorosis and dental caries will be continuously monitored as the ultimate test of this strategy.

Chlorhexidine, a widely used antimicrobial agent against *S. mutans*, carries a positive charge in solution, enabling it to bind to the bacterial cell wall and subsequently destroy it [37]. Cetylpyridinium chloride (CPC) disrupts microbial cell membranes by perturbing their electrical equilibrium [38]. Given its inhibitory impact on *S. mutans*, CPC is frequently integrated as an antimicrobial agent in mouthwashes, toothpastes, resins, and adhesives to effectively reduce the incidence of dental caries [39]. In order to extend the release duration of CPC, Matsuo et al. incorporated CPC into montmorillonite (CPC-Mont) for controlled release, thereby significantly enhancing its antibacterial efficacy (Figure 4B) [39]. However, the cytotoxicity of CPC requires careful consideration. Research has shown that CPC dilutions exhibit cytotoxic effects on L929 cells [40], which is attributed to its mitochondrial inhibitory activity, specifically through the inhibition of mitochondrial oxygen consumption and ATP synthesis *in vitro*. Additionally, mouthwashes containing CPC have been found to be cytotoxic to neonatal melanocytes [41]. Therefore, it is crucial to carefully regulate the dosage of CPC to mitigate potential cytotoxic effects.

The inhibitory effects of silver nanoparticles, zinc nanoparticles, and gold nanoparticles on *S. mutans* have been extensively investigated (Figure 4C) [42], with silver nanoparticles being the subject of the most comprehensive studies. The antibacterial activity of silver compounds is attributed to their ability to disintegrate the cell membrane, penetrate into the interior of bacterial cells, and disrupt intracellular organelles. Additionally, silver compounds exhibit an additional mechanism that enhances their efficacy by inhibiting bacterial DNA replication capability and inactivating bacterial enzymes [43]. The incorporation of silver nanoparticles into adhesive systems and composite resins has demonstrated significant efficacy in the prevention of secondary caries [44, 45]. However, it is imperative to further evaluate their biosafety implications. Compared to pure metal nanoparticles, metal oxide nanoparticles demonstrate lower cytotoxicity to the human body [46] and are more cost-effective [47]. Although their precise antimicrobial mechanisms remain under debate, several distinctive mechanisms have been proposed. These include the generation of reactive oxygen species, the release of metal ions, internalization of particles into bacterial cells, and direct mechanical disruption of bacterial cell walls and/or membranes [48]. Zinc oxide nanoparticles can be incorporated into conventional glass without altering its fundamental mechanical properties [49], thereby imparting antimicrobial characteristics beneficial for dental restorations. However, it has been observed that the incorporation of Zinc oxide nanoparticles into composite resins affects their chemical and mechanical properties [50], thus limiting their clinical applications. In addition, copper oxide nanoparticles are often added to adhesives to prevent the development of early carious white spot lesions [51]. Given the variations in antimicrobial activity, biocompatibility, and dispersibility among different nanoparticles, the combination of various metals and metal oxides holds the potential to produce a wide array of antimicrobial materials with enhanced properties.

Antimicrobial peptides (AMPs)

Antimicrobial peptides (AMPs) represent a widely distributed class of peptides found in living organisms, which serve as a defense mechanism against foreign microorganisms and certain mutated cells. As a primary line of defense in innate immunity, antibacterial peptides exhibit broad-spectrum antimicrobial activity and a lower propensity for drug resistance compared to fluoride and chlorhexidine [52, 53]. The bactericidal mechanism of AMPs involves their positively charged properties and their interaction with the negatively charged surface of microorganisms. These peptides exhibit antibacterial activity by displacing lipids and integrating themselves into the outer leaflet of the lipid bilayer in the cytoplasmic membrane (Figure 5A) [54]. The mechanisms of 'barrel-stave', 'carpet', or 'toroidal-pore' facilitate the adherence and insertion of AMPs into membrane bilayers (Figure 5B) [55]. Additionally, some AMPs inhibit biofilm formation by competing with bacteria for adherence [56].

The initial AMPs identified in mammals are known as defensins, which can be categorized into two subfamilies in humans: α-defensin (HNP) and β-defensin (hBD). The expression of hBDs (hBD-1, hBD-2, and hBD-3) has been observed in dental pulp and odontoblasts [56, 57]. Defensins hBD-2 and hBD-3 demonstrated activity against various oral pathogens, particularly the cariogenic organism *S. mutans* [58]. Moreover, LL37, α-defensins (HNP 1–3), and Histatin-5 all exhibited inhibitory effects against *S. mutans* [59–61]. In order to facilitate the application of AMPs in caries management, researchers are continuously studying synthetic analogs or fragments of natural AMPs derived from humans or other species. Due to the relatively short amino acid sequences of some AMPs, chemical synthesis offers a convenient approach to producing peptides that are structurally and functionally identical to their natural counterparts. The most commonly employed method is solid-phase peptide synthesis [62]. The core principle of

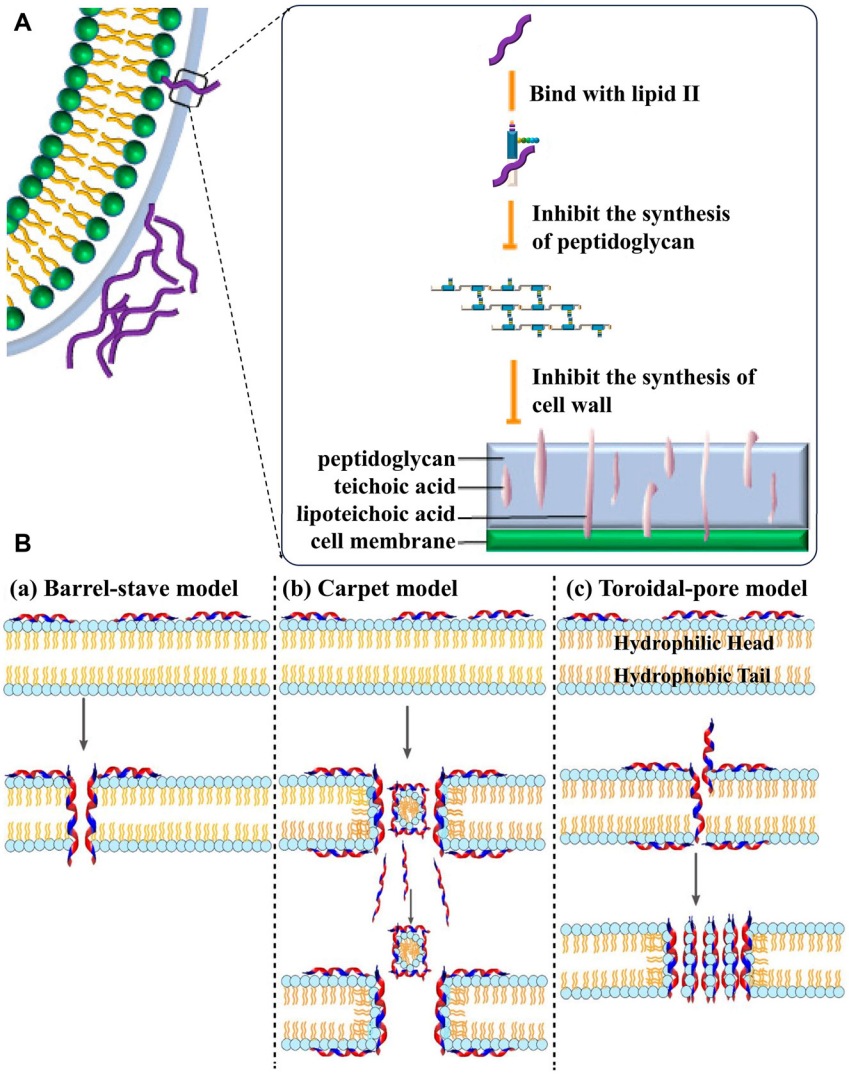

Figure 5: Schematic representation of the bactericidal mechanism of AMPs. (A) Disruption of the cell membrane by AMPs (image source: Luo et al. [54] with permission). (B) The 'barrel-stave' (a), 'carpet'. and (b), 'toroidal-pore' models of membrane disruption by AMPs (image source: Hafeez et al. [55] with permission).

solid-phase peptide synthesis involves anchoring the carboxyl terminus of an amino acid to a polystyrene resin support through chemical linkers. The amino terminus is then exposed to facilitate peptide chain elongation. The incoming amino acids are protected at their amino terminus and side chain groups, with only the carboxyl terminus activated for the coupling reaction. This activated carboxyl terminus reacts with the exposed amino terminus on the resin. By sequentially removing the amino protective group, adding an amino acid, and repeating this deprotection-coupling cycle, the desired peptide chain is synthesized iteratively [63].

The stability and inhibitory activity of AMPs against oral bacteria can be improved through amino acid substitutions, introduction of hydrophobic groups, and shortening of amino acid residues based on the structural characteristics of different AMPs [64, 65]. The AMP pleurocidin, derived and engineered from the epidermal mucus of Pleuronectes americanus exhibits potent bactericidal effects against *S. mutans* [66]. The derived peptide AT-7 from Lactobacillus, the *de novo* designed amphipathic α-helices peptide GH12, and the novel gallic acid (GA)-grafted AMP cathelicidin LL37 have all shown favorable inhibitory effects on *S. mutans* [67–69]. The recent advancements in designing AMPs for caries prevention have primarily focused on specifically targeting *S. mutans*, with the aim of restoring a healthy microbial community.

Xiang et al. employed virtual screening of lipopeptide libraries to develop C10-KKWW, which effectively inhibits and disrupts *S. mutans* biofilms by specifically targeting the L-ascorbate-specific PtxA component of its phosphoenol-pyruvate sugar phosphotransferase system, as confirmed through software simulations [70]. SspB (390-T400K-402), a peptide derived from the adhesin SspB, exhibits high affinity for salivary glycoprotein-340 peptide SRCRP2, competitively inhibiting the adhesion of *S. mutans* to saliva and impeding

biofilm formation [71]. Another targeting strategy involves pH-activated AMPs, which exhibit potent antimicrobial activity exclusively in acidic environments while remaining ineffective under neutral physiological conditions [72]. The dual-sensitive AMP, pHly-1, engineered by Zhang et al., undergoes a conformational transition from coil to helix upon interaction with bacterial membranes within the acidic cariogenic biofilm microenvironment, effectively eradicating cariogenic bacteria [73]. Conversely, under normal physiological conditions, pHly-1 adopts a β-sheet conformation and self-assembles into nanofibers, resulting in minimal cytotoxicity towards oral microbes. Jiang et al. engineered LH12 to incorporate histidine-rich sequences, thus enhancing its antimicrobial efficacy in acidic environments [74]. Protonation of LH12 in the acidified cariogenic microenvironment results in increased cationicity and improved interactions with bacterial membranes, enhancing the competitiveness of commensal bacteria under acidic conditions.

The limited half-life of AMPs presents a significant obstacle as therapeutic agents, impeding their clinical utility. Moreover, the economic challenges associated with AMP development should not be disregarded. Hence, ongoing efforts in caries prevention and treatment are focused on identifying or synthesizing medications that offer optimal safety profiles, consistent effectiveness, and economic viability for human use.

Natural medicines

The diverse range of chemical constituents, extensive origins, potent pharmacological activity, and negligible toxicity make natural medicines a pivotal reservoir of efficacious therapeutic agents that have been harnessed and explored for over three millennia [75]. Therefore, screening natural compounds for effective agents against *S. mutans* is a promising approach towards developing anti-caries drugs.

Phenolic compounds derived from Galla chinensis, *Magnolia officinalis*, and green tea have been extensively utilized in studies focused on dental caries prevention and control [76–78]. Phenolic compounds are secondary metabolites characterized by the presence of multiple phenolic hydroxyl groups, readily combining to form polyphenols or phenolic acids such as catechins and tannins. Their antibacterial effect primarily involves inducing the denaturation of pellicle proteins and bacterial cell lysis (Figure 6A) [79]. Additionally, polyphenols contribute to addressing periodontitis, halitosis, and oral cancer (Figure 6B) [80], making them key components in toothpaste formulations, mouthwash solutions, and chewing gum products (Figure 6C) [80]. Furthermore, phenolic compounds possess antioxidant and anti-inflammatory properties, rendering them essential constituents of numerous traditional Chinese medicines that exert significant pharmacological effects [81].

The therapeutic potential of honokiol has been utilized for generations in the traditional herbal treatments of China, Japan, and Korea [82]. In caries research, it has been demonstrated that the high permeability of honokiol exerts bactericidal effects on *S. mutans* biofilms [83]. Ren et al. investigated the specific mechanism underlying their resistance against *S. mutans* and discovered that honokiol, a Gtf inhibitor, effectively impeded biofilm formation and EPS accumulation. Furthermore, it exhibited inhibitory effects on the down-regulation of the lactate dehydrogenase gene in *S. mutans*, resulting in reduced lactic acid production and tooth demineralization [82].

Galla chinensis extract (GCE), obtained from leaf galls induced by parasitic aphids, primarily comprises hydrolyzable tannins such as gallotannin and GA [84]. The growth-inhibiting and metabolic effects of GCE on dental caries pathogens, along with its capacity to promote enamel remineralization and prevent demineralization, have been substantiated by extensive *in vitro* and *in vivo* experimentation [85, 86]. These advantageous properties can be attributed to GCE's interference with bacterial physiological processes and suppression of Gtfs activity [87]. However, the inefficacy of GCE against diverse biofilms under alkaline conditions underscores the optimal pH for applying GCE solutions as an anticariogenic agent to be 5.5 [88]. Nonetheless, it is important to note that a lower pH level may potentially exacerbate enamel demineralization, thus limiting the application of GCE due to this property.

The global consumption of tea is extensive, leading to variations in its polyphenol composition and content as a result of diverse processing methods. Notably, green tea contains active constituents such as catechins including gallocatechin and epigallocatechin-3-gallate (EGCG) [89]. The inhibitory effect of EGCG on the growth and viability of *S. mutans* was observed only within the concentration range of mg/mL, while its ability to inhibit *in vitro* biofilm formation occurred at a minimum inhibitory concentration level of 15.6 μg/mL [90]. These findings suggest that one mechanism underlying the antimicrobial activity of EGCG contributes to the inhibition of biofilm formation, which was further confirmed by Real-time PCR analysis, which demonstrated its ability to suppress Gtfs genes [91]. Therefore, though the polyphenol concentration in the oral cavity cannot be consistently maintained at a high level following green tea consumption, it remains sufficient to

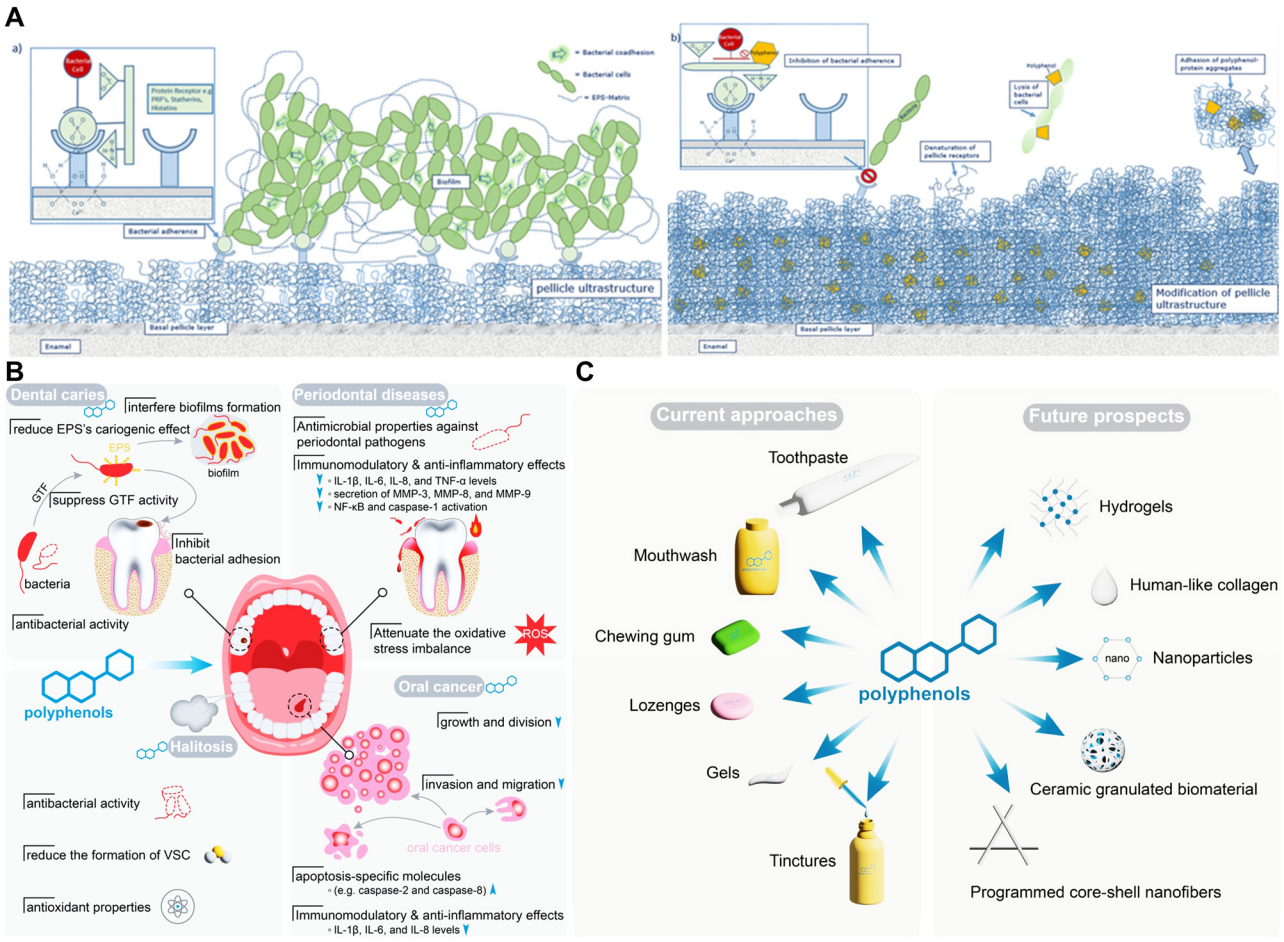

Figure 6: The antimicrobial mechanisms and applications of polyphenols. (A) Antimicrobial mechanisms of polyphenols (image source: Flemming et al. [79] with permission). (B) Polyphenols in dental caries, periodontal diseases, halitosis, and oral cancers [80]. (C) Current approaches and prospects of polyphenols-based oral health (image source: Guo et al. [80] with permission).

effectively inhibit biofilm formation. This finding has been confirmed by randomized clinical studies [92]. Overall, these findings underscore the potential of phenolic compounds, particularly those derived from natural sources, as promising agents for preventing and controlling dental caries. Their multifaceted properties make them valuable candidates for oral care products and traditional medicine formulations.

In summary, effective management of plaque biofilms is crucial for preventing dental caries. Strategies aimed at disrupting biofilm formation and targeting cariogenic bacteria constitute the fundamental approach in the prevention and control of caries. However, solely relying on antibacterial treatment while overlooking the repair of the defective tissue is insufficient for preserving the integrity and functionality of the tooth. In the subsequent section, we delve into the research progress on remineralization, with demineralization as a pivotal clinical manifestation of caries.

Remineralization: an efficient strategy for dental caries management

Enamel, an acellular tissue, comprises 96 %–97 % of its weight as hydroxyapatite (HAP), rendering it the hardest substance within the human body [93]. At the ultrastructural level, enamel consists of long enamel rods, serving as its fundamental structural units and extending from the enamel-dentinal junction to the enamel surface. These rods have an average diameter of 4–5 μm, each composed of meticulously arranged HAP crystals aligned parallel along the C-axis [94]. Nevertheless, around 10 % of PO_4^{3-} within these crystals undergo substitution with carbonate ions CO_3^{2-}, causing a rotational shift of approximately 40°–60° in the crystal orientation within the interprismatic areas [95], resulting in structural anomalies within the enamel crystal lattice [96].

The interstitium of enamel rods is permeable with organic matter and water, providing a diffusion pathway for small molecules and ions [97]. The intricate crystal structure of enamel makes it susceptible to dissolution in acidic solutions. Bacteria within dental plaque metabolize carbohydrates on the tooth surface, leading to the production of organic acids that readily diffuse in all directions [98]. Upon contact of an organic acid with the surface of a susceptible mineral crystal, the dissolution of calcium and phosphate within the mineral occurs in the surrounding aqueous phase between these crystals, initiating demineralization [99]. Undoubtedly, the human body employs various mechanisms to counteract or impede demineralization, including saliva buffering as well as the provision of calcium and phosphate to facilitate remineralization [7]. However, in the face of persistent bacterial acidogenic assault, dental caries eventually manifests in diverse forms and locations within the oral cavity. Therefore, the reversibility of the mineral loss process can be achieved through robust interventions in remineralization, or at least its prevention.

The biomineralization process of enamel and dentin

To achieve the remineralization of hard dental tissues, it is crucial to understand the intricate natural mineralization processes of enamel and dentin. Despite the absence of cellular components in mature enamel tissue, its formation remains a sophisticated cascade of events meticulously regulated by the secretion of protein by cells [100]. Enamel formation occurs within a confined extracellular space between dentin and ameloblasts [95], where the secretion of an extracellular matrix rich in amelogenin takes place [101]. This matrix undergoes self-assembly to establish structural framework within mineralized environment. The aggregation of mineral ions and clusters results in the formation of amorphous calcium phosphate (ACP), which nucleates at the interface between organic and inorganic components under the regulation of the organic matrix. Subsequently, it undergoes further modulation by the organic matrix to develop into HAP crystals with distinct structure and morphology. During enamel maturation, proteinases degrade proteins that are adsorbed between the crystals, which facilitates their thickening and fusion [100]. Eventually, a majority of the organic matrix in enamel is replaced by inorganic minerals. In contrast to enamel, dentin is a porous, fluid-filled mineralized tissue consisting of approximately 70 % minerals, 20 % organic matter, and 10 % water by weight [102]. During dentin development, differentiated dentinoblasts meticulously secrete the dentin matrix [103]. This formation process, essentially the precipitation of inorganic substances onto an organic matrix, involves odontoblasts secreting collagen and synthesizing phosphorylated proteins. These proteins facilitate the linkage of collagen fibrils with Ca^{2+}, which, in combination with PO_4^{3-}, initiates and structures the nucleation process following the arrangement of the collagen fibrils [104]. In other words, the formation of distinctive hierarchical structures in biominerals is governed by the nucleation, growth, and aggregation of inorganic substances at the organic-inorganic interface, under the meticulous regulation of organic molecular assemblies [105, 106].

Although current technology is still far from achieving the reconstruction of the natural enamel and dentin structure, researchers persist in exploring the process of natural mineralization and drawing inspiration from it to optimize this objective. Materials for remineralization should possess biocompatibility, enabling sufficient release or absorption of mineral ions from the microenvironment. However, due to the limited mineral content in saliva, additional mineral supplementation is often used to enhance the rate of remineralization. As a precursor to HAP, the direct ACP delivery technology has emerged as a promising strategy for enhancing the efficacy of dental caries remineralization, which has received considerable attention among researchers. Figure 7 illustrates the schematic representation of remineralization under the concept of direct ACP delivery [107]. The presence of ACP and its subsequent oriented arrangement are consistent with the natural enamel mineralization process. Moreover, the newly formed enamel layer should exhibit a tightly bonded connection with the original enamel while maximizing restoration of its structural hierarchy and mechanical properties. It is essential to emphasize that remineralized enamel needs to exhibit a crystalline restoration, promoting mineral gains within the lesion rather than simply forming a solid deposit on the original enamel surface [108]. The following section presents a systematic explanation of remineralized materials obtained from recent research.

Advances in the study of remineralized materials

Calcium phosphate system

The presence of mineral ions is essential for the progression of mineralization, and the inclusion of additional Ca^{2+} and PO_4^{3-} proves advantageous in expediting the process of mineralization under conditions of insufficient salivary secretion, while also enhancing fluoride-mediated

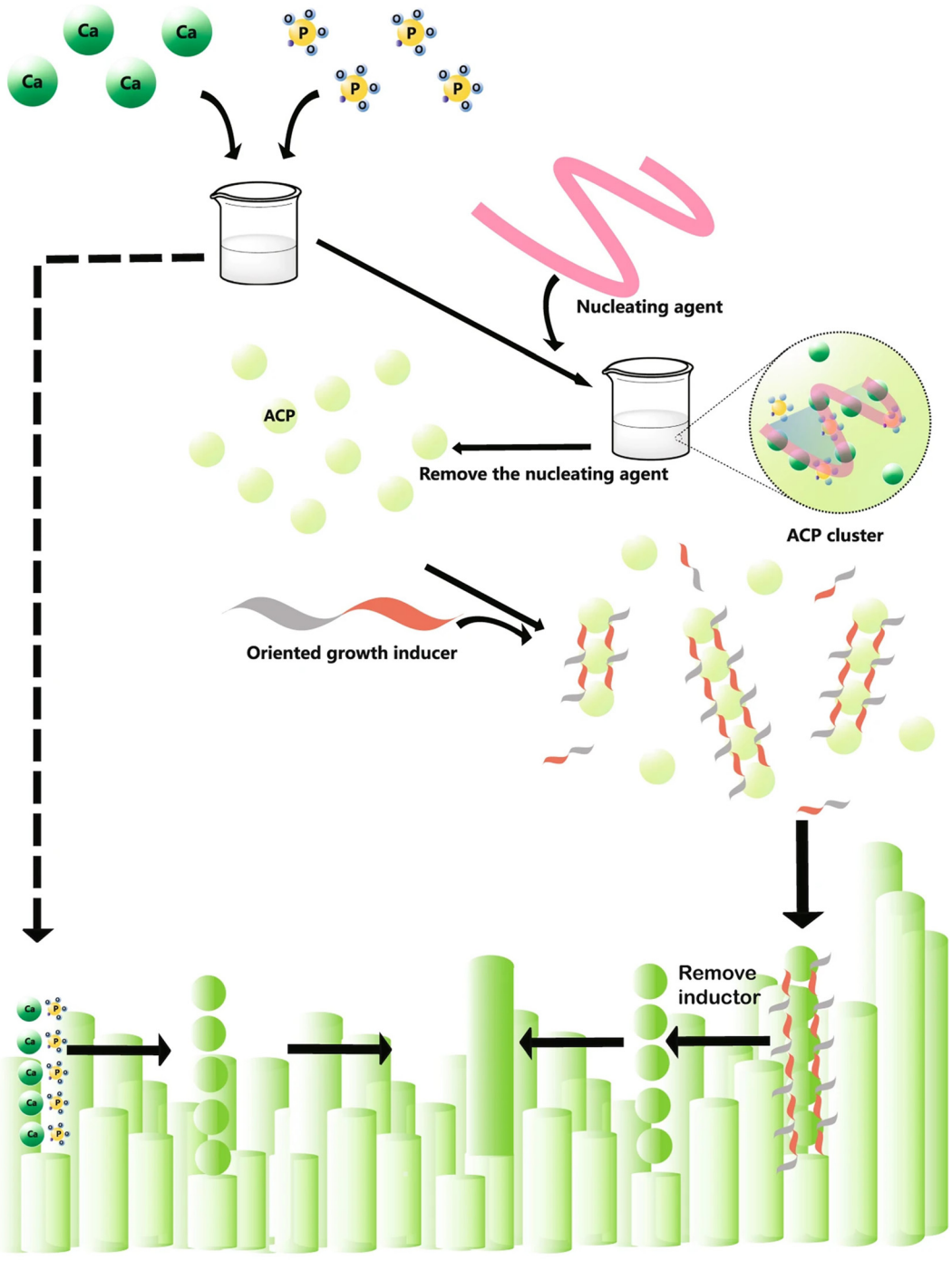

Figure 7: A schematic model of the formation of ACP and transform into enamel-like crystals for biomineralization (image source: Wang et al. [107] with permission).

remineralization [109]. The rationale for employing nano-hydroxyapatite (NHAP) in achieving remineralization is substantiated by the predominant constituents of enamel minerals. NHAP demonstrates a structure and chemical formula comparable to that of enamel crystals, while its nanoscale dimensions confer enhanced bioactivity and heightened surface energy, facilitating robust binding with the enamel surface [110]. The incorporation of NHAP into toothpaste formulations is a common practice for the prevention of dental caries [111]. Moreover, the utilization of this toothpaste after orthodontic treatment has been demonstrated to effectively alleviate the roughness and

sensitivity associated with post-debonding tooth surfaces [112]. While the mineralization process described adheres to the classical theory of crystal formation through ion deposition, it fails to consider the involvement of other elements in enamel development [113] and is no longer regarded as the prevailing paradigm in mineralization theory.

The uniqueness of ACP in remineralization has been elucidated in the preceding chapter. In addition, ACP demonstrates a significantly higher release of Ca^{2+} and PO_4^{3-} compared to other calcium phosphate systems, including HAP, due to its exceptional solubility as the most soluble calcium phosphate phase [114]. However, ACP is thermodynamically unstable and susceptible to transformation into more stable crystalline phases such as octacalcium phosphate and HAP. Therefore, prior stabilization is necessary before application, which is commonly achieved through pairing with various stabilizers and includes casein phosphopeptide-amorphous calcium phosphate (CPP-ACP). Casein, the primary phosphoprotein found in milk, predominantly functions as a calcium phosphate-stabilized micellar complex. The excellent biocompatibility of CPP-ACP makes it a commonly used principal active ingredient in toothpastes for the management of caries and desensitization purposes. This also exemplifies the direct ACP delivery technology. It exerts a long-lasting remineralizing effect on early carious lesions [115, 116]. The clinical applications of CPP-ACP, however, are limited due to allergic reactions in certain populations, thus hindering further advancements in its usage.

ACP mineralized systems, which are typically in liquid form, pose challenges for clinical application due to their state. One proposed solution is integrating ACP particles into various dental resins, a concept introduced in the early 20th century [117]. However the mechanical properties of ACP composites are relatively inferior, with their flexural strength being approximately half that of unfilled resins, rendering them unsuitable for use as dental filling materials [118]. Xu et al. developed nanoscale amorphous calcium phosphate (NACP) composites, which exhibited comparable release of Ca^{2+} and PO_4^{3-} to previous CaP composites at a 20 % NACP content, while demonstrating at least twice the strength of previous ACP composites [119]. This superior performance can be attributed to the higher specific surface area of NACP compared to ACP, enabling enhanced release of Ca^{2+} and PO_4^{3-} even at low filler levels, as well as providing additional space for glass fillers to achieve exceptional mechanical properties. The composite, containing 40 % NACP, is capable of rapidly elevating the pH level of its surroundings from 4.0 to 5.7 in 10 min, effectively mitigating mineral degradation caused by acidity [120, 121]. What's more, to achieve long-term remineralization, Zhang et al. developed a rechargeable NACP composite that incorporates pyromellitic glycerol dimethacrylate capable of chelating with external Ca^{2+}, which can facilitate both the charging and re-release of mineral ions [122]. However, the practical clinical applications should consider the pertinent biosafety concerns.

Amelogenin and its analogs

Amelogenin constitutes more than 90 % of the enamel matrix and is believed to play a crucial role in regulating crystal growth and directing alignment during the process of enamel biomineralization [101]. Amelogenin protein is characterized by its relatively hydrophobic nature and consists of three distinct structural domains: a tyrosine-rich N-terminal domain with pronounced hydrophobicity that facilitates intermolecular interactions, a C-terminal domain rich in hydrophilic residues capable of establishing multiple charged interactions with the mineral surface, and a central region abundant in hydrophobic proline [123, 124]. Amelogenin demonstrates conformational versatility in diverse environments and upon interaction with various molecules. In the presence of Ca^{2+} and PO_4^{3-}, amelogenin undergoes self-assembly into nanospheres, exhibiting a propensity for further extension into nanochains and nanofibers [125]. This hierarchical assembly confers advantages in stabilizing ACP and regulating crystal arrangement. Numerous studies have shown that recombinant human amelogenin possesses the capability to effectively synthesize fibrous apatite crystals from calcium phosphate saturated solutions. This phenomenon can be attributed to the contrasting charges exhibited by amelogenin and apatite [126]. In addition, the combination of amelogenin and fluoride can induce the formation of oriented bundles in needle-like fluorapatite [127].

Given the challenges associated with synthesizing full-length amelogenin and the potential immunogenicity of non-functional amelogenin sequences, recent research has been dedicated to developing various analogues of amelogenin for mineralization reproduction. Therefore, a comprehensive understanding of the specific structure and physiological function of amelogenin is imperative. The conservation level is high for both the hydrophilic C-terminus and hydrophobic N-terminus of amelogenin. However, unlike the recombinant full-length amelogenin, amelogenin with a truncated mutation in its hydrophilic C-terminal region showed an incapability to self-assemble into nanochains or induce parallel bundle formation of apatite [128]. Subsequently, upon deletion of peptide 14P2 from the N-terminus region, it was observed that the formation of nanoribbons was impeded even in the presence of calcium and phosphorus ions [129]. Therefore, the

N-terminal domain plays a pivotal role in facilitating the self-assembly of amelogenin into amyloid-like aggregates through β-sheet stacking and providing a structural template for the growth of HAP crystals. Conversely, the C-terminal domain is responsible for promoting parallel alignment among these crystals [130].

In recent years, the technique of selective splicing has been utilized to synthesize truncated peptide fragments derived from major functional segments of amelogenin, such as tyrosine-rich amelogenin peptide (TRAP) and leucine-rich amelogenin peptide (LRAP) [127, 131]. Notably, LRAP demonstrates the capacity to substitute for the full-length amelogenin, thereby inducing the transformation of disordered calcium phosphates into organized crystals and facilitating the formation of enamel-like structures [132, 133]. However, extracting and purifying amelogenin and non-amelogenin, natural proteins presents challenges due to their susceptibility to denaturation and the risk of potential contamination [134].

In order to overcome the aforementioned limitation, Fang et al. devised an innovative approach where they genetically modified LRAP by incorporating a 3-tyrosine peptide domain at its N-terminus, resulting in a novel polypeptide called mLARP [135]. This fusion protein combines the advantageous features of both TRAP and LARP. Additionally, mLARP was successfully combined with non-amelogenin proteins to create enamel matrix proteins that could significantly enhance the biomineralization process. The outcomes of mineralization experiments clearly demonstrated that the regenerated enamel displayed prismatic and interprismatic structures similar to those observed in natural enamel, thus offering a promising strategy for promoting HAP crystal growth. Mukherjee et al. engineered peptides P26 and P32 by manipulating and fusing distinct functional domains within amelogenin [136]. Both peptides demonstrated the ability to generate HAP layers *in situ* with comparable crystal morphology and mechanical properties. However, P32 induced larger structural dimensions of peptide assemblies and crystal size *in vitro* compared to P26, which could be attributed to its two additional polyproline repeat motifs. This suggests that an increased number of polyproline repeat motifs could significantly alter the size of HAP crystals. Additionally, P26 and P32 exhibitrf significant potential in facilitating dentin remineralization [137]. Ding et al. successfully intercepted Gln-Pro-X, a highly conserved sequence in amelogenin, and developed QP5 peptide consisting of five repeats of Gln-Pro-X along with the C-terminus [138]. QP5 demonstrates robust affinity towards HAP, which is crucial for promoting enamel remineralization (Figure 8A) [124]. It effectively stimulates the formation of well-organized bundles of HAP and enhances the efficiency of fluoride-induced remineralization in its presence. By co-loading QP5 with bioactive glass within a hydrogel matrix, Ca^{2+} and PO_4^{3-} are supplied to QP5 by the bioactive glass, resulting in the formation of a remineralized layer that can exhibite excellent resistance against both erosion and abrasion [139]. However, the synthesis of peptides is consistently costly irrespective of their length. Hence, there exists a necessity to discover a straightforward and cost-effective approach to imitate the function of amelogenin.

It has been observed that lysozyme (lyso), when catalyzed by a reducing agent that disrupts disulfide bonds, can undergo a phase transition and generate phase-transforming lysozyme (PTL) with numerous β-sheet structures [140]. PTL effectively emulates the amyloid-like structure present in the N-terminal end of amelogenin. Based on this, Wang et al. combined PTL with C-terminal synthetic peptides (C-AMG matrix), resulting in engineered materials capable of replicating both *in vivo* and *in vitro* growth of ordered HAP crystals (Figure 8B) [130]. Moreover, the aligned structure of these materials closely resembles natural enamel.

In conclusion, the strategy of emulating the function and structure of amelogenin for enamel tissue regeneration from a developmental promising data. However, the steep cost associated with peptides may pose a significant constraint and hinder their broader application in research.

Polymer system

In recent years, extensive research has been conducted to design and develop polymers with protein-like functionalities aimed at preventing and treating early enamel caries. These polymers aim to achieve enamel remineralization by mimicking the stabilizing effect of amelogenin proteins on ACP *in vivo*. Polyacrylic acid (PAA), a superabsorbent polymer known for its non-cytotoxic and biocompatible nature, demonstrates carboxylic acid activity [141]. Qi et al. found a positive correlation between the concentration of PAA and its ability to inhibit the aggregation of ACP prenucleation clusters at the initial crystallization stage [142]. Conversely, reducing PAA concentration increases the kinetics of crystallization from ACP to nanoapatite. Liu et al. introduced a biomimetic mineralization strategy using polyphosphate, where sodium trimetaphosphate (STMP) was used alongside PAA to stabilize ACP [143]. The anionic surfactant STMP phosphorylates PAA, resulting in the production of highly phosphorylated PAA that effectively remineralizes artificial carious lesions, particularly in areas lacking seed crystallites. Furthermore, polymers such as polyaspartic acid, polyglutamic acid, polyacrylamide hydrochloride, polylysine,

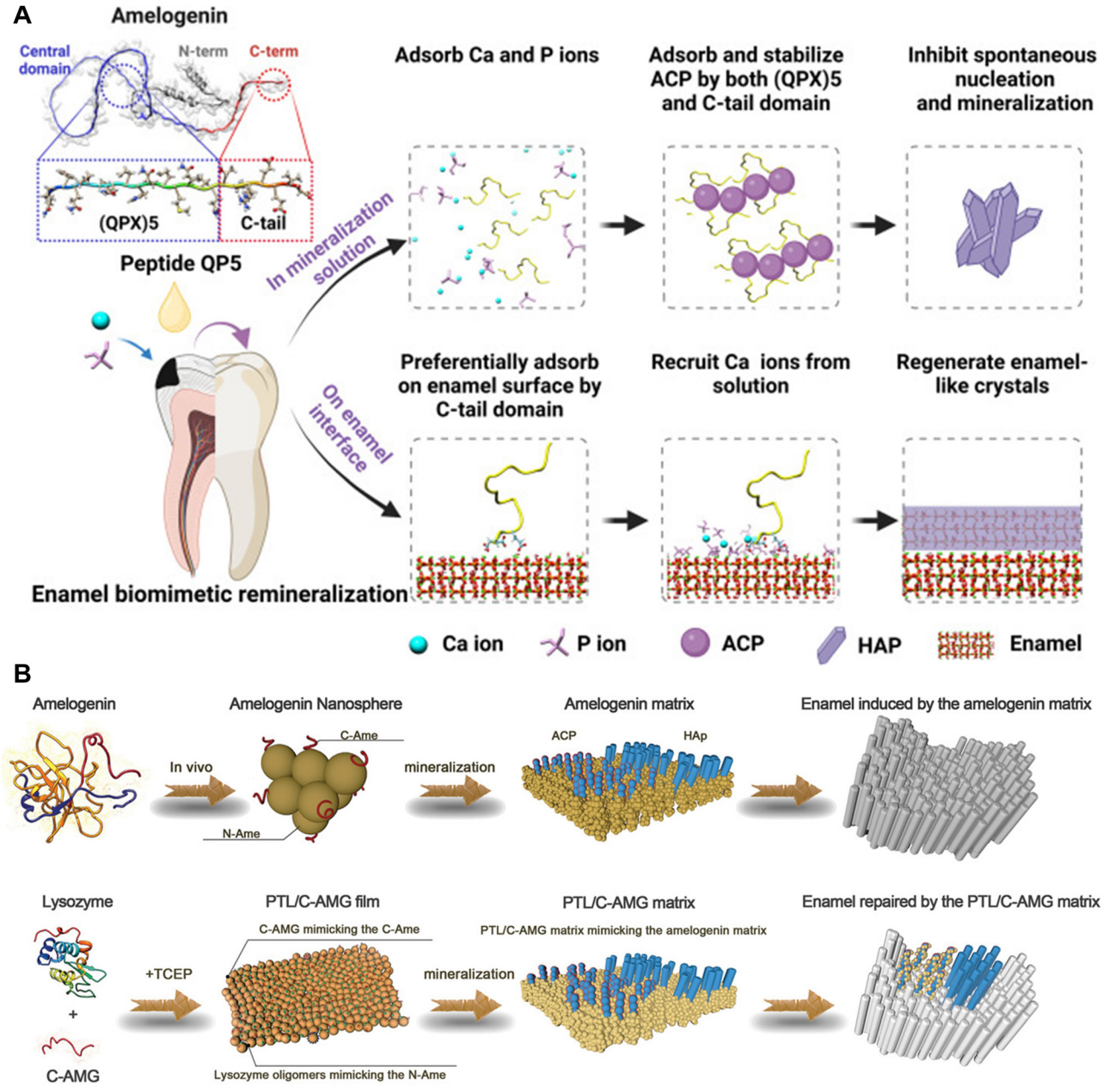

Figure 8: Schematic demonstration of (A) amelogenin-derived peptide QP5 for promoting enamel biomimetic remineralization (image source: Hu et al. [124] with permission); (B) amelogenin and the PTL/C-AMG matrix to mediate the transition from ACP to HAP on enamel for *in situ* remineralization (image source: Wang et al. [130] with permission).

and carboxymethyl chitosan exhibit a close resemblance to the mineralization mechanism of PAA [144–146]. These polymers possess the ability to facilitate biomimetic restoration of enamel by stabilizing ACP and promoting its transformation into crystalline structures.

The utilization of the carboxyl terminus of branched polymers has demonstrated promising outcomes in attracting Ca^{2+} ions, however, the mineral content of remineralized layers typically remains suboptimal due to the limited availability of carboxyl groups [147]. For effective biomineralization control, ACP stabilizers, akin to NCPs, should have a well-defined steric structure. Poly (amidoamines) (PAMAMs) are notable examples, characterized by their high branching, multiple reactive terminal groups, specific dimensions, forms, and internal cavities. PAMAMs function as effective nucleation templates, chelating and binding Ca^{2+} and PO_4^{3-} electrostatically, securing nano-sized ACP particles, and enhancing

remineralization [148, 149]. The size and shape of HAP can be modulated in a concentration-dependent manner by modifying the surface groups of PAMAMs [150]. HAP nanorods induced by carboxylic-terminated PAMAM (PAMAM-COOH) and hydroxyl-terminated PAMAM (PAMAM-OH) exhibit distinct shapes and lengths, with PAMAM-COOH resulting in more elongated rods compared to PAMAM-OH due to variations in nucleation site localization [151]. Fan et al. conducted a comparative study on the *in vitro* remineralization capacities of PAMAM-OH, PAMAM-COOH, and amine-terminated PAMAM (PAMAM-NH_2) [152]. The results revealed that among them PAMAM-NH_2 exhibited the highest remineralization capacity while PAMAM-OH demonstrated the lowest capacity. This difference can be attributed to their distinctive surface charges. Precisely, enamel surfaces are known for their negative charge; however, PAMAM-NH_2 carries a positive charge, PAMAM-COOH exhibits a negative charge, while PAMAM-OH remains electrically neutral. As a result of electrostatic attraction, the binding affinity between PAMAM-NH_2 and the enamel surface is significantly enhanced. Therefore, it is crucial to enhance the affinity between remineralized material and enamel in order to facilitate the formation of a mineralized layer. To accomplish this, Wu et al. incorporated alendronate (ALN) into PAMAM-COOH, which facilitated ligand exchange with the HAP surface and significantly improved the structure and mechanical properties of the newly generated enamel layer (Figure 9A) [153]. In view of the abundance of phosphate groups in amelogenin that stabilize ACP, Chen et al. synthesized PAMAM-PO_3H_2, a phosphate-terminated PAMAM derivative, by incorporating phosphate groups into PAMAM (Figure 9B) [154]. The strong affinity between the phosphate group and Ca^{2+} facilitated the formation of an 11.23 μm-thick enamel remineralization layer, whereas PAMAM-COOH only achieved a thickness of 6.02 μm. Moreover, *in vivo* experiments demonstrated promising remineralization effects of PAMAM-PO_3H_2.

Previous studies have predominantly focused on stabilizing ACP or utilizing amelogenin and its analogues to interact with mineral ions, aiming to achieve enamel-like crystal formation. However, these approaches still fall short in accurately replicating the columnar structure of natural enamel and fully restoring its mechanical properties to normal levels. Moreover, it is imperative not to overlook the nucleation of non-amelogenins and the degradation of amelogenin by proteinases [100]. In the enamel remineralization system developed by Ye et al., PTL functioned as a mimic of amelogenin, while carboxymethyl chitosan and hypochlorite served as imitations of non-amelogenins and proteinases, respectively (Figure 9C) [155]. Through synchronous self-assembly and mineralization, the regenerated mineral crystals exhibites an oriented structure and mechanical properties akin to natural enamel. Therefore, it is imperative to further investigate and focus on restoring the entire *in vitro* biomineralization process for achieving rapid and effective repair of demineralized enamel.

Infiltration technology: enhancing dental conservation

The current primary approach for caries treatment is filling therapy. However, as an invasive procedure, it compromises the integrity of the tooth structure and perpetuates a cycle of "treatment-retreatment", commonly referred to as a "death spiral". Fillings can potentially cause more harm than benefit, particularly in the early stages of caries. Existing research has demonstrated that non-invasive methods such as oral health education, dietary guidance, and topical fluoride interventions can effectively slow down or even remineralize early-stage caries. These approaches prevent dental tissue destruction and alleviate patient discomfort. Nevertheless, when caries progresses to deeper enamel or superficial dentin layers without cavity formation, the efficacy of remineralization becomes uncertain. Moreover, if patients do not cooperate with treatment protocols, remineralization attempts often prove unsuccessful. Consequently, there is a pressing need for less painful caries treatments that can preserve greater amounts of tooth tissue. Minimally invasive treatment options encompass the utilization of polyurethane foils, low viscosity composite resins, in addition to dental adhesives and sealants [156–158]. Nevertheless, their efficacy is constrained by the shallow infiltration of resin into the demineralized enamel pores on tooth surfaces [159]. New requirements are subsequently subjected to these dental materials: permeability.

In dentistry, infiltration technology is extensively employed for various purposes such as the treatment of dentin hypersensitivity with desensitizing agents [160]. To achieve a long-lasting blocking effect on dentin tubules, these agents must possess excellent permeability in order to deeply penetrate, seal the tubules, and effectively insulate them from external stimuli. Similarly, adhesives and resin monomers need to infiltrate demineralized pores for long-term stability without detachment [161]. Furthermore, root canal irrigants require good permeability in order to eliminate bacteria that invade deep within the dentin tubules and ensure a successful prognosis for root canal treatment [162]. This purpose is served by combining sodium hypochlorite with surfactant [163].

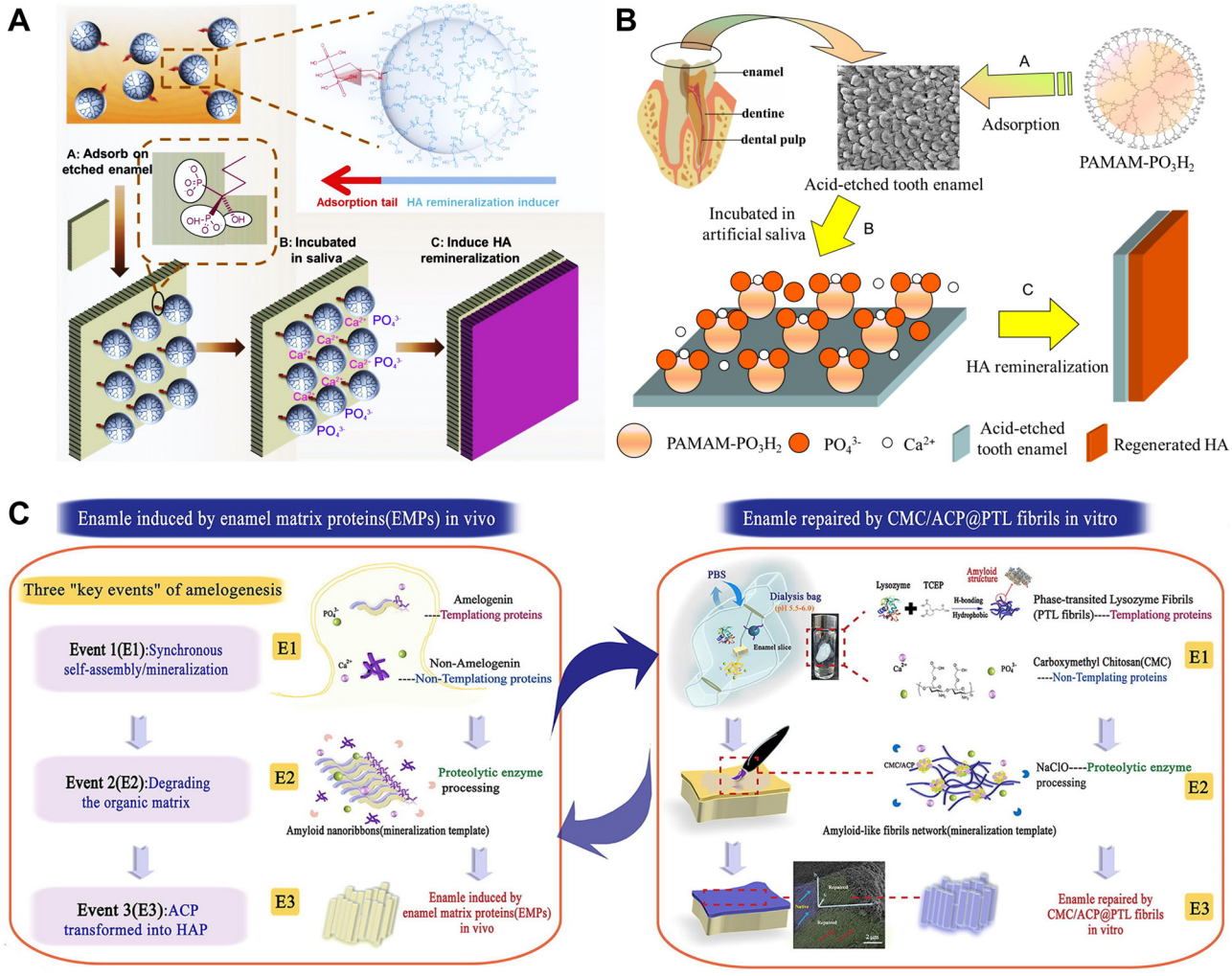

Figure 9: Schematic demonstration of (A) the specific adsorption of ALN–PAMAM–COOH on the surface of tooth enamel and the subsequent *in situ* remineralization of HAP (image source: Wu et al. [153] with permission); (B) the adsorption of PAMAM-PO_3H_2 on the surface of tooth enamel and the subsequent *in situ* remineralization of HAP (image source: Chen et al. [154] with permission); and (C) amyloid-like matrix of PTL fibrils (mimicking the templating protein), CMC/ACP (mimicking the non-templating protein) and NaClO (mimicking the proteinase) accomplish the three "key events" of biomineralization, *de novo* remineralization enamel *in vitro* (image source: Ye et al. [155] with permission).

The utilization of infiltration techniques is also essential in the management of dental caries. Therefore, a novel technique called caries infiltration has been developed as a minimally invasive treatment strategy to establish a protective barrier within these compromised porous structures through diversion and obstruction of acid diffusion routes and mineral dissolution processes to impede further decay [164]. The current application of caries infiltration involves the utilization of methacrylic resins with high permeability coefficients. *In vivo* and *in vitro* experiments have substantiated the efficacy of resin infiltrants in effectively impeding caries progression [165, 166]. Following polymerization, the infiltrated resin fills the original pores, thereby preventing enamel surface collapse and cavity formation [167]. Compared to conventional adhesives, resin infiltrants demonstrate rapid capillary penetration, low viscosity, a reduced contact angle with enamel, and enhanced surface tension [168], which result in deeper penetration and infiltration within the lesion body. The clinical procedure of resin infiltration is straightforward and well-received by both practitioners and patients.

The extensive development of infiltrating resins can be attributed to their exceptional ability to penetrate. Previous studies have confirmed that the incorporation of ethanol and polyethylene glycol can enhance the penetration coefficient [164, 169], facilitating rapid resin ingress into the lesion and permeation through its pores via capillary action, thereby improving infiltration depth. However, this may

compromise the mechanical properties of the resin layer. Moreover, due to the absence of inorganic fillers in infiltrating resins, they are particularly susceptible to water sorption and enzymatic hydrolysis by salivary and bacteria-produced enzymes, raising concerns regarding long-term stability [170]. Therefore, researchers are actively focused on enhancing the properties of infiltrating resins. Compared to micron-scale materials, nanometer-scale materials can penetrate deeper into the fissures of the tooth surface, leading to a more effective and tighter seal of these fissures. Dai et al. utilized a spray-drying technique to prepare NACP and incorporated it into the infiltrating resin [171], thus presenting a promising approach for caries management by combining remineralization with infiltration technology. In addition to NACP, other remineralization components such as CPP-ACP with fluoride, bioactive glass, and calcium coacervates can be added to infiltrating resins to enhance their mechanical property and long-term efficacy [172–174]. Additionally, infiltrating resins were formulated with antimicrobial properties in mind, and the incorporation of quaternary ammonium monomers, ZnO, and AgNPs significantly augmented their antimicrobial efficacy while maintaining penetration [175, 176]. By employing the synthetic bioderived monomer bis(methacrylate) isosorbide and the zwitterionic compound 2-methacryloyloxyethyl phosphorylcholine as starting materials, Yang et al. successfully developed a novel infiltrant IBMA devoid of triethylene glycol dimethacrylate [177]. This newly formulated infiltrating resin demonstrates enhanced biocompatibility in comparison to conventional infiltrating resins, alongside exceptional hydrolysis resistance. The multifunctional properties exhibited by novel infiltrants hold immense promise for their potential applications in caries management, rendering it highly significant from a clinical perspective.

However, due to the distinct pathological disparities between enamel and dentin caries, the sealing efficacy in dentin is 82 % for resin infiltrants (99.1 % for enamel caries) [178]. Furthermore, microleakage may occur as a result of polymerization-induced contraction stress caused by the resin infiltrant, while the roughened tooth surface resulting from infiltration can also serve as a breeding ground for biofilm formation [168]. Therefore, an integrated and multifaceted approach encompassing infiltration, remineralization, and antimicrobial properties represents an optimal strategy to comprehensively address the aforementioned inquiries. Only through such a systematic amalgamation of scientifically standardized treatment measures can we genuinely achieve the objective of preventing and arresting caries progression while maintaining excellent oral health.

Caries control material based on IDC concept

After conducting the aforementioned analysis, it is imperative for an ideal caries control material to possess a high level of efficacy in biofilm control and homeostasis management to effectively control caries at its source. Furthermore, it should exhibit rapid and efficient mineralization capabilities, enabling it to adequately fill micropores or form a remineralization layer within larger cavities. The newly formed remineralized layer should grow along the periphery of the original residual crystals or demonstrate a strong affinity towards dental hard tissue while closely resembling its mechanical properties, so as to prevent microleakage. Thirdly, the material must possess exceptional penetration capabilities and can be applicable without requiring decay removal or extensive mechanical debridement, effectively halting caries progression with minimal trauma. The materials within the IDC framework may encompass composite materials achieved through physical blending or weak interactions between antimicrobial and remineralizing agents, as well as synthetic materials formed by chemically grafting a remineralizing agent onto an antimicrobial agent. Detailed descriptions are provided below.

Synthetic materials

Peptides

The absence of microbial resistance development in AMPs is a crucial characteristic that allows for the fusion of AMPs with remineralizing peptides, creating bifunctional peptides for both antimicrobial and remineralization purposes. Wang et al. successfully linked TD7, a functional peptide located at the C-terminal end of amelogenin, to the N-terminal end of GH12 (α-helical AMPs), which resulted in the formation of a bifunctional peptide called TDH19 [179]. To enhance its positive charge, glutamic acid and aspartic acid residues in TDH19 were substituted with glutamine and asparagine respectively, leading to the creation of TNH19. Furthermore, by replacing the asparagine residue in TNH19 with valine, TVH19 was generated to increase hydrophobicity. The comparison of the bacterial and remineralization capacities of the three bifunctional peptides revealed that TVH19 exhibited superior antimicrobial activity and induced the formation of optimal crystal morphology. These findings suggest that charge and global hydrophobicity are crucial structural parameters than can influence the efficacy of amphiphilic α-helical AMPs [180], with positive charge

promoting peptide interaction with microbial surfaces, while global hydrophobicity facilitates effective insertion into biofilms. These results provide novel insights for designing subsequent bifunctional peptides.

Zhou et al. chose to synthesize the bifunctional peptide Sp-H5 by incorporating histone 5 (H5), a salivary antimicrobial component, and grafting phosphoserine (Sp) onto its N-terminal end [181]. Importantly, in addition to its broad range of antibacterial and antifungal activities, H5 plays a vital role as a constituent of the acquired enamel pellicle and actively inhibits enamel demineralization [182]. The presence of Sp allows for binding to HAP and facilitates the attraction of free Ca^{2+} for nucleation and initiation of mineralization, which are commonly investigated in studies related to tooth and bone regeneration. The application of Sp-H5 on the tooth surface has been demonstrated to generate a novel bioactive tooth surface with antibiofouling and mineralizing properties. Through the presence of positively charged amino acid residues, Sp-H5 adheres to the enamel surface and attracts Ca^{2+} via negatively charged residues, thus initiating the process of enamel surface mineralization. Simultaneously, Sp-H5 exhibits bactericidal effects against planktonic *S. mutans* and protects enamel from acidic environments through electrostatic repulsion. Moreover, its user-friendly application allows for tight sealing of demineralized surfaces, effectively promoting *in situ* caries self-healing. However, subsequent investigations revealed that the long-term antimicrobial and remineralization capabilities of Sp-H5 were insufficient, which promoted further enhancements [183]. The SpSp (DPS) structural domain was incorporated to enhance the Ca^{2+} chelating capacity and subsequently grafted onto the C-terminus of P-113, which is the smallest antimicrobial fragment in H5. This resulted in the construction of P-113-DPS (Figure 10) [183]. Notably, P-113-DPS demonstrated superior adsorption ability, antibiofouling properties, demineralization inhibition, remineralization promotion, stability, and remineralization compared to Sp-H5. The incorporation of DPS not only facilitated increased attraction to Ca^{2+}, but also induced rapid nucleation and growth of hexagonal prismatic crystals. Furthermore, by localizing on bacterial surfaces and cross-linking with bacterial membrane phospholipids, P-113-DPS is effectively destructive against *S. mutans*. These findings highlight the potential of P-113-DPS in managing dental caries.

In addition to enamel caries, bifunctional peptides can also be valuable in the management of dentin caries. Niu et al. developed a bifunctional peptide called GA-KR12 [184], where GA serves as the functional group grafted onto the KR12 peptide derived from LL-37, which is the sole human cathelicidin variant. The antimicrobial efficacy of GA requires no further elaboration for its phenolic compound nature and pyrogallol moiety has been demonstrated to induce and expedite mineralization [185]. Treatment with GA-KR12 resulted in remineralization of the extrafibrillar portion of dentin and inhibition of *S. mutans* biofilm growth in artificial dentine caries models. However, intrafibrillar mineralization was not achieved possibly due to hinderance by a size exclusion mechanism. Overall, while enamel caries arrest and dentin caries arrest processes differ, they both require remineralization capacity and antimicrobial efficacy.

Nano-coatings

The effective sealing of pits and fissures on tooth surfaces is vital for preventing dental caries [186]. However, long-term microleakage may still occur due to inherent disparities between sealers and enamel composition. Henceforth, an enduring solution for dental caries necessitates sealers with remineralization capabilities alongside antimicrobial properties. PTL's diverse reactive groups including carboxyls, hydroxyls, and amines enable strong adhesion to various substrate surfaces. Capitalizing on this feature, Yang et al., enhanced PTL's hydrophilicity by grafting poly (ethylene glycol) (PEG) onto lyso while simultaneously reducing disulfide bonds through reductive means (Figure 11A) [187]. Consequently, forming lyso-PEG oligomeric nanoparticles measuring only 30 nm in aqueous solutions, which is one-10th the size compared to traditional resin-based sealants, facilitates deep penetration into pit-fissure structures. When a solid interface is present, lyso-PEG aggregates to form a seamless nano-film coating that acts as an adhesive surface for attracting Ca^{2+} and PO_4^{3-} from saliva. This promotes epitaxial growth of enamel without any marginal gaps between the newly mineralized layer and natural enamel. Consequently, this process successfully restores the mechanical properties of enamel while simultaneously inhibiting bacterial adhesion through cell wall perturbation, thus showing great potential for caries prevention.

In recent years, hydrophilic and antifouling PEG have gained increasing prominence in the field of biomedical applications. PEG acts as a brush-like barrier to effectively inhibit the nonspecific adsorption of bacteria, making it widely recognized as the "gold standard" for antibiofouling polymers [188]. Hou et al. utilized polyaspartic acid (PAsp) to mimic amelogenin's ability to induce biomineralization, capitalizing on the role of aspartic acid found in amelogenin in facilitating binding with HAP (Figure 11B) [189]. By combining PEG with PAsp, a multifunctional material possessing both antifouling and remineralization properties can be achieved. The PAsp-PEG coating effectively prevents

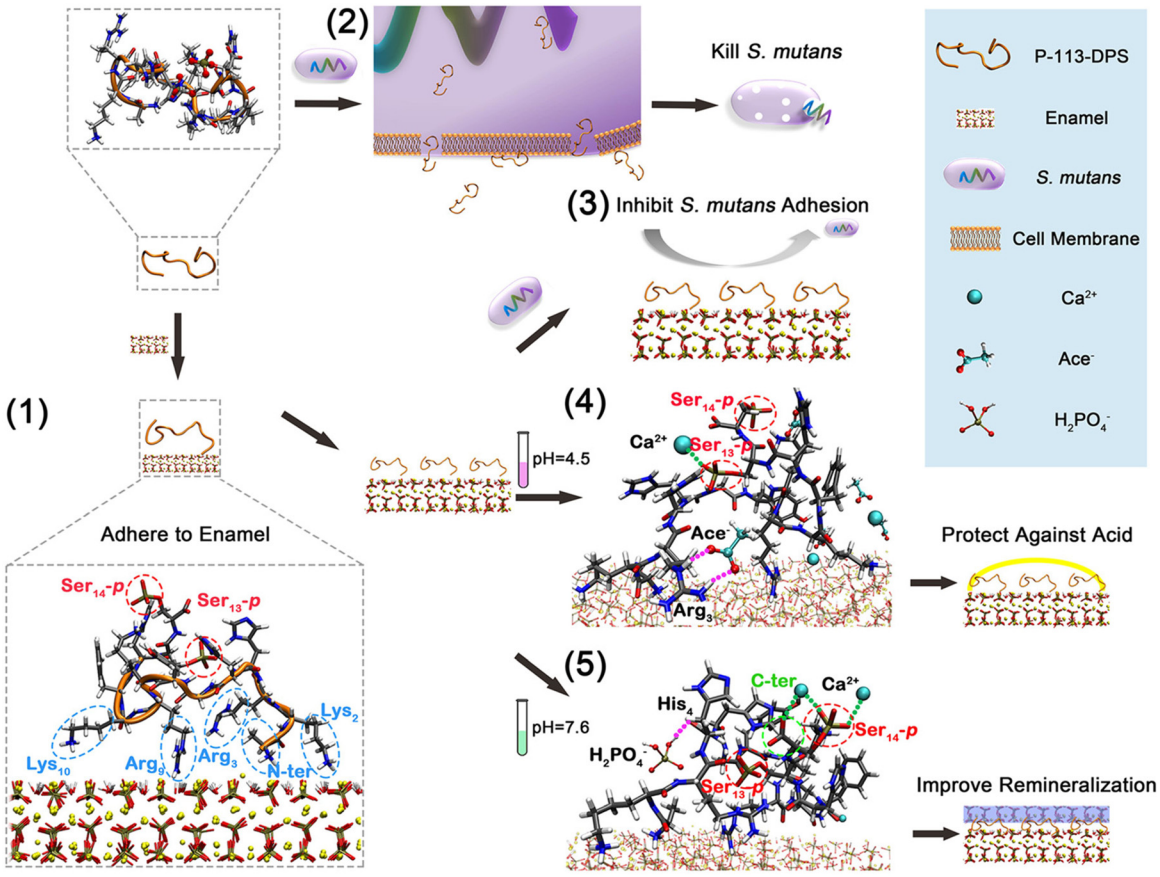

Figure 10: Schematic diagram of multiple functions of P-113-DPS in this study. (1) P-113-DPS adheres to the enamel surface via positively charged amino acids attracted to negatively charged $PO_4^{3-}$of HA. (2) P-113-DPS kills planktonic *Streptococcus mutans*. (3) Coating of P-113-DPS on enamel inhibits the adhesion of *S. mutans*. (4) Coating of P-113-DPS on enamel protects the enamel surface against demineralization. (5) Coating of P-113-DPS on enamel increases the thickness of the regenerated crystal layer. Ser13-p and Ser14-p are in the red circles. Carboxyl is in the green circle. Green dotted lines show the coordinate bond; the pink dotted lines show the hydrogen bond (image source: Zhou et al. [183] with permission).

bacterial adhesion on dental surfaces through hydration and steric hindrance effects, without inducing an inflammatory or immune response due to the absence of viable and non-viable bacteria. However, the limited availability of carboxyl groups in the coatings and their weak binding affinity to Ca^{2+} constrain their potential for remineralization. To address this issue, Chu et al. utilized ALN sodium for copolymer conjugating to optimize the material and provide an abundance of PO_4^{3-} groups (Figure 11C) [190]. The experimental results confirmed that compared to PAsp-PEG, PEG-PAsp-ALN demonstrated enhanced absorption capacity on the enamel surface, improved stability, and induced a thicker mineral layer, thereby achieving superior effects in caries prevention and control. Furthermore, taking inspiration from the intricate process of enamel formation and recognizing the significance of organic-inorganic interactions in mineral assembly, Wong et al. utilized a layer-by-layer deposition technique to precisely manipulate the crystallization process and facilitate the self-assembly of crystals [191]. Through the combination of graphene oxide, alginate, and chitosan, they successfully synthesized a macroscopic bioactive material that closely emulates enamel in terms of its chemical composition, mechanical properties, and crystal structure. The exceptional antibacterial adhesion property and outstanding biocompatibility demonstrated by this material offer innovative perspectives for synthesizing an enamel remineralization layer.

In addition to addressing the requirements for antimicrobial activity and remineralization, Xu et al. have also taken into consideration the aspect of anti-inflammation, as long-term plaque accumulation and demineralization can potentially trigger dentin hypersensitivity and gingivitis [192]. Turkish gall extract (TGE) has gained attention due to its multifaceted properties including anti-inflammatory, antimicrobial, and astringent effects [193]. Furthermore, it has been observed that TGE is capable of

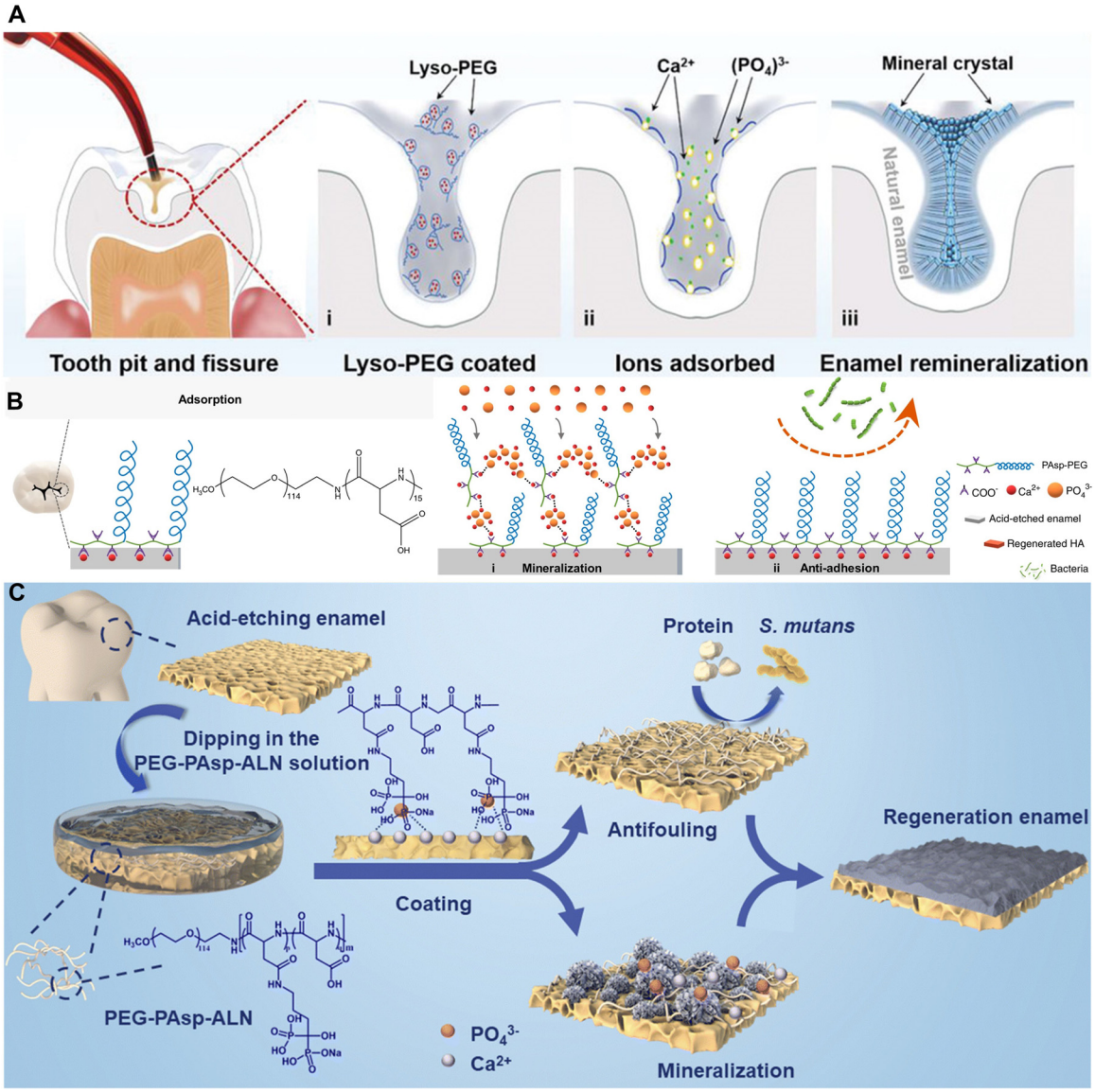

Figure 11: Nano-coatings based on IDC concept. (A) The scheme illustrates the rapid formation of lyso-PEG oligomer nanoparticle-based nanofilm coatings in the deep zone of pits and fissures, followed by ion adsorption from saliva and spontaneous remineralization toward the formation of enamel-like HAP structures in pits and fissures to achieve *in situ* biomimetic sealing (image source: Yang et al. [187] with permission). (B) The PAsp-PEG compound interacts with calcium ions on the acid-etched enamel surface, effectively chelating free calcium and phosphate ions in the solution to enhance mineralization, and forming a brush-like barrier on the enamel surface to inhibit bacterial adhesion (image source: Hou et al. [188] with permission). (C) Schematic illustration of PEG-PAsp-ALN block polymers to mediate enamel remineralization and resist adhesion of bacteria and proteins (image source: Chu et al. [189] with permission).

forming a thin film and generating precipitates on the tooth surface when exposed to artificial saliva. Subsequent *in vivo* and *in vitro* experiments have provided evidence for the potential of TGE in facilitating *in situ* self-healing [192]. The polyphenols in TGE possess multiple hydroxyl groups, demonstrating a strong affinity for the tooth surface. Upon interaction with TGE, a coating is formed on the tooth surface, resulting in the formation of a robust TGE-HAP complex that exhibits significant affinity towards Ca^{2+}. Moreover, it exerts concentration-dependent inhibition on the growth of *S. mutans*. The anti-inflammatory potential of TGE can also be attributed to its polyphenolic constituents that effectively mitigate inflammation by inhibiting the formation of hydrogen peroxide and superoxide anion O_2. Following 7 days of treatment with TGE rinsing, all gingivitis indicators in rats showed significant improvement, leading to an effective reduction in inflammatory factors IL-6 and IL-1β content and achieving a comprehensive anti-caries effect.

Composite materials

Using ACP as a mineral source

Direct delivery of ACP technology presents an effective and straightforward approach in restorative dentistry. However, due to its thermodynamic instability, ACP tends to convert into an apatite phase prior to use, necessitating combination with other constituents to maintain its efficacy and enhance its performance. The combination of EGCG and ACP by Dai et al. involved the utilization of EGCG's phenolic hydroxyl group to stabilize Ca^{2+} and inhibit their binding to phosphate ions, thereby effectively stabilizing ACP [194]. However, this chelation process requires a partial depletion of phenolic hydroxyl groups in EGCG, which may slightly compromise its antimicrobial activity. Furthermore, in a cariogenic acidic environment, the release of ACP from EGCG-ACP exceeded 80 % within 12 h, thereby raising concerns regarding its long-term remineralization efficacy. To enhance the availability of carboxyl groups and optimize antimicrobial properties, He et al. developed poly (carboxybetaine acrylamide) (PCBAA), a polyzwitterion utilized for the stabilization of ACP (Figure 12A) [195]. The inspiration for PCBAA is derived from carboxybetaine polymers, which are characterized by a high abundance of quaternary amino groups [196]. These cationic groups exhibit potent bactericidal properties in acidic environments and possess exceptional resistance to nonspecific protein adsorption, bacterial adherence, and biofilm formation due to electrostatically induced hydration. Upon the introduction of calcium ions into the PCBAA solution, they engage in electrostatic interactions with carboxyl groups. Following this, PO_4^{3-} adsorb onto and establish complexes with both quaternary ammonium groups and Ca^{2+}. This action reduces the saturation of mineral ions in solution, thereby enhancing the potential barrier for ACP crystallization and facilitating enamel remineralization. Additionally, the PCBAA/ACP composite possesses a smaller particle size, allowing for deeper penetration into dentin tubules and effective interfibrillar remineralization. Consequently, PCBAA/ACP exhibits significant potential in preventing and treating both dentin caries and enamel caries.

Using CaP as a mineral source

It is widely acknowledged that the primary goal of dentin remineralization lies in achieving intrafibrillar mineralization, as this specific type of mineralization governs the mechanical properties of dentin [197]. Yuan et al. developed an antimicrobial nanocomplex utilizing quaternary ammonium salt as the antimicrobial agent, anionic polymer γ-polyglutamic acid as the template for mineralization, and CaP as a source of minerals [198]. After a three-day treatment with the nanocomposites, microcrystals were observed within the fibrils, exhibiting a structure similar to that of native fibrils. Moreover, dentin caries was effectively interrupted while the mechanical properties were restored excellently. Due to the high proportion of organic matter and limited residual crystal seeds, dentin remineralization often poses a significant challenge. Extensive research has been conducted on caries interrupting strategies that not only facilitate dentin remineralization but also possess antimicrobial properties [199–203], effectively arresting cavity progression while managing dentin hypersensitivity and preventing chronic pulpitis (Figure 12B).

In recent years, enhanced management strategies implemented at specific sites and in a controlled manner have emerged as a prominent topic of discussion in the field of oral health management. Ingeniously designed responsive materials can effectively identify the caries microenvironment, enabling targeted intervention to prevent caries development. This innovative approach demonstrates significant potential for enhancing the safety and efficacy of antimicrobial anti-caries materials. Li et al. developed a magnesium organic framework with a unique structure that exhibits collapse in an acidic environment associated with caries, enabling the controlled release of GA and Mg^{2+} upon loading [204]. Moreover, polydopamine was incorporated and coated onto the surface to achieve pH and photothermal dual responsiveness, while CaP was added as a mineral source to enhance remineralization ability. This responsive material effectively responds to low pH induced by cariogenic bacteria, eradicating bacterial biofilms at multiple levels including elemental composition, genetic factors, and adhesion through photothermal effects. Additionally, the regulated release of mineral ions from CaP promotes orderly formation of new HAP crystals, preventing demineralization progression. However, a common challenge faced by acid-responsive materials is their potential for incorrect response when exposed to acidic foods [205], thus necessitating more appropriate responsive designs.

No additional mineral sources

While the ability of PAMAM to control HAP crystallization is well established, its remineralization capacity should not be the sole focus. Jia et al. characterized the surface morphology of their remineralized layers and observed that compared to the NaF group, PAMAM-COOH and PAMAM-NH_2 induced smoother surfaces with tighter HAP stacking, effectively reducing adhesion of *S. mutans* [206]. To

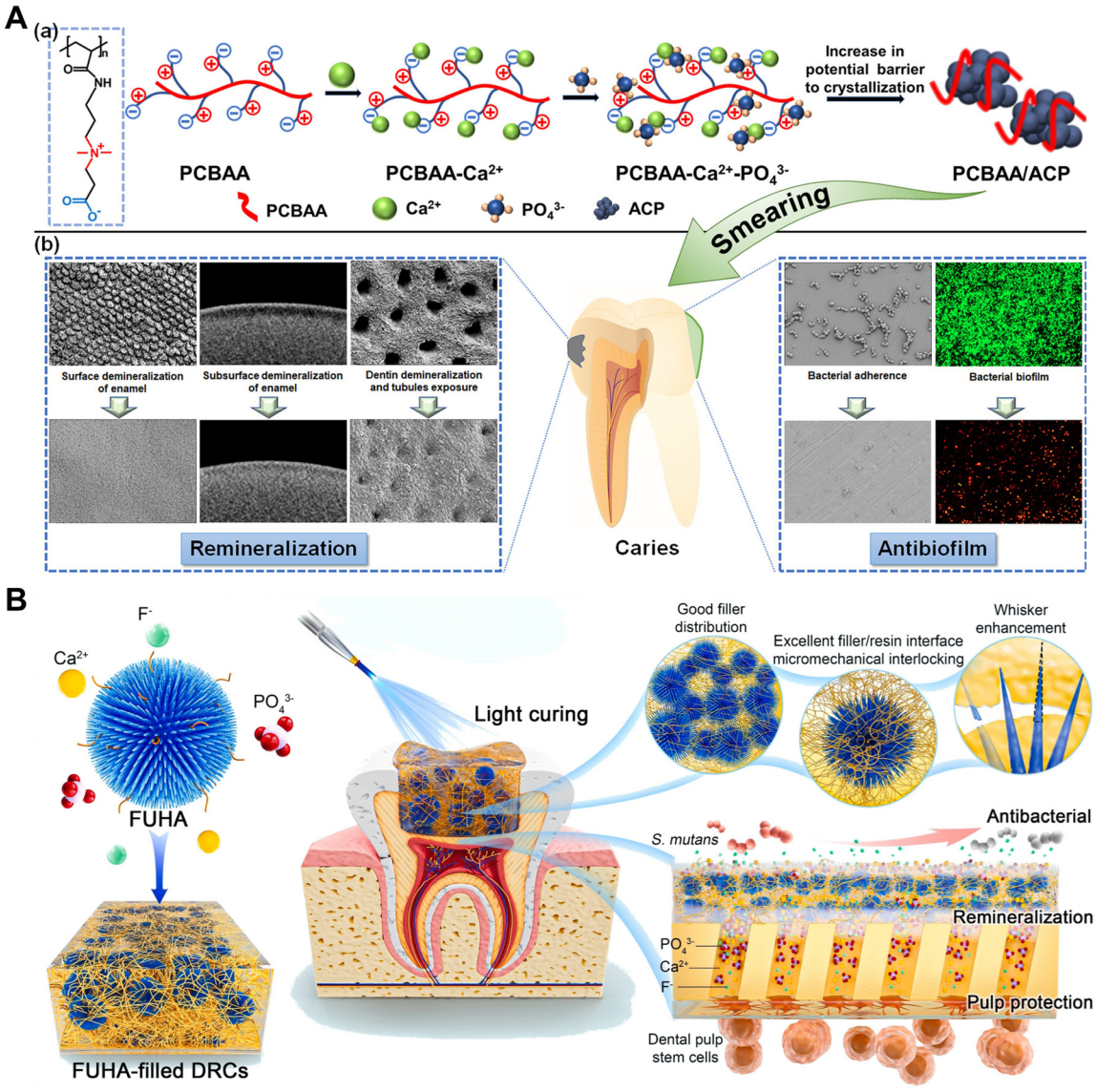

Figure 12: IDC materials with additional minerals. (A) Schematic illustration of the PCBAA/ACP nanocomposite with dual antibiofilm and remineralization functions. (a) The zwitterionic PCBAA polymer has both positive quaternary ammonium groups ($-R_3N^+$) and negative carboxyl groups ($-COO^-$). When Ca^{2+} is added into the PCBAA solution, it preferentially binds to the negatively charged carboxyl groups on the PCBAA side chains via electrostatic attraction. After the addition of PO_4^{3-} ions, some of the anions adsorb to the positively charged quaternary ammonium groups, and the others are attracted by Ca^{2+}. (b) Evaluation of the effect of the PCBAA/ACP nanocomposite on inhibiting cariogenic bacterial adhesion and biofilm formation on the enamel surface and promoting enamel remineralization and dentin tubules occlusion (image source: He et al. [195] with permission). (B) Scheme for fluorinated urchin-like hydroxyapatite-filled light-curing dental resin composites to protect dentin and deep pulp by inhibiting bacterial adhesion and growth in dentin caries restorations (image source: Zhang et al. [197] with permission).

enhance antimicrobial efficacy, Tao et al. loaded honokiol into the hydrophobic interval cavity of PAMAM-COOH to achieve prolonged antimicrobial activity in honokiol-loaded PAMAM (PAMH) [207]. Honokiol, a naturally derived antibacterial agent from plants, demonstrates excellent biological safety [208]. It effectively enhances bacterial membrane permeability and inhibits the activity of glucose transferases, thereby exerting the ability to against *S. mutans*. Additionally, it has been observed that the carboxyl group and amino group of PAMAM exhibit distinct dissociation states under different pH conditions [207]. As a result, honokiol is completely released from the cavity of PAMAM within 96 h at pH 7.0, while it requires 300 h for complete release at pH 5.5. This sustained release effect in acidic conditions promotes the long-term antibacterial efficacy of honokiol. However, the cytotoxicity associated with

PAMAM has always been a significant concern, particularly for cationic PAMAM dendrimers such as PAMAM-NH_2 [209], which exhibit relatively higher toxicity and therefore necessitate meticulous consideration during their application. Serum albumin, the predominant protein in plasma, plays a pivotal role in maintaining blood osmotic pressure and facilitating the transportation of small molecules [210]. Bovine serum albumin (BSA), which shares similarities with human serum albumin, is extensively employed in drug delivery technology due to its non-cytotoxic nature [211]. Furthermore, BSA demonstrates the capability to undergo a phase transition resulting in the formation of amyloid-like structures [212]. These dense protein membranes possess remarkable stabilization and substrate adhesion properties attributed to their abundance of functional groups. The cationic surface-active antimicrobial compound octenidine (OCT) has been selected as an antimicrobial ingredient due to its absence of systemic or local toxicity [213]. BSA forms a complex with OCT through hydrogen bonding, electrostatic interactions, and hydrophobicity that undergoes a phase transition to generate a nanofilm (Figure 13) [9]. *In vivo* experiments have demonstrated that this nanofilm exhibits antimicrobial and mineralization sealing effects, effectively preventing both primary and secondary caries. These findings support the proposal of IDC.

Collectively, these remarkable findings emphasize the practicality of caries management strategies under the IDC concept. In conclusion, the strategy of combining remineralization technology with antimicrobial technology, complemented by good penetration properties, offers a compelling opportunity to develop the next generation of functional biomaterials for caries management.

Summary

There has been a paradigm shift in research on caries interruption materials over the past two decades, transitioning from “inert” treatments to “active” materials with remineralization, antimicrobial, and penetration capabilities. The integration of remineralizing and microbicidal agents for precise delivery to the caries site represents a pivotal direction for future therapeutic interventions. While research on interrupting dental caries conception and material science holds immense value in slowing caries progression and improving patients’ quality of life, current studies have certain limitations that require closer scrutiny in future investigations.

In terms of remineralization, enamel remineralization has shown superior results compared to dentin remineralization *in vitro*. However, our understanding of the underlying mechanistic processes involved in enamel development is not as comprehensive as that for dentin mineralization mechanisms. The process of dentin mineralization depends on collagen fibrils mineralization while enamel contains minimal organic matter and experiences complex organic matter degradation during its formation, which makes it difficult to accurately replicate this process *in vitro*. Moreover, most mineralization studies have documented favorable restoration of rod-like structure. Nevertheless, it is important to acknowledge that this restoration is confined to the micrometer scale. Although the regenerated structure exhibits perpendicular alignment with respect to the enamel surface, a manifestation of optimized crystal growth energy, it fails to exert macroregulation of organic matter on crystal growth. Consequently, the resultant morphology of the remineralized layer resembles rodless enamel, indicating impaired regulation of organic matter. Therefore, a comprehensive understanding of not only amelogenin but also non-amelogenin and proteinases in the mineralization process is crucial. *In vitro* simulations that achieve synchronized self-assembly behavior between these three components in time and space may hold the key to rapidly and effectively restoring the natural structure of enamel.

Regarding antimicrobial properties, comprehending the complex interaction between microorganisms and materials is essential for controlling adhesion and biofilm formation on biomaterial surfaces. However, the mechanisms underlying the antimicrobial activity of small molecules and nanoparticles with antibiofilm properties remain unclear, while broad-spectrum bactericidal drugs are prone to induce bacterial resistance, and both structural stability and functional activity of AMPs pose challenges. Furthermore, the effective integration of the antimicrobial component with the remineralization component presents a significant consideration, as careful evaluation of encapsulation quantity is necessary when utilizing a delivery platform and accounting for the impact on active functional groups during chemical combination. Besides, the necessity for permeability imposes limitations on the choice of antibacterial and remineralizing elements, given that the molecular structure, size, shape, and solubility all influence permeability effectiveness. However, infiltration technology is crucial for achieving optimal remineralization and antibacterial efficacy. A high degree of penetration allows the active agents to infiltrate deeply into the microstructure, precisely repairing the hard tissues of the dentin. Moreover, infiltration technology ensures the uniform distribution of remineralization and antibacterial components within the dentin’s hard tissues,

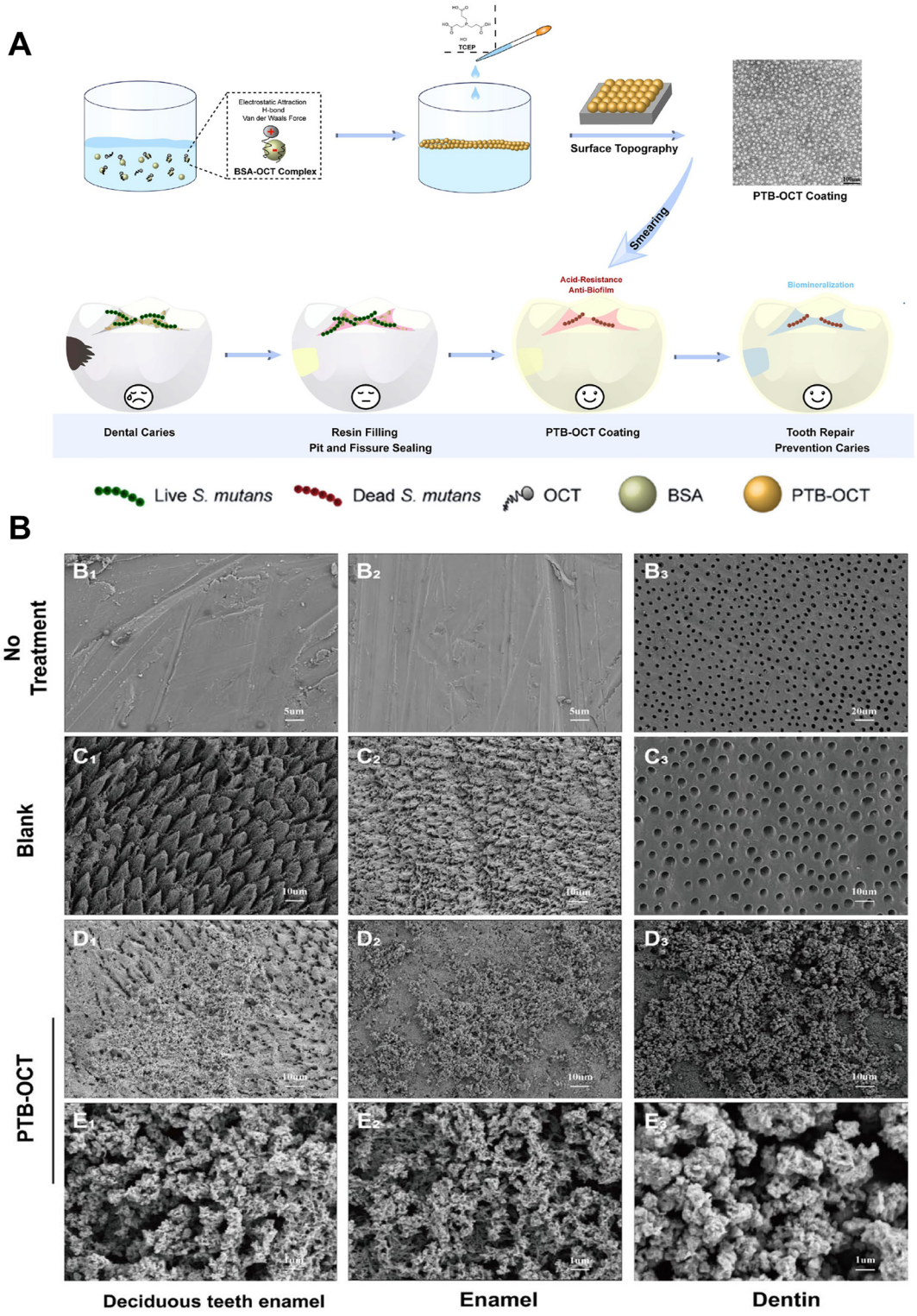

Figure 13: PTB-OCT coating for managing dental caries. (A) Schematic representation of PTB-OCT coating formation and its ability to prevent primary and secondary caries. (B) Evaluation of the effect of the PTB-OCT coating on enamel and dentin remineralization *in vitro* (image source: Lu et al. [9] with permission).

facilitating strong adhesion between the material and the tissue surface. This, in turn, enhances the overall therapeutic outcomes. In addition to its efficacy in interrupting caries, clinical applications also require addressing concerns regarding material toxicity and rapid removal under saliva washout. As the understanding of mineralization

processes continues to advance and materials undergo ongoing updates, caries interruption will become an achievable avenue.

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