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Review article

Advanced biomaterials for targeting mature biofilms in periodontitis therapy

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ABSTRACT

Periodontitis is a chronic inflammatory disease primarily caused by bacteria, leading to inflamed and bleeding gums, periodontal pocket formation, and bone loss. Affecting 70%–90% of adults over 65, periodontitis is a leading cause of tooth loss and significantly impacts quality of life. Standard treatments, including subgingival scraping and antibiotics, have limitations, and antibiotic resistance among periodontal pathogens is an increasing concern. Biofilms are barriers to drugs and immune responses, contributing to bacterial resistance and reducing antibiotic effectiveness. Due to their adjustable physicochemical properties, bioactive materials potentially eliminate bacterial biofilms, presenting a promising alternative for periodontitis therapy. In this review, the recent innovations in biomaterials for removing mature biofilms in periodontitis are examined, and their broader potential is discussed. Additionally, the compositions of bacterial biofilms, formation pathways, and intrinsic drug resistance mechanisms are discussed. Finally, the strategies for optimizing subgingival biofilm removal in periodontitis are highlighted, such as targeting biofilms-embedded bacteria, disrupting the extracellular polymeric substances, and utilizing combined approaches. A comprehensive understanding of the properties of biomaterials guides the rational design of highly targeted and effective therapies for periodontitis.

1. Introduction

Periodontitis is increasingly prevalent worldwide. The Global Oral Health Status Report (2022) identifies severe periodontal disease as a significant global health issue. The World Health Organization now prioritizes its prevention and treatment [1]. Periodontitis is the primary cause of tooth loss in adults, affecting aesthetics and function of the oral and jaw systems [2]. In addition, periodontitis is linked to various systemic diseases, such as diabetes, cardiovascular disease, and Alzheimer's disease [3,4].

Bacterial biofilm infections, especially those formed by subgingival plaque, play a central role in the pathogenesis of periodontitis. Biofilms protect bacteria from immune responses and antibacterial agents. They not only contribute to the persistence of chronic inflammation and tissue damage but also further accelerate the deterioration process of periodontitis by interfering with the normal remodeling process of bone as well as promoting bacterial resistance.

The main non-surgical treatment for periodontitis is mechanical root debridement. This procedure includes subgingival scaling and root planing (SRP), which aims to remove subgingival plaque biofilms and halt the progression of periodontitis. However, SRP struggles to fully eliminate mineralized biofilms (calculus) in complex areas, such as curved roots, concave areas of roots, and deep periodontal pockets [5]. Periodontal endoscopy is often used as an adjunct to root debridement,

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allowing the removal of calculus and granulation tissue under direct vision, which minimizes tissue damage and patient discomfort [6]. Despite these interventions, recolonization of periodontopathogen occurs shortly after mechanical treatment alone, potentially leading to the recurrence of periodontitis. To improve outcomes and prevent recolonization, mechanical treatment may be supplemented with topical antibiotics [7].

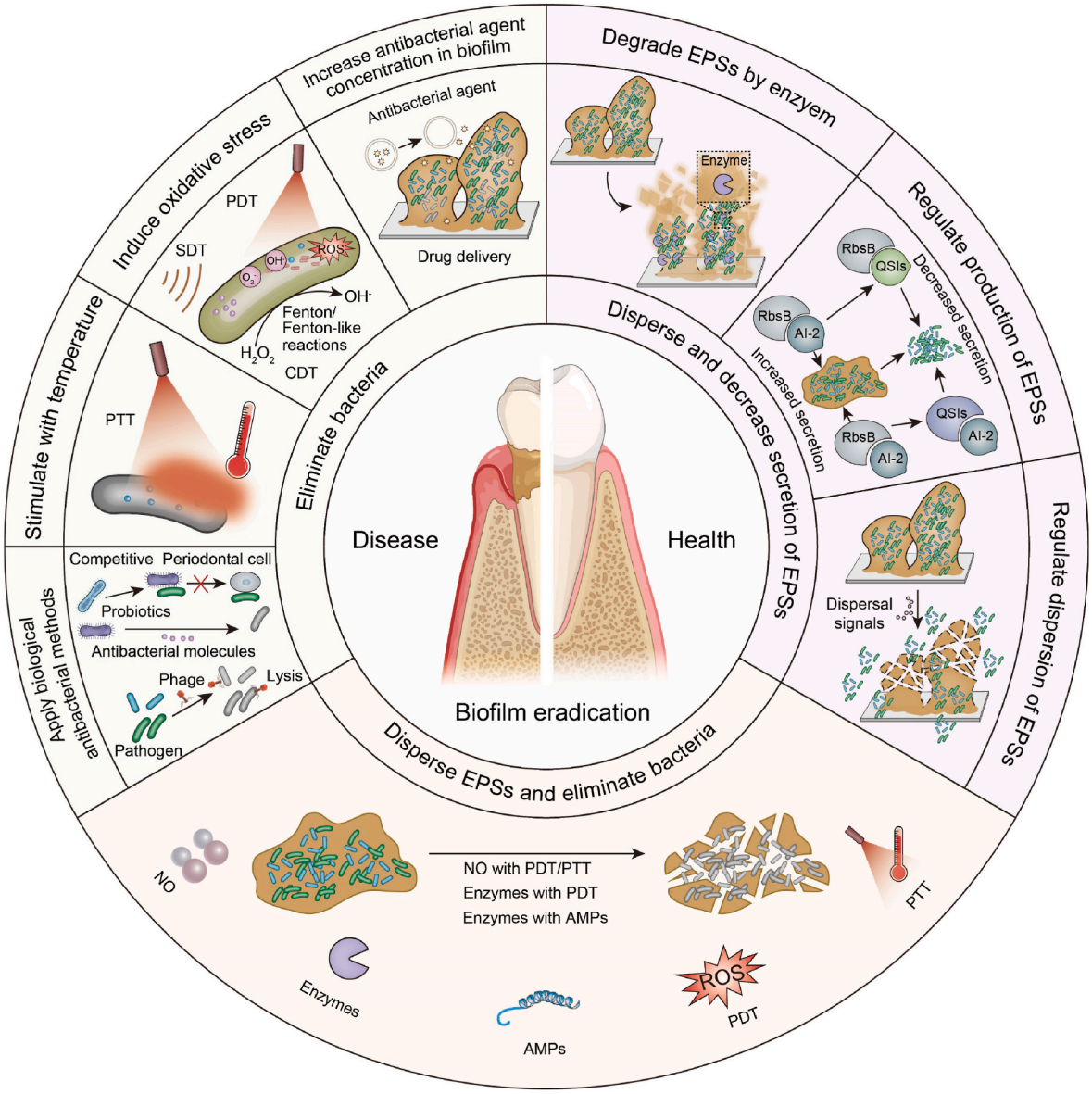
Mouthwashes like chlorhexidine reduce plaque and gingival inflammation but are not recommended for long-term use due to adverse effects, including tooth staining [8]. Various topical antibiotics are available on the market, several of which have received US Food and Drug Administration (FDA) approval, including Arestin® and PerioChip®. Additionally, eliminating bacteria within biofilms with antibiotics often requires high doses, which may lead to antibiotic resistance. This issue underscores the need for alternative antibacterial agents for treating bacterial biofilm infections.

Recent advancements in therapeutic approaches for treating periodontitis caused by biofilm infections include antibacterial photodynamic therapy (aPDT), probiotic therapy, and other innovative strategies. Biomaterials play a critical role in enhancing the efficacy of these treatments. Recent advances in materials and technological have highlighted the role of biomaterials in dentistry, particularly in the elimination of periodontal plaque biofilms [9,10]. By modifying surface structures with specific chemical or bioactive molecules, these materials interact with biofilms, disrupting their complex structures and impacting biofilm stability and functionality. Various biomaterial-based antibacterial agents have effectively removed subgingival plaque biofilms [11,12].

This review describes the composition and formation of bacterial biofilms and their pathological roles in periodontitis. Based on the knowledge of bacterial biofilm composition, the recent advances in bioactive materials for subgingival plaque biofilm removal under different strategies are discussed, as shown in Scheme 1. Finally, the challenges and opportunities these materials face in anti-biofilm therapy for periodontitis are discussed.

2. Role of biofilms in periodontitis

The human oral cavity contains over 700 species of bacteria present in saliva, as well as on the surface of teeth, the epithelium of gums, and



Scheme 1. Anti-biofilm strategies involving bioactive materials in periodontitis therapy. Created in BioRender. Y. Sun (2025) BioRender.com/d82q856.

other oral surfaces [13]. Anaerobic bacteria, such as *Porphyromonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleatum* (*F. nucleatum*), are prevalent in infected periodontal tissues [14,15]. They form subgingival plaque biofilms on the surface of teeth and periodontal tissues, which are challenging to remove [16]. Bacterial biofilms are stable and complex three-dimensional (3D) mesh structures formed by microorganisms adhering to living and non-living surfaces. These microorganisms are encased in a self-secreted matrix of extracellular polymeric substances (EPSs), which enables them to adapt to their environments [17].

Biofilm formation initiates immediately after oral cleansing, as proteins in saliva form an acquired salivary pellicle on the surface of teeth, mediating the adhesion and coaggregation of early-colonizing bacteria [18] (Fig. 1). As biofilm matures, bacterial gene expression and intercellular signaling (quorum sensing, QS) regulate its development. Increased bacterial proliferation triggers the secretion of EPSs, which provides mechanical stability to biofilms and gradually leads to mature bacterial biofilms. Once biofilm growth stabilizes, bacteria secrete extracellular hydrolases to break down EPSs, leading to bacterial dispersal. At the appropriate moment, planktonic bacteria colonize another biohabitat and initiate new biofilm formation cycles, causing persistent infections [19,20].

Bacteria within biofilms exhibit a markedly higher resistance to antibacterial drugs than planktonic bacteria. Once shed from biofilms, bacteria rapidly regain susceptibility to antibacterial drugs [21]. Biofilm drug resistance mechanisms are complex and synergistic. First, the EPSs secreted by bacteria form a dense and negatively charged barrier that hinders the penetration of positively charged antibacterial drugs into the interior of biofilms, fostering drug resistance among bacteria deep within biofilms. Second, hypoxia and nutrient deficiency slow the metabolism of bacteria in the deeper layers of biofilms, with some bacteria entering a dormant state that makes them insensitive to environmental stresses and drugs [22]. Third, bacteria upregulate the expression of specific genes, including those associated with efflux pumps, in response to stress, altering their biological behaviors. Fourth, resistant bacteria within biofilms may share resistance genes through horizontal gene transfer. Finally, QS signals regulate biofilm formation and the generation of virulence factors, enhancing bacterial resistance to host immune defenses [23].

Biofilms create a stable environment for periodontal pathogens, enabling the continuous stimulation of immune response and facilitating immune evasion, leading to the secretion of pro-inflammatory factors and tissue-degrading enzymes that trigger chronic inflammation [24]. Additionally, biofilms exacerbate the progression of periodontitis by inhibiting osteoblast differentiation and bone matrix synthesis while simultaneously enhancing osteoclast activity and bone resorption [25]. These combined effects ultimately lead to bone loss, destruction of periodontal tissues, and eventual tooth loosening or loss in the host [26]. A greater concern is the persistence of biofilms in periodontal pockets facilitates the spread of periodontal pathogens to other body systems, including the nervous system. Research shows periodontal pathogens in subgingival biofilms, like *P. gingivalis*, invade the brain, inducing low-grade inflammation [27], and are linked to Alzheimer's features like neuronal damage and amyloid plaques [28,29].

Bacterial biofilms play a critical role in the pathogenesis of periodontitis by forming complex structures that protect bacteria and increase their resistance to antibiotics and immune responses. Unlike conventional biomaterials, which primarily target planktonic bacteria, anti-biofilm materials are designed to disrupt the biofilm structure [30]. This approach overcomes the resistance barrier created by EPSs, a key challenge in treating biofilms-related infections. Conventional therapies

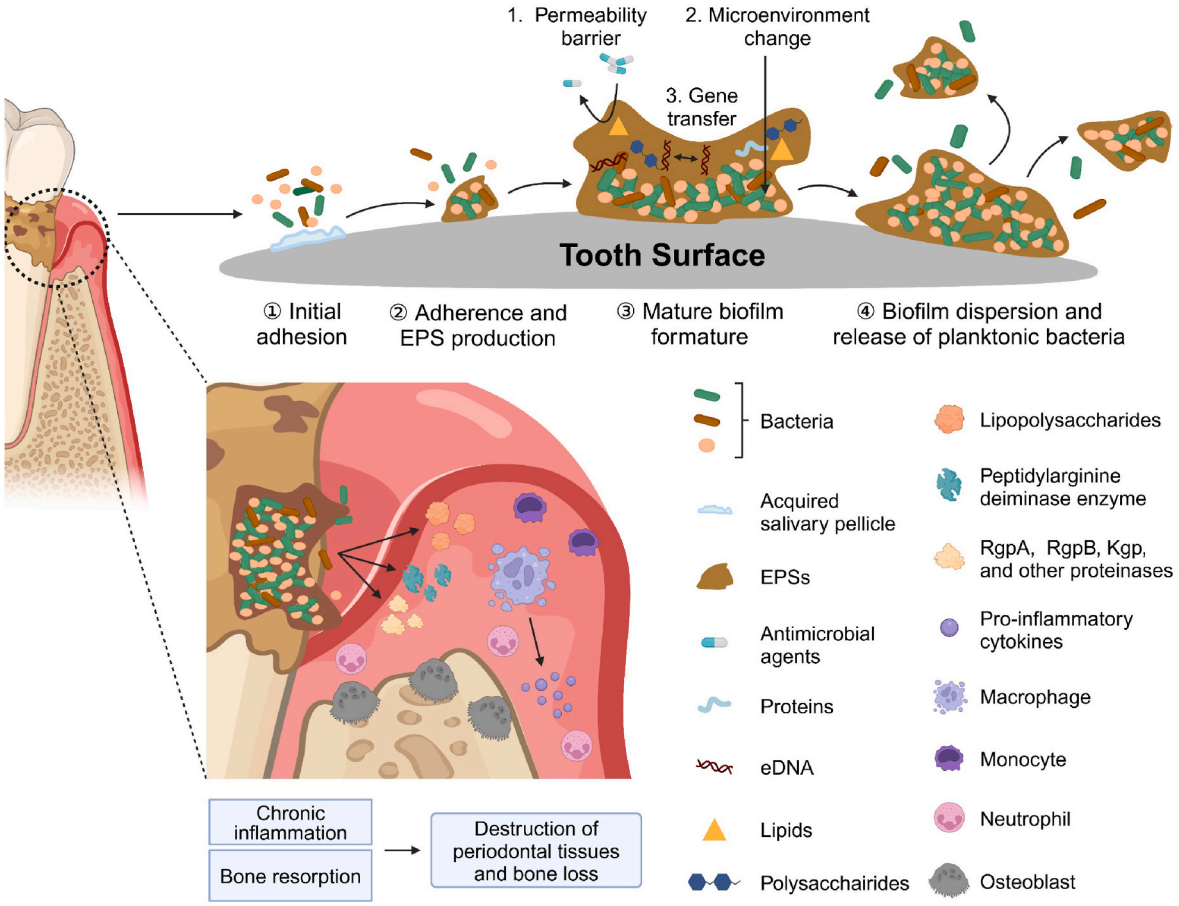


Fig. 1. Formation of biofilm, drug resistance mechanisms, and their effects on periodontium. Created in BioRender. Y. Sun (2025) BioRender.com/w83v494.

often struggle to penetrate biofilms, which limits their effectiveness [31]. By understanding the composition of biofilms and their role in periodontitis, researchers develop advanced strategies, such as nanotechnology and multifunctional designs, to mitigate the effects of biofilms. This enhances the efficacy of anti-biofilm biomaterials and reduces the recurrence of periodontitis. The disruption and removal of subgingival plaque biofilms through these innovative biomaterials has been increasingly recognized as an effective strategy for preventing and treating periodontitis, as will be discussed in the next section.

3. Strategies involving advanced biomaterials for combating mature biofilms

3.1. Strategies targeting bacteria

The primary goal of treating periodontal infections is the eradication of bacteria. As bacteria grow, they secrete EPSs, which gradually thicken biofilms and strengthen their structures [19]. Simultaneously, bacterial division and proliferation increase the bacteria population within biofilms. Additionally, biofilms shield bacteria from host immune responses, adversely impacting the host's physiological functions [32]. Therefore, eradicating bacteria within biofilms is crucial for directly addressing the root causes of biofilm persistence and drug resistance in biofilm-associated infections.

Various approaches are used to eradicate biofilm bacteria, such as antibiotics, nanoantibacterial agents, the production of reactive oxygen species (ROS) and heat, and the use of antibacterial peptides (AMPs) and phages [33–35]. Each method has specific advantages and limitations. Selecting the most appropriate approach, or combination of approaches, is key to achieving optimal therapeutic outcomes. Fig. 2 shows the interactions between bioactive materials and bacteria within biofilms and the disruption of biofilms.

3.1.1. Increase of antibacterial agent concentration

The formation of plaque biofilms diminishes the effectiveness of conventional antibacterials, often requiring high concentrations to eradicate plaque biofilms. Localized antibiotic administration increases the drug concentration in the periodontal pocket, reducing the required dosage and enhancing biofilm removal efficacy [36]. Many biomaterial-based antibacterial agents and topical drug delivery systems serve for intra-pocket drug delivery, allowing lower antibiotic concentrations than conventional systemic methods for treating biofilms-induced periodontitis. The strategies involving bioactive materials in increasing antibacterial agent concentration in biofilms are summarized in Table 1.

However, these delivery systems face challenges, as they cannot retain the pharmaceutical agent at the lesion site for extended periods or provide sustained release of the therapeutic drug, resulting in suboptimal treatment duration [42]. Furthermore, the negative charge characteristics of biofilms play a crucial role in drug resistance. Anionic groups in EPSs, such as phosphate and carboxyl, hinder the diffusion and penetration of positively charged antibiotics while capturing negatively charged drugs, thereby reducing their effective concentration at the lesion site.

To address these challenges, Li et al. [37] developed an innovative mouthwash for the localized delivery of minocycline, incorporating chitosan modified with cyclodextrin and 3-(3,4-dihydroxy phenyl) propionic acid (hydrocaffeic acid, HCA). Chitosan had a high positive charge density, effectively neutralizing the negative charge of biofilms through electrostatic interactions, thereby enhancing its adsorption capacity on the biofilm surface and promoting deeper drug penetration. The catechol moiety in HCA covalently attached to thiol or amine groups on the biofilm surface through a Michael addition reaction, allowing prolonged exposure and the sustained release of minocycline. The strong local adhesion of the system extended its attachment to biofilms for up to 12 h, while the ability for sustained release improved drug penetration and enhanced anti-biofilm activity.

Outer membrane vesicles (OMVs) released by Gram-negative bacteria have recently attracted considerable attention as drug delivery systems. OMVs are spherical bilayer nanostructures, typically 20–30 nm in diameter, primarily composed of bacterial outer membrane components, including lipopolysaccharides (LPS), phospholipids, and associated proteins. These components facilitate OMV fusion with bacterial cell membranes, enabling the release of encapsulated drugs either into the cell membrane or inside the bacteria [43]. Furthermore, positively charged OMVs penetrate biofilms more effectively through electrostatic interactions with the negatively charged EPSs [44].

Huang et al. [38] demonstrated that encapsulation of antibiotics using OMVs from *Acinetobacter baumannii* (*A. baumannii*) was effective in targeting enterotoxigenic *Escherichia coli* (ETEC) with a similar

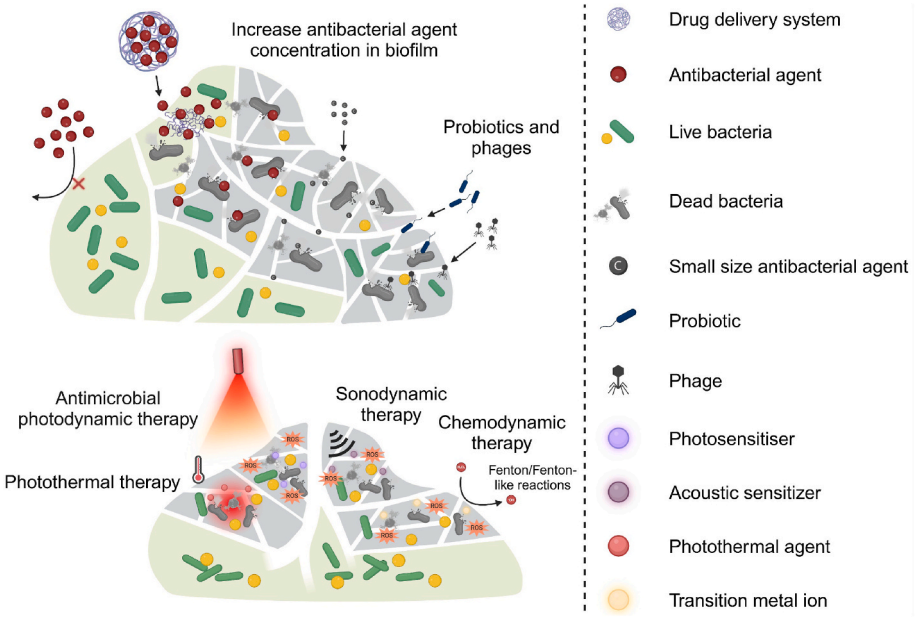


Fig. 2. Interactions between bioactive materials and bacteria within biofilm, and disruption of biofilm. Created in BioRender. Y. Sun (2025) BioRender. com/f70k230.

Table 1
Strategies involving bioactive materials in increasing antibacterial agent concentrations in biofilms.

Strategies	DDS/Bioactive materials	Structure	Action Mechanism	Ref.
Localized drug delivery	Mouthwash	Chitosan, cyclodextrin, HCA	Chitosan's positive charge enhances biofilm adhesion, while HCA's catechol moiety binds to thiol or amine groups for sustained minocycline release.	[37]
	OMVs	*A. baumannii* OMVs	OMVs from *A. baumannii* fuse with the cell membranes of enterotoxigenic *E. coli* due to their similar membrane structure.	[38]
	Polymersome	PCL-*b*-P(Lys-*co*-Phe, PEG-*b*-PCL	PEG-*b*-PCL resists protein adhesion for polymersome penetration, while P (Lys-*co*-Phe) adds charge to enhance bacterial adhesion and membrane disruption.	[39]
Increased biofilm permeability	CD	tinidazole CD, metronidazole CD	The small size of CD has the potential to penetrate biofilms *via* intrafilm channels.	[40]
	Dual-polymer nanoparticle	(Dimethyl amino)ethyl-riched polymer, phosphate group-rich polymer, melanin, AgNPs	(Dimethyl amino)ethyl-rich polymers gain charge in acidity for biofilm penetration, while phosphate-rich polymers chelate Ca^{2+} for hydroxyapatite adhesion.	[10]
	Magnetic nanoparticle	Fe_3O_4 magnetic nanoparticle, minocycline	The magnetic forces enable nanoparticles to penetrate biofilms and eliminate bacteria residing deep within.	[9]
	Magnetic nanoparticle	Vanc/RL-conjugated Ag@Fe_3O_4 magnetic nanoparticle	Nanoparticles rapidly penetrate biofilms upon exposure to external magnetic field, and kill the bacteria within biofilms.	[41]

membrane structure, significantly enhancing antibiotic efficacy. It demonstrates the potential of OMVs as biomimetic nanocarriers to provide insights into localized drug delivery to treat periodontitis [45].

On the other hand, polymersomes, artificially synthesized nanocarriers, also show remarkable potential for drug delivery. These structures form through the self-assembly of amphiphilic block copolymers in solution, creating liposome-like nanocarriers. Compared to natural vesicles, polymersomes offer lower production costs, improved stability, and sustained drug-release properties [46]. However, single-corona polymersomes have a single function, which makes it difficult to meet the complex demands of biofilms. For this reason, double-corona polymersomes have emerged to achieve multifunctional integration by co-assembling two different functional copolymers.

These structures possess two distinct hydrophilic coronas, enabling the integration of diverse functionalities without the need for complex chemical modifications. Xi et al. [39] developed a polymersome composed of poly(ε-caprolactam)-*block*-poly(lysine-*co*-phenylalanine) (PCL-*b*-P(Lys-*co*-Phe)) and poly(ethylene glycol)-*block*-poly(ε-caprolactam) (PEG-*b*-PCL) for antibiotic delivery. PEG-*b*-PCL resists protein adhesion, reducing the EPSs-mediated barrier and facilitating the penetration of polymersome into biofilms. Simultaneously, P(Lys-*co*-Phe) imparts a positive charge to the vesicle surface, promoting adhesion to bacteria and enabling antibacterial activity through membrane disruption. Experiments showed that encapsulating antibiotics in double-corona vesicles significantly inhibited *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) biofilms and halved the antibiotic dosage.

EPSs present a major obstacle to antibacterial drug penetration due to EPS adsorption and the complexity of their structures. Some antibacterial drugs cannot penetrate biofilms due to size limitations, reducing the accumulation of these drugs within biofilms and diminishing their bactericidal effects [47]. Future therapeutic strategies for biofilm infections must address the barrier of EPSs by exploring alternative antibacterial drugs capable of effectively penetrating EPSs and acting directly on bacteria [10,41]. Notably, EPSs in biofilms feature water-filled channels and pores, ranging from 10 nm to a few micrometers, that facilitate the transport of nutrients and metabolic waste removal [48]. Given these characteristics, nanomedicine—particularly carbon dots (CDs), a carbon-based nanomaterial—has shown promise in biofilm treatment, as their minuscule size enables efficient EPS penetration [49].

Liang et al. [40] synthesized tinidazole CDs (TCDs) and metronidazole CDs (MCDs) through a hydrothermal method using tinidazole and metronidazole as raw materials. Dynamic light scattering analysis confirmed the small size of CDs (~15−16 nm), demonstrating their potential to penetrate biofilms *via* intrafilm channels. After treatments with TCDs and MCDs, the bacterial counts in biofilms were significantly reduced, with the TCDs achieving an inhibition rate against *P. gingivalis* of over 80%. A comparative *in vitro* analysis of TCDs and tinidazole alone revealed that TCDs, at concentrations above 50.0 μg mL^{-1}, significantly penetrated biofilms and eliminated *P. gingivalis*, whereas tinidazole alone had no discernible effect. These findings indicated that TCDs are capable of infiltrating *P. gingivalis* biofilms and eliminating the bacteria within.

Yet, removing subgingival plaque biofilms always leads to rapid pathogenic bacterial recolonization in periodontal tissue, leading to the recurrence of periodontitis [50]. To prevent this challenge, researchers have developed bacteria-responsive, drug-release strategies that intelligently regulate drug release based on the presence and activity of bacteria or specific physiological microenvironments, *e.g.*, pH and enzyme activity, allowing consistent control of periodontal disease activity [47,51]. During the onset of periodontitis, bacteria greatly increase alkaline phosphatase (ALP) secretion—a key indicator of the active state of disease. Monitoring ALP levels allows clinicians to assess periodontitis progression and make timely treatment adjustments [52].

Xia et al. [53] designed an ALP-responsive biomaterial tailored for periodontitis treatment, immobilizing poly(ethylene glycol)-modified amoxicillin (PEG-AML) on mesoporous silica nanocarriers *via* phosphate groups. Notably, when exposed to ALP secreted by bacteria, the nanocarriers' phosphate groups were cleaved, triggering the controlled release of PEG-AML. This mechanism effectively eliminated bacteria and reduced the risk of periodontitis reoccurrence—showcasing the potential of smart biomaterials for precise treatment and recurrence prevention in periodontitis management.

However, with the growing prevalence of antibiotic resistance, the prudent use of antibiotics has become essential. Therefore, recent research has increasingly focused on non-antibiotic antibacterial agents, such as AMPs, for treating periodontal infections [54]. AMPs interact with bacterial cell membranes through electrostatic forces, exhibiting bacteriolytic activity and minimizing the risk of resistance due to their non-specific mechanisms [55]. AMPs disrupt biological membranes or create transmembrane channels, which allows them to interfere with the early bacterial adhesion, as well as disrupt mature biofilms by inducing microbial cell detachment or killing microbial cells [34,56]. For example, Roky et al. [57] found that two compounds structurally similar to functional groups in AgI/II peptides, NITVK and VQDLL—vital for *P. gingivalis* adhesion to *Streptococcus*—effectively inhibit *P. gingivalis* adhesion, thereby controlling *P. gingivalis* recolonization.

Nevertheless, natural AMPs as topical therapeutical agents face limitations, including high synthesis costs and vulnerability to enzymatic degradation by oral microorganisms. To mitigate these challenges and enhance efficacy, strategies like structural modification and

chemical synthesis are employed. Synthetic PCP-III-201, a mimetic of a natural peptide substrate recognized by *P. gingivalis* minor fimbrial antigen (Mfa), inhibits *P. gingivalis* and *Streptococcus gordonii* (*S. gordonii*) adhesion by disrupting the interaction between Mfa and *S. gordonii* antigens I/II, thereby preventing biofilm formation [58]. AMP templates also enable physicochemical modifications that overcome limitations, including degradation by the host enzymes and low yield, enhancing their efficacy.

The structural diversity and modification of AMPs are crucial for improving therapeutic outcomes. For instance, P-113, a histidyl peptide derived from salivary histone proteins, exhibits bactericidal effects against significant oral cavity pathogens like *Streptococcus* and *Staphylococcus* [59]. However, its antibacterial potency diminishes under physiological conditions due to the high salt concentrations in saliva and bodily fluids. Wang et al. [60] address this limitation by substituting tryptophan or histidine residues with β-naphthylalanine and β-(4, 4′-biphenyl)alanine, creating Nal-P-113, which inhibits and kills planktonic bacteria and prevents biofilm formation even in high-salt conditions. In addition to structural modifications, AMPs can be doped onto the surface of polymers through specific surface chemistry or encapsulated into polymeric carriers, enhancing peptide activity and localized delivery.

One study highlighted a peptide (BAR) derived from *S. gordonii* that inhibits the adhesion of *P. gingivalis*, reducing its colonization potential and pathogenicity in the oral cavity [61]. However, disrupting established *P. gingivalis/S. gordonii* biofilms require high concentrations of BAR. To enhance peptide activity, Mahmoud et al. [62,63] encapsulated BAR within poly(lactic-*co*-glycolic acid) (PLGA) and methoxy poly (ethylene glycol)−poly(lactic-*co*-glycolic acid) nanoparticles (mPEG−PLGA NPs). The BAR-encapsulated PLGA and mPEG−PLGA NPs provided higher localized peptide doses and proved more effective than free peptides in disrupting *P. gingivalis/S. gordonii* biofilms at equimolar concentrations.

Overall, topical antibiotic administration in periodontal pockets is capable of extending drug residence time at lesion sites and improving biofilm penetration. However, the risk of antibiotic resistance necessitates cautious antibiotic use, and routine antibiotic application in managing periodontitis is not advised. Anti-biofilm therapy employing biomaterials as antibacterial agents or drug carriers—with bioactive or stimuli-responsive components—enhances drug efficiency, prolongs action duration, and enables controlled release, thereby improving therapeutic effects.

Research continues to explore the integration of bioactive agents, such as AMPs, into biomaterials to remove plaque biofilms. AMPs, with their distinct antibacterial mechanisms, present promising strategies for plaque biofilm removal. Nonetheless, the extraction of AMPs remains complex, production at scale is challenging and costly, and their activity may diminish in biological fluids. Additionally, the safety of certain non-human-derived peptides requires evaluation.

Ongoing advancements in nanotechnology and synthesis, modification, and polymer combination techniques are essential for the practical applications of AMPs. Simultaneously, addressing challenges associated with AMP production and reduced activity in biological fluids is essential for ensuring AMP safety and efficacy, ultimately expanding the possibilities for personalized periodontitis treatment.

3.1.2. Generation of reactive oxygen species

ROS are chemically active oxygen atom or oxygen atom-containing groups, including hydrogen peroxide (H_2O_2), hydroxyl radicals (·OH), singlet oxygen ($^1O_2$), and superoxide anion ($\cdot O_2^-$) [64]. Recent research has highlighted ROS as an effective alternative for biofilm disruption, as they impair bacterial function and structure, thereby effectively inactivating microorganisms, including Gram-negative bacteria that dominate subgingival plaques in advanced periodontitis [65,66]. Various methods produce ROS for inducing antibacterial and anti-biofilm effects. ROS-based antibacterial agents are summarized in Table 2.

Table 2
ROS-based anti-biofilm agents.

Bioactive material	Method of generating ROS	Species of generated ROS	Remark	Ref.
RB and dextran	aPDT	·OH, $^1O_2$, and H_2O_2	Under light, RB generates $^1O_2$ and ·OH, with dextran groups aiding adhesion and biofilm penetration.	[67]
Ce6 and MnO_2 nanolayer	aPDT + nanoenzyme	$^1O_2$	MnO_2 converts H_2O_2 to O_2 *in situ*, which further boosts $^1O_2$ production by PDT with Ce6.	[68]
ICG−RAPA	aPDT	$^1O_2$	ICG−RAPA boosts ROS and heat under 808-nm laser, inhibiting adhesion and biofilm formation by enhancing bacterial movement.	[69]
ZnO@Bdello	aPDT	$^1O_2$ and ·OH	The collision of ZnO@Bdello with prey leads to ZnO polarization and ROS production.	[70]
Airon NP	CDT	·OH	Airon nanoparticle rapidly catalyzes the production of toxic ·OH from H_2O_2.	[71]
ZnO_2/Fe_3O_4@MV NP	CDT	H_2O_2 and ·OH	ZnO_2 NP release H_2O_2 by decomposition, and Fe_3O_4 NP catalyzes the production of highly reactive ·OH.	[72]
Pd@Pt-T790	SDT	$^1O_2$	US irradiation recovers the activity of nanozyme that catalyzes the decomposition of endogenous H_2O_2 into O_2.	[73]
Au/Pt NCs@GOX	Nanoenzyme	H_2O_2	Au/Pt NCs@GOX, with enhanced POD-like reactivity, enables the conversion of harmless glucose into gluconic acid and H_2O_2.	[74]
FeSN	Nanoenzyme	·OH	Histidine residues in FeSN nanoenzyme enhance H_2O_2 affinity, enabling pathogen biofilm detection and structural breakdown.	[75]

3.1.2.1. Biomaterials for antibacterial photodynamic therapy. APDT is a non-aggressive method of infection control. This process involves the absorption of photosensitizers by target cells or tissues, followed by irradiation with a specific wavelength, resulting in energy transfer to oxygen (O_2) and ROS generation [76]. These ROS exert toxic effects against periodontal pathogens, significantly reducing bacterial colonization and inhibiting plaque growth. Recent studies highlight promising strategies for clinical treatment of periodontitis. Among these, aPDT has proven effective as an adjunct to SRP, generating ROS to disrupt bacterial structures and improve clinical parameters in periodontitis patients compared to SRP alone [77]. In treating periodontitis, photosensitizers, such as phenothiazine, porphyrin, and indocyanine green, are widely recognized for their efficiency and safety [78–80].

A series of biomaterials have emerged with the continued advancement of aPDT technology. The results of many scientific studies have demonstrated that these biomaterials, which produce ROS, have shown excellent anti-biofilm properties *in vitro* and *in vivo*. However, the effectiveness of aPDT is influenced by several critical therapeutic parameters, including the concentration of photosensitizer, the depth of

periodontal pocket, and so on. To enhance the retention and penetration of photosensitizers within complex biofilm structures, researchers have developed advanced biomaterials, such as nanoparticles and hydrogels loaded with photosensitizers.

For instance, Xu et al. [80] synthesized a dopamine-grafted sodium alginate (SA–DA) hydrogel loaded with the photosensitizer methylene blue (MB) and PLGA microsphere containing Sema3A (Fig. 3A). As shown in Fig. 3B, the hydrogel demonstrated excellent tissue adhesion due to the catechol moiety in dopamine, enhancing bioadhesion through amidation with sodium alginate. Stress-strain curve analysis revealed that the MB/Sema3A@SA–DA hydrogel exhibited enhanced strength and compressive resistance, maintaining integrity even at 50% strain, making it suitable for topical application in periodontitis (Fig. 3C). MB acted as an efficient photosensitizer to treat periodontal disease. A ROS-sensitive probe, DPBF, monitored ROS generation. As shown in Fig. 4D, UV–visible spectral analysis showed a significant reduction in DPBF absorbance over time, indicating that the hydrogel released MB rapidly (Fig. 3E), with subsequent ROS generation, demonstrating antibacterial and anti-biofilm activity *in vitro* and *in vivo* (Fig. 3F and G).

Furthermore, the depth of periodontal pockets poses challenges for photosensitizer efficiency, as limited light penetration restricts ROS generation and, consequently, weaker antibacterial effects. To address this limitation, Kong et al. [82] developed a Z-type hetero-structured Bi_2S_3/Cu-TCPP nanocomposite. Its interfacial regions enhance the adsorption of O_2 and ·OH, thereby increasing ROS production due to its heterogeneous structure. This nanocomposite demonstrated optimized

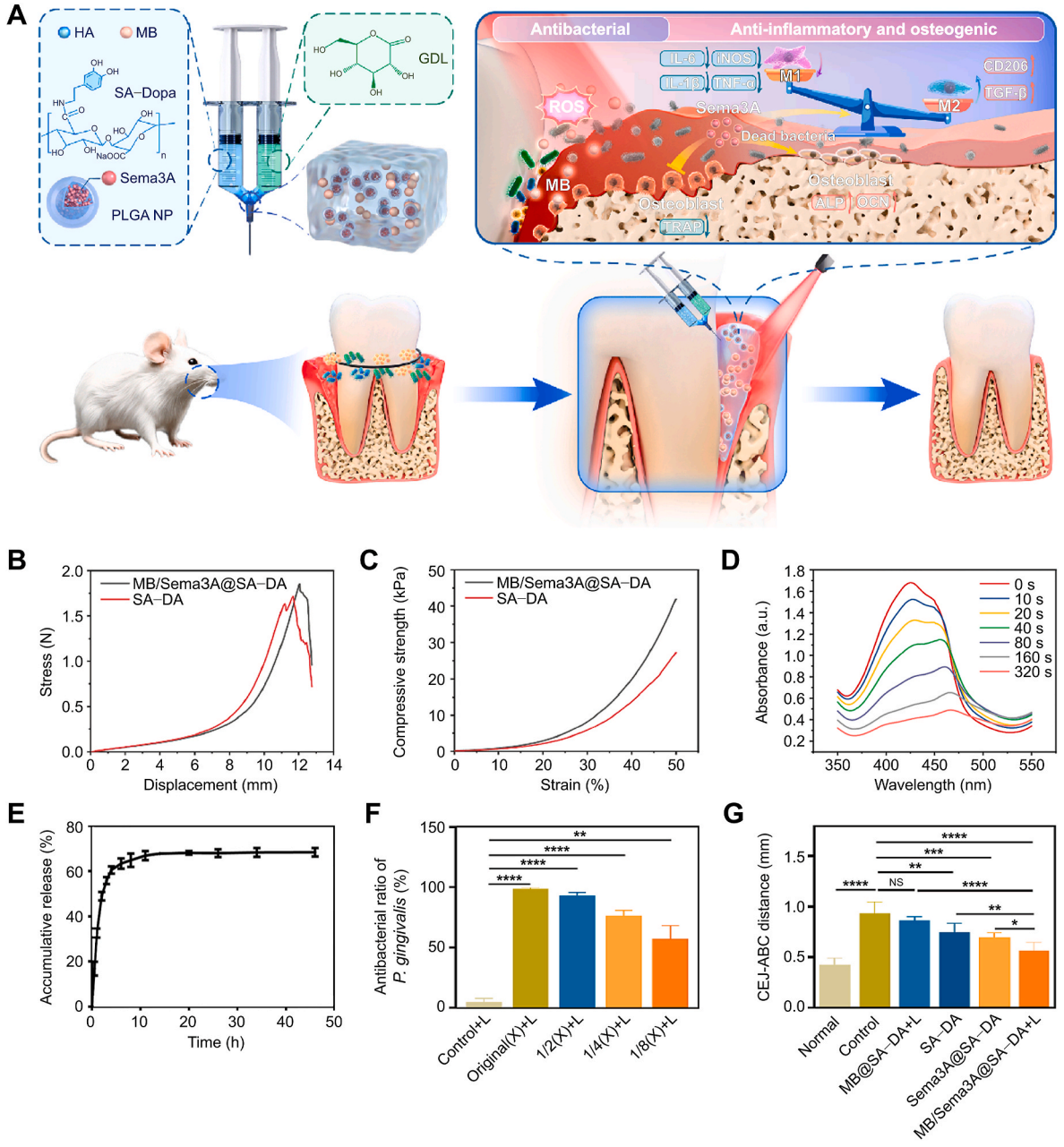


Fig. 3. SA–DA hydrogel system for sequential release of Sema3A and MB. (A) Synthesis, antibiotic activity, inflammation-reducing activity, and periodontal tissue regeneration facilitation of MB/Sema3A@SA–DA. (B) Attachment test force-displacement curve. (C) Stress-strain curve for hydrogel compression experiment. (D) Ultraviolet absorbance spectra of MB/Sema3A@SA–DA + Light. (E) *In vitro* release of MB. (F) Antibacterial rates of *P. gingivalis* following treatment with varying concentrations of MB/Sema3A@SA–DA extract. (G) CEJ-ABC distances of rats. All statistical data are represented as mean ± SD ($n = 3$ for F, $n = 5$ for G; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$, NS represents no significant difference). Reproduced with permission [80]. Copyright 2023, Elsevier.

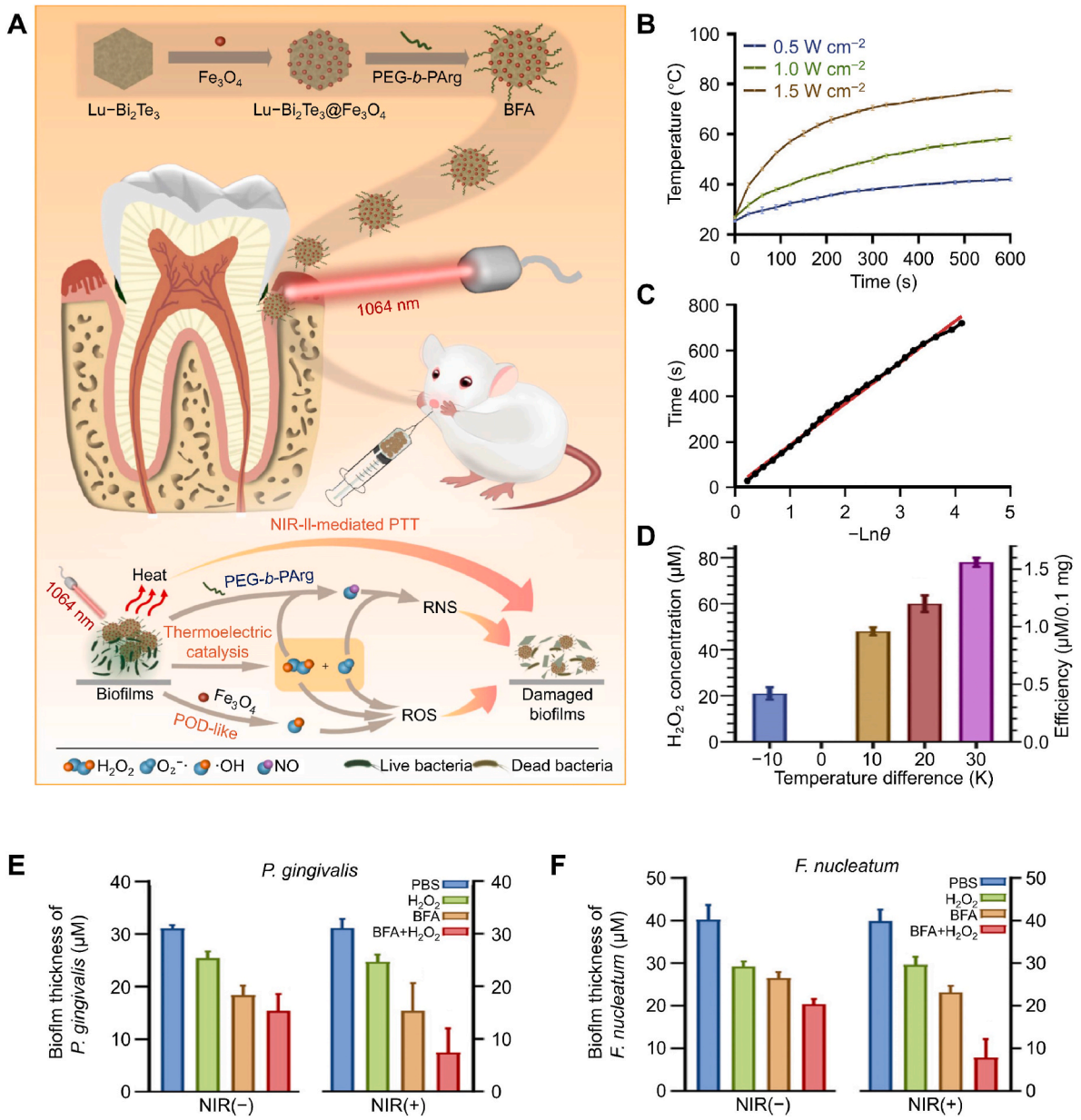


Fig. 4. A nanoplatform combining PTT with heat-induced ROS/RNS was developed for the eradication of biofilms and to facilitate recuperation. (A) Synthesis and biological activity of BFA. (B) Thermal variation of BFA (100.0 μg mL^{-1}) under varying 1064-nm laser irradiances of 0.5, 1.0, and 1.5 W cm^{-2}. (C) PCE of BFA in deionized water. (D) Lu-Bi_2Te_3-mediated (5.0 mg mL^{-1}) H_2O_2 production under varying thermal gradients. (E,F) Average thicknesses of (E) *P. gingivalis* biofilm and (F) *F. nucleatum* biofilm present within different groups. All statistical data are represented as mean ± SD (n = 3). Reproduced with permission [81]. Copyright 2023, Elsevier.

photocatalytic abilities for eradicating dense biofilms, even in deep pockets.

Another challenge is the poor bioavailability of hydrophobic photosensitizers. To improve this, Hu et al. [83] developed a near-infrared (NIR) light-responsive nanoscale drug delivery system using upconversion nanoparticles (UCNPs), mesoporous silica, and carvacryl alcohol (CA). This system increases CA's water solubility and bioavailability. The UCNPs convert NIR light to blue light, activating CA deep within periodontal pockets and improving its therapeutic potential.

A hypoxic microenvironment within periodontal pockets poses additional challenges for aPDT, as the production of ROS mainly depends on O_2 availability [84]. In addition, the insufficient oxygen concentration in biofilms slows down the metabolic rate of deep-seated bacteria and boosts their resistance to antibacterial agents. The hypoxic microenvironment also reduces the effectiveness of antibiotics [85,86]. Therefore, increasing the O_2 content in periodontal pockets and biofilms would help kill the bacteria within [87]. To address this issue, Tonon et al. [88] developed a superhydrophobic (SH) polydimethylsiloxane film that isolated the photosensitizer chlorin e6 onto a non-smooth, solid SH film with channels facilitating O_2 diffusion to the photosensitizer surface, ensuring adequate O_2 supply even in deep periodontal pockets and biofilms. This approach enabled the diffusion of gaseous $^1O_2$ from the SH coating to biofilms, showing a potent bactericidal effect against biofilms.

In addition to nanocarriers delivery, *in situ* O_2 generation is feasible for alleviating biofilm hypoxia [89]. Necrotic tissue at the site of infection often leads to increased intracellular GSH, which rapidly reduces ROS, weakening its antibacterial effect. Sun et al. [68] synthesized a smart nanocomposite with O_2 autogeneration capabilities (Fe_3O_4-silane@Ce6/C6 NP), incorporating MnO_2-modified amphiphilic silane

shells that consume GSH, protecting ROS from rapid reduction by GSH. Furthermore, MnO_2 functioned as a catalytic nanoenzyme, decomposing hydrogen peroxide to provide additional O_2, alleviating hypoxia in periodontal pockets, and enhancing the effectiveness of aPDT. This approach selectively generates O_2 and consumes excess GSH, targeting anaerobic pathogens while protecting periodontal non-pathogenic aerobic bacteria, presenting the potential for treating periodontitis and other anaerobic infections [90].

3.1.2.2. Biomaterials for chemodynamic therapy. Chemodynamic therapy (CDT) is a recently devised biofilms-targeting strategy where a Fenton or Fenton-like reaction, catalyzed by transition metal ions, *e.g.*, iron, copper, manganese, titanium, silver, nickel, and cobalt, breaks down H_2O_2 to produce highly cytotoxic ·OH under acidic conditions, without requiring well-oxygenated microenvironments or external energy input [91]. The highly toxic ·OH exerts a potent destructive effect on bacterial cell walls or membranes, demonstrating excellent efficacy against bacterial infections. However, the low concentration of H_2O_2 in the external microenvironments of biofilms limits the reaction efficiency of CDT, making it essential to design biomaterials that either self-supply H_2O_2 or enhance the conversion efficiency to improve the efficiency of CDT against subgingival plaque biofilms [92].

Recent studies have introduced several promising strategies to address this limitation. Cao et al. [72] reported an H_2O_2 self-supplying nanocomposite (ZnO_2−Fe_3O_4@MV NP) encapsulated in an *S. gordonii* membrane. Fluorescence co-localization analysis showed that the *S. gordonii* membrane vesicles (MVs) exhibited markedly enhanced carrier internalization, with a 5-fold increase in Syto9 and a 3-fold increase in DiI fluorescence, compared to conventional liposomes. This finding indicated that *S. gordonii* MVs more efficiently deliver nanotherapeutics to target bacteria, selectively enhancing drug internalization in *S. gordonii*. This strategy disrupted the basal bacterial layer, leading to the collapse and removal of the symbiotic biofilms.

Under acidic conditions, Fe_3O_4 NP converts H_2O_2 generated by ZnO_2 NP into highly reactive ·OH through the Fenton reaction. Using a 3,3′,5,5′-tetramethylbenzidine (TMB) probe, the authors observed increased absorption peaks at 370 and 652 nm in the UV–vis absorption spectra as the pH dropped from 7.4 to 4.5, indicating that ZnO_2−Fe_3O_4@MV NP generated and decomposed H_2O_2 under acidic conditions, achieving H_2O_2 self-sufficiency and promoting the Fenton reaction. This catalytic process generated cytotoxic ·OH, effectively killing bacteria. To confirm the anti-biofilm effect of ZnO_2−Fe_3O_4@MV NP, the authors conducted a *z*-scan of the symbiotic biofilms and assessed the fluorescence staining intensity of *S. gordonii* and *P. gingivalis*. Results showed that ZnO_2−Fe_3O_4@MV NP effectively destroyed the symbiotic biofilms and eliminated *P. gingivalis*, the symbiotic bacterium. This self-sustaining H_2O_2 and nanocatalytic approach effectively eradicates biofilms formed by *S. gordonii* and *P. gingivalis*.

It is also important to note that the periodontal microenvironments contain a significant amount of non-pathogenic oral flora and the indiscriminate action of ·OH may lead to oral dysbiosis. Seeking to mitigate these effects, Chen et al. [93] designed a CuS/MnS@MnO_2 nanosystem composed of a MnO_2 shell layer and hexagonal CuS/MnS nanocrystal, achieving selective bactericidal effects by generating O_2 through H_2O_2 decomposition, favoring the survival of non-pathogenic bacteria over anaerobic pathogens. Additionally, CuS enables the photothermal removal of biofilms and transfers heat directly to MnS, enhancing the Mn^{2+}-mediated CDT process. This system utilizes endogenous H_2O_2 produced by streptococci within biofilms to generate cytotoxic ·OH, which, combined with photothermal therapy (PTT), disrupts extracellular DNA and biofilms' structures. This multi-modal biofilm eradication strategy holds promise for the clinical management of periodontitis.

3.1.2.3. Biomaterials for sonodynamic therapy. The catalytic efficiency of CDT in treating recalcitrant bacterial biofilms is significantly reduced in complex periodontitis cases involving multiple bacteria species. Sonodynamic therapy (SDT) generates ROS by activating acoustic sensitizers with ultrasound irradiation, inducing cytotoxicity in a broad range of bacteria [94]. SDT offers several advantages: it is non-invasive, high selective in time and space, resistant to bacterial adaptation, capable of deep tissue penetration, and cost-effective. Additionally, SDT shows good efficacy against drug-resistant bacterial infections, making it a promising tool for antibacterial therapy in periodontitis [95,96]. Nevertheless, low ROS production limits SDT's effectiveness. Combining SDT and CDT offers a synergistic approach to address the limitations of each, with promising clinical potential.

Xin et al. [97] designed a multi-functional nanoplatform composed of TiO_2 and Ag that combines SDT and CDT to generate a robust ROS response against periodontitis. Under ultrasonic irradiation, TiO_2 is activated, transferring energy to O_2 and water molecules to produce ROS. The addition of Ag enhances the absorption spectrum of the composite, further increasing the ROS yield. Simultaneously, a Fenton-like reaction between Ag and H_2O_2 generates ·OH. This hybrid SDT and CDT nanoplatform enhances the catalytic efficiency of ROS and exhibits excellent antibacterial effects against pathogens in periodontal tissue, *in vitro* and *in vivo*, demonstrating great potential for clinical application.

3.1.2.4. Nanoenzymes. Numerous studies show that nanoenzymes with peroxidase-like activities catalyze the formation of highly reactive ·OH from low concentrations of H_2O_2, offering an innovative strategy for biofilm control. Nanoenzymes with excellent antibacterial effects have been widely applied in treating periodontitis [98,99]. Au NPs, known for their intrinsic enzyme-like properties, have shown significant biomedical potential. Ultrasmall gold nanoclusters (AuNCs) exhibit high catalytic activity due to an increased number of active sites [100]. However, the non-specific action of ·OH complicates its targeted delivery *in vivo*, limiting its antibacterial potential. Wang et al. [74] incorporated platinum (Pt) atom into Au NC, modifying the catalytic active site to create Au/Pt NC and coupling with glucose oxidase (GOX) to form Au/Pt NC@GOX, which enabled a cascade reaction that converts non-toxic glucose into highly toxic ·OH at the bacterial site, effectively inhibiting or eradicating *F. nucleatum*-induced biofilm. In addition, the synergy between Au and Pt atoms enhances the peroxidase-like (POD-like) activity of the nanocluster, offering an effective nanoenzymes-based approach for periodontitis treatment.

While many studies demonstrate the antibacterial and anti-biofilm effects of ROS-generating nanomaterials, their long-term clinical effectiveness remains uncertain due to limited data. The efficacy of aPDT relies on optimizing key therapeutic parameters, including photosensitizer concentration and irradiation dose. Strategies like CDT, SDT, and the use of nanoenzymes show therapeutic promise, yet their complexity, low biocompatibility, and potential cytotoxicity present challenges. Consequently, comprehensive basic research and clinical trials are crucial for validating their effectiveness and safety.

3.1.3. Photothermal therapy

Over the past few years, PTT has gained traction as a non-antibiotic antibacterial approach. PTT relies on NIR light irradiation of a photothermal agent (PTA), which converts optical energy into thermal energy, raising the target area's temperature to irreparably damage bacteria and biofilm structure [101]. This physical mechanism prevents the development of drug resistance, as bacteria cannot easily adapt to heat. PTA is activated by irradiation to generate heat, which disrupts biofilm structure and kills bacteria within biofilms. In addition, it promotes deeper penetration of antibacterial agents into biofilms while disrupting them, resulting in a synergistic anti-biofilm effect [102]. Accordingly, PTT shows great promise for treating drug-resistant bacteria and biofilms.

PTAs, which can be nanomaterials or small molecules encapsulated

in nanoparticles, are crucial for PTT effectiveness. Achieving controlled delivery of PTAs is vital for optimal therapeutic outcomes. Dong et al. [103] developed a multi-functional nanoplatform (E-Au@H) composed of a gold nanoparticle-modified hydrogel loaded with the tea polyphenol epigallocatechin gallate (EGCG). E-Au@H was quickly heated to 50.7 °C within 5 min under NIR light, showing strong photothermal activity that efficiently eliminates biofilms. Meanwhile, NIR light-regulated the release of EGCG, enhancing its antibacterial effects. This NIR-responsive hydrogel presents a therapeutic option for periodontitis.

Traditional PTT approaches using visible or first near-infrared (NIR-I) light face challenges in reaching deep periodontal pockets. In contrast, NIR-II light exhibits greater tissue penetration and is generally well tolerated, with a maximum permissible exposure [MPE] of 1.0 W cm^{-2} for 1064-nm NIR-II and 0.33 W cm^{-2} for 800-nm NIR-I [104]. By optimizing PTA efficacy and the thermoelectricity of PTT, treatment safety and effectiveness can be improved. Periodontitis can be effectively treated by modifying the PTAs.

Dai et al. [81] designed a bismuth telluride (Bi_2Te_3)-based nanosheet as a PTA for NIR-II PTT due to their strong NIR-II absorption and high photothermal conversion efficiency (PCE). They created a multi-functional photothermal catalyst (BFA NP) by doping Lu-Bi_2Te_3 with Fe_3O_4 and poly(ethylene glycol)-*block*-poly(L-arginine) (PEG-*b*-PArg) (Fig. 4A). Lu-doped BFA showed excellent photothermal properties, with the temperature of a 100-μg mL^{-1} BFA solution increasing from 25 to 41.2 °C at a low power density of 0.5 W cm^{-2} (Fig. 4B). The PCE of BFA in deionized water reached 34.14% (Fig. 4C). BFA promoted the generation of H_2O_2, which increased with temperature (Fig. 4D). H_2O_2 reacts with Fe_3O_4 to produce ·OH and catalyzes the formation of NO from PEG-*b*-PArg. NO then reacts with $\cdot O_2^-$ to form peroxynitrite ($ONOO^-$), which is a reactive nitrogen species (RNS), along with ROS, acts as a broad-spectrum antibacterial, damaging bacterial and sensitizing bacteria to heat, thus amplifying the antibacterial effect of PTT. The anti-biofilm effect of this approach was assessed by measuring biofilm thickness (Fig. 4E and F). Biofilm thickness significantly decreased, from 31.09 ± 1.58 to 7.40 ± 4.26 μm for *P. gingivalis* and from 39.89 ± 2.48 to 7.85 ± 4.02 μm for *F. nucleatum*, following the combined treatment with BFA, H_2O_2, and NIR-II light, showing substantial biofilm removal.

While PTT has shown promising results in treating bacterial infections, it has limitations. The antibacterial effect of PTT correlates with photothermal temperature, requiring temperatures above 50 °C for effective infection control. However, high localized temperatures, prolonged laser exposure, and high PTA doses may damage surrounding healthy tissues [105]. Furthermore, traditional PTAs often exhibit poor hydrophilicity and stability, reducing their anti-biofilm efficacy. These factors limit the standalone use of PTT in periodontitis treatment. In contrast, combining aPDT with PTT may overcome the high-temperature requirement of PTT and aPDT's limited penetration, yielding better therapeutic outcomes through synergistic effects [106,107].

Certain NIR light absorbers, such as indocyanine green (ICG), demonstrate photothermal and photodynamic properties. ICG, which has been FDA-approved since 1959, enhances ROS production and increases temperature under NIR irradiation, providing dual-mode antibacterial effects with strong safety [108]. Xiao et al. [69] developed indocyanine green−rapamycin nanoparticle (ICG−RAPA NP), which increased ROS and temperature levels under NIR exposure, amplifying photodynamic and photothermal effects. This dual approach not only killed periodontal bacteria but also elevated ATP levels, boosting bacterial motility to prevent biofilm formation. However, the negative charge and water solubility of ICG limit its ability to penetrate the negatively charged bacterial cell membrane, constraining its PTT and aPDT effectiveness. To enhance the permeability of ICG, Shi et al. [79] synthesized a star-shaped polycationic brush, poly[2-(dimethylamino) ethyl methacrylate] (sPDMA), using atom transfer radical polymerization. The distinctive brush-like structure of sPDMA improves ICG's adsorption and biofilm permeation, significantly enhancing its PTT and aPDT properties.

Dual-modality phototherapy, combining aPDT and PTT, has shown substantial advantages in antibacterial and anti-biofilm applications. PTT uses longer wavelengths of light capable of penetrating the sites of infection, generating heat that increases the permeability of the pathogen's cell membrane and facilitates ROS entry. This synergy compensates for the low ROS penetration in aPDT and reduces bacterial heat resistance, lowering the temperature threshold needed for effective PTT [109]. Furthermore, the distinct mechanisms of aPDT (chemical destruction of bacteria) and PTT (physical destruction by heat) make it difficult for bacteria to develop simultaneous resistance, significantly reducing the risk of treatment failure.

Despite its potential, dual-modality phototherapy faces challenges, including limited tissue penetration depth of photosensitizers and PTAs, along with possible phototoxicity [110,111]. Efficiently delivering and enriching photosensitizers and PTAs at lesion sites remains challenging. Nanotechnology offers promising solutions, enabling targeted and controlled drug release. For instance, biomaterials encapsulate photosensitizers and PTAs, directing them precisely to the lesion site or releasing them under specific conditions, *e.g.*, light and pH change. This approach improves stability and targeting, enables on-demand treatment, and minimizes accumulation in non-target tissues, reducing toxicity risks [112,113].

3.1.4. Biological antibacterial methods: Probiotics and phages

Probiotics are "living bacteria in sufficient quantities in the host organism that benefit host health". They have shown significant potential in the treatment of periodontitis. Probiotic species, such as *Lactobacillus* and *Bifidobacterium*, are widely utilized for managing periodontal diseases [114]. These probiotics inhibit the growth of periodontal pathogens and increase the proportion of healthy commensal bacteria in subgingival biofilms, thereby correcting dysbiosis and aiding in the resolution of periodontal inflammation [115,116].

The mechanisms of action include competitive inhibition, where probiotics occupy oral surfaces and prevent pathogen attachment and colonization. This reduces pathogen levels and alters plaque composition [114]. Probiotics also produce antibacterial mediators, such as lactic acid and bacteriocins, which inhibit pathogens and disrupt biofilm structure. Furthermore, they interfere with pathogen signaling pathways, hindering biofilm formation and maintenance [117]. Collectively, these actions effectively limit excessive biofilm development and offer promising strategies for preventing and treating periodontitis.

Probiotic therapy also complements traditional treatments, enhancing their overall efficacy. Currently, probiotics are commonly delivered through immediate-release formulations, such as lozenges, mouthwashes, and toothpaste [118–120]. However, the constant flushing by gingival fluid and saliva reduces the retention and colonization of probiotics in periodontal pockets. As a result, frequent use of these products is required to maintain therapeutic effects, which often compromises patient compliance. To address this issue, developing targeted delivery systems capable of transporting probiotics directly into periodontal pockets is essential for improving treatment outcomes.

Nanofibers show great promise as a nanodrug delivery system for probiotics. Their bioadhesive polymers allow adhesion within periodontal pockets, enabling extended drug release [121]. Grilc et al. [122] incorporated spores of probiotic strains *Bacillus* 27.3.Z and *Bacillus* 25.2.M into hydrophilic PEG and composite PEG/alginate nanofiber, achieving a high loading capacity and viability retention after storage. The inclusion of alginate allowed a sustained release of spores, improving delivery. Additionally, bacteria surface modifications enhance probiotics' antibacterial activity [123]. Tang et al. [70] reported a material-enhanced approach by modifying *Bdellovibrio bacteriovorus*, a natural Gram-negative bacterial predator, with ZnO nanorod. Upon collision with pathogens, these ZnO-coated bacteria generated

ROS, aiding plaque biofilm removal. Probiotics exert bacteriostatic actions and metabolites, making them a potential method for preventing and treating periodontitis. However, further research is needed to understand their mechanisms, safety, and efficacy through clinical studies.

Bacteriophages (phages) are viruses that specifically infect bacteria and restore the oral microecological balance following periodontitis onset. Phage therapy involves using virulent phages as antibacterial agents to infect and lyse pathogenic bacteria within biofilms, helping to control infection [124]. Phages penetrate dense biofilms and destabilize their structures, a key advantage in treating bacterial infections in periodontitis [125]. For example, *F. nucleatum*, a key contributor to the formation of oral biofilms and progression of periodontitis, can be targeted by the phage FnpΦ02, which significantly inhibits biofilm formation, helping to suppress periodontitis [126].

Despite their therapeutic potential, phages face challenges in clinical use, such as safety concerns, potential endotoxin release, and immune recognition, which may necessitate a single-use strategy. Additionally, determining effective therapeutic doses can be complex. Genetic engineering and modifications may overcome these issues, enhancing phage effectiveness and safety. For instance, Tinoco et al. [127] engineered the *Enterococcus faecalis* (*E. faecalis*)-specific phage ϕEf11 to broaden its bactericidal activity, effectively reducing the biofilm biomass of both vancomycin-sensitive and vancomycin-resistant *E. faecalis* strains. Delivery methods like hydrogels, ointments, and mouthwashes optimize phage therapy in periodontitis treatment [128–130].

Phage formulations in thermoreversible gel, such as Poloxamer 407 (P407), have shown extended phage activity for up to a month, significantly reducing *E. faecalis* cell counts *in vivo*. These gel-based, slow-release formulations are well-suited for periodontitis therapy, adapting effectively to the complex shapes of periodontal pockets [131]. Phage encapsulation into polymeric systems allows sustained release, enhancing residence time at the site of infection and therapeutic efficacy. Naturally occurring oral phages, genetically engineered phages, and those combined with suitable delivery agents lyse bacterial cells effectively, promoting the amplified release of phage progeny within bacteria and increasing antibacterial effects.

Although promising, phage therapy for periodontitis still requires more research, particularly due to the challenges in replicating the complex, multi-microbial subgingival microenvironments in animal models. Factors including phage interactions with the oral microbiota, stability during administration, and impact on the immune response affect the therapeutic efficacy of phages in periodontitis. Extensive preclinical and clinical studies are necessary to fully understand phages' roles and optimize their use in periodontal therapy. Future advancements may involve combining biomaterials and phage therapy to enhance the prevention and treatment of periodontitis.

3.2. Strategies targeting extracellular polymeric substances

Biofilm dispersion occurs through both passive and active processes. Passive dispersion involves releasing individual or aggregated bacteria due to external forces, such as enzymatic degradation or physical disruption of the biofilm matrices. In contrast, active dispersion is a natural biofilm process triggered by unfavorable environmental conditions, including nutrient deficiency, hypoxia, or elevated nitric oxide (NO) [132,133]. The migration of bacteria from biofilms to more favorable microenvironments typically involves the degradation of EPSs. EPSs are one of the dense ECMs that encapsulate bacteria, mainly water, polysaccharides, proteins, extracellular deoxyribonucleotides, and lipids. It immobilizes bacteria on the surface of tissues, forming a 3D biofilm that protects bacteria from antibacterial agents and immune responses [19]. By disrupting EPSs, dispersed planktonic bacteria

Table 3
Strategies involving bioactive materials for EPS disruption.

Disruption Strategy	Core material/Bioactive material	Action Mechanism	Bacterial biofilm	Ref.
Disturb the balance of electrostatic forces among EPSs and the enzymatic degradation of EPSs	Cationic polymer polyethyleneimine	Cations disrupt electrostatic forces, maintaining the adhesive gel structures of biofilms.	*P. aeruginosa*	[135]
	Bovine trypsin	Bovine trypsin hydrolyzes EPS proteins, disperses biofilms, and reduces EPSs and bacterial biomass.	Multispecies biofilms of *P. gingivalis*, *F. nucleatum*, *A. viscosus*, and *A. actinomycetemcomitans*	[136]
	Papain and trypsin	Papain and trypsin degrade FimP and FimA, key proteins in *Actinomycetes* biofilms, reducing biofilm formation.	Biofilm of *Actinomyces oris*, Multispecies biofilms of samples collected from the tongue dorsum	[137]
	DNase I, DspB, and chitosan-streptomycin hydrogel	Incorporating DNase I and DspB into the hydrogel significantly enhances its reduction of *P. aeruginosa* and *S. aureus* biofilm biomass.	Biofilms of *P. aeruginosa* and *S. aureus*	[138]
Reducing EPS production	D-Galactose	D-galactose binds competitively to the AI-2 receptor in *F. nucleatum*, inhibiting AI-2 activity and reducing biofilm formation.	Biofilms of *F. nucleatum*、*P. gingivalis*, and *T. forsythia*	[139]
	Synthetic *N*-acyl homoserine lactones analogues	Synthetic *N*-acyl homoserine lactone analogues inhibit quorum sensing, reducing biofilm formation in *P. gingivalis*.	Biofilm of *P. gingivalis*	[140]
	3-(Dibromomethylene) isobenzofuran-1(3H)-one derivatives	3-(Dibromomethylene)isobenzofuran-1(3H)-one derivatives, as bromofuranone analogues, inhibit AI-2 activity and reduce biofilm biomass and thickness in *F. nucleatum*, *P. gingivalis*, and *T. forsythia*.	Biofilms of *F. nucleatum*, *P. gingivalis*, and *T. forsythia*	[141]
	Coumarin	Coumarin inhibits AI-2 activity and interacts with the HmuY protein	Biofilm of *P. gingivalis*	[142]
EPS dispersion	Hyperbranched polykanamycins and polyamidoamines	Releasing NO to prevent biofilm formation and disperse established biofilms.	Biofilms of subgingival plaque samples	[143]
	D-leucine, D-lysine, and EcNis	D-amino acids disrupt the bacterial biofilms, EcNis produce hydrogen, antibacterial peptides to kill bacteria.	Biofilms of *P. gingivalis*, *Staphylococcus aureus*, and EcN	[123]

Abbreviations: *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; *A. viscosus*, *Actinomyces viscosus*; Airon NP, amorphous iron nanoparticle; AMP, antibacterial peptide; aPDT, antibacterial photodynamic therapy; Arg, arginine; Au/Pt NC, gold/platinum nanocluster; CD, carbon dot; CDT, chemodynamic therapy; Ce6, chlorin e6; EPS, extracellular polymeric substance; EcNis, *E. coli* Nissle; *F. nucleatum, Fusobacterium nucleatum*; GOX, glucose oxidase; HCA, hydrocaffeic acid; ICG, indocyanine green; MB, Methylene blue; MCD, Metronidazole carbon dots; MV, Membrane vesicles; NP, nanoparticle; NIR, near-infrared; NO, nitric oxide; OMV, outer membrane vesicle; *P. aeruginosa*, *Pseudomonas aeruginosa*; *P. gingivalis, Porphyromonas gingivalis*; PCE, photothermal conversion efficiency; POD-like, peroxidase-like; PTT, photothermal therapy; QS, quorum sensing; RB, rose bengal; RNS, reactive nitrogen species; ROS, reactive oxygen species; *S. aureus*, *Staphylococcus aureus*; SDT, sonodynamic therapy; *T. forsythia*, *Tannerella forsythia*; TCD, Tinidazole carbon dots; TMB, 3,3′,5,5′-tetramethylbenzidine; US, ultrasound.

become more susceptible to antibiotics, making EPSs an important therapeutic target for breaking down biofilm structural and restoring the bacterial sensitivity to treatment [134]. The strategies involving bioactive materials for EPS disruption are summarized in Table 3.

3.2.1. Degradation of extracellular polymeric substances

EPSs can be destroyed based on the properties of their various components. Typically, bacterial biofilms contain only one type of cationic polymer and several anionic polymers, *e.g.*, polysaccharides, DNA, or proteins. Electrostatic forces between macromolecules maintain the adhesive gel structure of biofilms [144]. Adding cations disturbs this balance, causing a phase transition from gel to solution, which breaks down EPSs and increases bacterial susceptibility to antibiotics. Li et al. [135] introduced cationic polymer polyethyleneimine into established biofilms, causing a phase transition that led to matrix disintegration. However, given the diversity of biofilm components and complex macromolecule interactions, advanced techniques are needed to explore the kinetic of these phase transitions in biofilms.

Enzymes are also effective anti-biofilm agents, as they degrade structural components of the biofilm matrices, making it more vulnerable to removal (Fig. 5A). Trypsin, a serine protease, hydrolyzes EPS proteins, disrupting the intercellular skeleton and biofilm structure [145]. Mugita et al. [137] demonstrated that papain and trypsin significantly degrade FimP and FimA, key fibrous proteins in *Actinomyces* biofilms, reducing biofilm formation *in vitro*. In addition, Niazi et al. [146] combined trypsin and chlorhexidine with ultrasound to effectively reduce the survival of bacteria and matrix coverage within biofilms. However, enzymes face limitations, such as sensitivity to protein hydrolysis, instability, high production costs, and limited availability, which currently restrict their clinical application. This situation underlines the need to improve the efficiency and cost-effectiveness of enzymes before their full potential can be realized.

3.2.2. Production regulation of extracellular polymeric substances

QS is a bacterial communication system that regulates the formation and dispersion of biofilms by secreting small molecules to sense the bacterial density and modulate the expression of genes [147]. *N*-acyl homoserine lactones (AHLs) are QS signals involved in biofilm development and pathogenic activities of Gram-negative bacteria in periodontal disease [148]. Quorum quenching (QQ) strategies targeting AHLs effectively control pathogen biofilms (Fig. 5B) [149]. Parga et al. [150] used the QQ enzyme Aii20J to treat subgingival biofilms from periodontitis patients, resulting in a significant decrease ranging from 30% to 60% reduction in biofilm mass.

Autoinducible factor 2 (AI-2) is another QS molecule associated with subgingival biofilm formation in periodontitis. Competitive binding to AI-2 receptors, *e.g.*, D-ribose and D-galactose binding proteins, disrupts QS, preventing biofilm formation by pathogens like *F. nucleatum*, *P. gingivalis*, and *S. gordonii* [151]. Furanone, a structural analog of AI-2, competitively binds to the receptor protein, blocking QS signaling [152].

The use of bioactive materials to disrupt QS and biofilm resistance mechanisms has gained significant attention in recent years [149,153]. Natural polyphenols, which possess a catechol/pyrocatechol structure, inhibit AI-2 signaling and the formation of biofilms, promoting the disintegration of biofilms. Incorporating these naturally derived molecules into bioactive materials offers innovative solutions for biofilm management. For instance, Li et al. [154] developed anti-biofilm

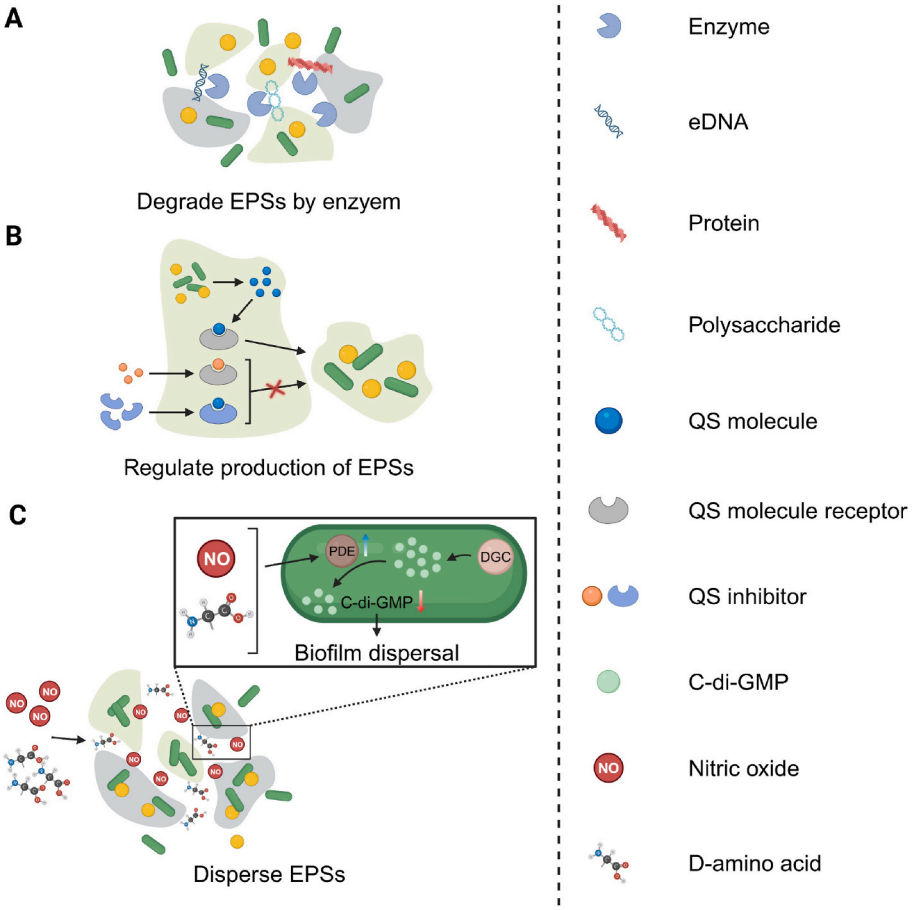


Fig. 5. Interactions between bioactive materials and extracellular polymeric substances and disruption of biofilms. (A) Degrade EPSs by enzyme. (B) Regulate production of EPSs. (C) Disperse EPSs. Created in BioRender. Y. Sun (2025) BioRender.com/j90k561.

nanoparticle using natural polyphenols and the antibiotics tobramycin. The polyphenols inhibit QS and the formation of biofilms, while tobramycin provides strong antibacterial activity. This combination enhances antibiotic penetration and the disruption of biofilm, offering an alternative approach for the removal of biofilms in periodontitis.

3.2.3. Dispersion regulation of extracellular polymeric substances

In addition to direct EPS degradation, dispersal factors trigger biofilm breakdown. These factors either disrupt or mimic natural dispersal signals within biofilms (Fig. 5C). The secondary messenger bis(3′–5′)-cyclic dimeric GMP (c-di-GMP), is a conserved signaling molecule synthesized by diguanosine cyclases (DGCs) and degraded by c-di-GMP phosphodiesterases (PDEs). This molecule is key in controlling biofilm formation and dispersion in pathogenic bacteria [155]. Typically, elevated c-di-GMP levels promote biofilm formation, while reduced levels facilitate biofilm dispersal. Therefore, anti-biofilm materials targeting DGCs and PDEs can be designed to degrade or inhibit c-di-GMP-induced biofilm dispersion [156,157].

NO serves as a signaling molecule in various organisms and pathological processes. Low, non-toxic concentrations of NO deplete exopolysaccharides in EPSs and promote biofilm dispersion. This effect occurs by down-regulating biofilms-related second messengers, suggesting biofilms can be dispersed by delivering NO [158]. However, achieving controlled delivery of NO to periodontal pockets remains challenging. Conventional NO donors, such as *S*-nitrosothiols (RSNOs) and *N*-diazepines (NONOates), lack stability and specificity for localized delivery. Encapsulating NO donors in polymers or modifying polymeric scaffolds allows localized release of NO for antibacterial and anti-biofilm applications [158,159].

Yang et al. [143] modified hyperbranched polyamidoamine (h-PAMAM) with an *N*-diazeniumdiolate NO donor to create NO-releasing polymers that reduced biofilm metabolic activity and eradicated bacteria. Polymers with higher NO payloads exhibited the greatest efficacy against multi-species subgingival biofilms, reducing pathogenic bacteria. Polymeric NO release holds significant potential as a periodontal therapy. Compared to small-molecule NO donors, the polymeric systems provide greater bactericidal effects due to their higher NO load and enhanced interactions with bacteria [160]. The structure of NO donor and release kinetics influence the efficiency of biofilm dispersion. Therefore, designing anti-biofilm NO systems should include positively charged functional groups and controlled, prolonged NO release [161].

In recent decades, an increase has grown in D-amino acids as potential biofilms-dispersing signaling molecules. D-Amino acids prevent biofilm formation or disperse existing biofilms in certain bacteria, suggesting their potential as a new approach to managing biofilms-associated infections [162]. The exogenous D-amino acids inhibit *P. gingivalis* activity and biofilm formation and disperse mature biofilms [123]. However, much current research has focused on evaluating D-amino acid's anti-biofilm properties alone or in synergy with antibiotics, and controlled delivery at therapeutic concentrations remains a challenge.

Addressing this challenge, Fan et al. [163] designed stepwise dual-stimulus-responsive azithromycin nanoparticle (CM/AZM@Tyr NP) with CA-Tyr shell that responded to the acidic microenvironments, releasing D-tyrosine to disrupt biofilms. Cationic CM/AZM micelle bound to negatively charged bacterial cell membrane, allowing for rapid release of AZM that killed bacteria within biofilm depth. Additionally, plasma polymer encapsulation technology is also being explored for the sustained release of drugs. Encapsulating D-amino acids in polymers improves their clinical applications. For instance, Khider et al. [164] encapsulated D-amino acids in plasma polymer (PPEDAA), allowing for their gradual release and disruption of *E. faecalis* biofilms. However, studies on D-amino acids for subgingival biofilm dispersion in periodontitis are limited, and further studies are needed to validate their efficacy in biofilm disruption.

Most biofilm dispersion involves degrading EPSs, rendering planktonic bacteria—now unprotected by the matrices—more susceptible to antibacterial agents [165]. Enzymes applied to degrade structural components of the biofilm matrices facilitate biofilm removal but face limitations in clinical settings, including vulnerability to proteolysis, low stability, and limited effectiveness [133]. Certain signaling molecules, such as AHL QS molecules, the secondary messenger c-di-GMP, and D-amino acids, rapidly disperse biofilms by inhibiting matrix formation or acting as dispersal signals. Reversing EPS gelation has also proven to be a simple yet effective strategy for biofilm elimination.

However, the use of signaling molecules to disperse subgingival biofilms in periodontitis remains underexplored, and further research is required to validate their effectiveness in periodontal applications. Given the diversity of pathogenic bacteria in periodontitis, most studies on signaling molecules are based on *in vitro* models, and additional *in vivo* studies are needed to assess their safety. The primary challenge is identifying and deploying agents that selectively target pathogenic bacteria without inhibiting symbiotic species. In the future, the biofilm dispersants may partially replace antibiotics, potentially reducing the prevalence of antibiotic resistance.

3.3. Synergistic approaches

Biofilms are complex, 3D structures that protect bacteria from antibiotics, making single-agent treatments often insufficient for effective infection control. Using biofilm dispersants as a therapeutic strategy has shown promise by increasing the susceptibility of dispersed bacteria to antibiotics [166]. However, there remains a risk of infection recurrence, as current antibacterial methods often fail to simultaneously remove biofilm structures, matrix debris, and dispersed bacteria. If not eliminated, residual or dispersed bacteria potentially migrate to new areas, allowing biofilm re-establishment and resulting in recurring infection. Therefore, combining dispersants with antibacterials offers a synergistic approach to more effectively eradicate biofilms [123,167].

Proteases are known to disrupt the structures of biofilms by hydrolyzing proteins associated with EPSs, facilitating deeper antibacterial penetration. Liu et al. [168] developed a combination therapy using matrices-degrading enzymes and AMPs. Plant-made AMP (PMAMP), which possess bactericidal activity and inhibit biofilm formation, were combined with proteases to penetrate biofilms and eliminate embedded bacteria. Gao et al. [169] designed nanoprotease-loaded CuS NP (CuS@A NP) that combined the degradation of biofilms by protease with the photodynamic and photothermal properties of CuS and demonstrated strong antibacterial activity against *F. nucleatum* biofilm.

In addition, Wu et al. [106] developed a core−shell nanocomposite (Ag_2S@ZIF−90/Arg/ICG) with synergistic PTT/aPDT and NO production effects. Under NIR light, the composite generated heat and ROS while oxidizing L-Arg to produce NO. NO activated c-di-GMP PDEs in mature biofilms, breaking down c-di-AMP and promoting biofilm decomposition. In addition, NO may react with ROS to form $ONOO^-$, which disrupted bacterial cell membranes. This material released NO within 2 min of 808-nm NIR light exposure, which stoped when the light was turned off, allowing laser-controlled NO release. *In vitro* experiments demonstrated that NO markedly enhanced the anti-biofilm efficacy of this material. In contrast to the control group, Ag_2S@ZIF−90/Arg/ICG+NIR (PTT/aPDT/NO) showed a 4-log CFU reduction in *P. gingivalis* biofilm following NIR exposure. Compared to the PTT (Ag_2S + NIR and Ag_2S@ZIF−90+NIR) and PTT/aPDT (Ag_2S@ZIF−90/ICG + NIR) groups, PTT/aPDT/NO yielded a higher bacterial dead rate and reduced biofilm area. NO synergy with PTT/aPDT enhanced deep-tissue biofilm eradication and prevented bacterial recolonization.

Furthermore, delaying or inhibiting biofilm formation represents an effective strategy to prevent the spread of biofilms-associated infections [170]. Cheng et al. [171] developed bifunctional nanoparticle by co-assembling quercetin, a natural compound with anti-QS properties,

and copper ion (Cu^{2+}), known for their antibacterial activity, using a simple fabrication method. This combination therapy effectively suppressed the QS process and reduced biofilm formation. Additionally, the bactericidal effect of Cu^{2+} directly eliminated both planktonic and biofilms-associated bacteria, thereby efficiently preventing the spread of biofilms-related infections.

While combination therapies with dispersants and antibacterials, or antibacterials combined with inhibition of biofilm formation, show potential, challenges remain for clinical application. Developing synergistic antibacterial materials always requires complex synthesis and modification, complicating preparation and increasing the risk of adverse effects. Ensuring that both drugs are present at the infection site in optimal concentrations is also difficult. Additionally, combination therapy may involve complex treatment regimens, higher costs, and potential antagonistic interactions. Future research should aim to simplify synthesis, enhance the biosafety of combined antibacterial materials, optimize drug concentrations, and address the challenges of co-administration.

4. Conclusions and perspectives

Periodontitis, a common biofilm-associated infection, presents significant treatment challenges due to the resistance of biofilm bacteria, which can be up to 1000 times more resistant than planktonic bacteria. Despite the ongoing research, biofilm infections remain problematic. Advances in biomaterials and a better understanding of biofilms have developed sophisticated biomaterials for subgingival plaque removal in periodontitis patients. The key to effective anti-biofilm biomaterial design lies in their ability to disrupt the biofilm's structural components—pathogenic bacteria and EPSs. Biofilms serve as a protective barrier, shielding bacteria from antibacterial agents and immune responses, which makes breaking down EPSs a critical strategy for combating biofilms-related infections. Furthermore, biomaterials can be designed to directly interact with the bacteria within biofilms and kill them, inhibiting EPS production or dismantling the biofilm structure.

The success of these biomaterials lies in their adaptable chemical and physical properties, allowing them to respond to the dynamic microenvironments of periodontal pockets for more precise and effective treatment. This review explored the therapeutic potential of diverse functional biomaterials for targeting subgingival plaque biofilms, guided by insights into the composition of biofilms.

Various strategies are currently employed to eliminate mature subgingival biofilms. These include the use of antibacterial agents, the induction of ROS to disrupt bacterial structures, localized high-temperature treatments to eradicate bacteria, and biocontrol strategies that harness probiotics and phages to target and eliminate pathogenic bacteria in biofilms. Additionally, strategies focus on degrading EPSs through enzymatic breakdown, the delivery of signaling molecules to promote EPS dispersion, or the interruption of bacterial communication pathways to prevent EPS formation. Combining these strategies synergistically enhances the effectiveness of biofilm removal [165].

Precise and selective bactericidal treatment is essential in periodontal therapy to maintain microbial balance [172]. One strategy exploits the oxygen sensitivity of anaerobic pathogens by using biomaterials that deliver or generate oxygen within periodontal pockets, selectively eliminating anaerobes while preserving commensal bacteria [173]. Targeting the QS in pathogenic bacteria within biofilms provides an effective approach for selective control. By introducing QS inhibitors, biofilm formation and virulence factor expression can be disrupted, achieving pathogenic bacterial suppression without direct bactericidal effects [174]. The unique microenvironments of periodontitis, such as acidity or glucose abundance, allow for responsive biomaterial designs that release antibacterials precisely, minimizing harm to beneficial species [175]. Probiotic and phage therapies further support microbial balance by targeting pathogens without affecting commensal bacteria [70,176]. These strategies collectively enhance the precision of periodontal therapy, promoting a healthy oral microbiome.

Developing biofilms-resistant biomaterials for periodontitis must address key challenges, such as biofilm complexity, bacterial resistance, and selective bactericidal action. Biomaterials should be designed to penetrate or disrupt biofilm matrices, delivering therapeutic agents directly to embedded bacteria. Drug-carrying nanoparticles are particularly promising, as their small size and surface modifications enhance biofilm penetration and binding, improving treatment precision [167]. Long-lasting release systems using polymeric nanoparticles sustain antibacterial activity and reduce drug toxicity, enabling prolonged therapy.

Smart bioactive materials are also highly effective, as they respond to biofilms-specific stimuli like pH, ROS, or enzymes, allowing for controlled, targeted drug release [177,178]. For example, pH-responsive biomaterials release antibacterial agents in the acidic biofilm microenvironments, activating drugs only at infection sites [179,180]. Similarly, enzyme-responsive materials leverage periodontitis- or biofilms-associated enzymes to trigger drug release, ensuring precise treatment [51]. Additionally, incorporating regenerative properties into these materials enables simultaneous infection control and tissue repair, providing a sustainable solution for periodontitis [181].

Among bioactive materials, nanoparticles, hydrogels, and peptides each offer unique advantages but also present challenges. Nanoparticles enhance antibacterial efficacy with modifiable surfaces and additional features like photothermal or magnetic responsiveness for improved biofilm removal [182]. However, their potential cytotoxicity limits long-term use, highlighting the need for safer designs. Peptides, known for low toxicity and selective antibacterial activity, are easily tailored for specific therapies but face stability issues and rapid degradation, limiting their sustained effectiveness [183]. Research should focus on enhancing peptide stability and extending their therapeutic duration. Hydrogels provide controlled drug release for prolonged effects, and their stimulus responsiveness and injectability make them ideal for targeting complex sites like periodontal pockets [184]. Combining the strengths of nanoparticles, hydrogels, and peptides while addressing their limitations through innovative design leads to the next generation of anti-biofilm biomaterials. These advancements promise safer, smarter, and more effective solutions for periodontitis treatment.

While significant strides have been made in treating subgingival biofilms with rationally designed biomaterials, several challenges remain. First, most studies have used single-species biofilm models that do not fully replicate the complex, multi-species biofilms in periodontitis. Developing more accurate models that reflect infected subgingival plaque biofilms will improve clinical relevance and reduce bias [185]. Additionally, producing high-quality biomaterials, cost-effective on a large scale, remains challenging due to their complex compositions. The feasibility of smart-response biomaterials may also be limited in clinical settings where using magnetic fields or NIR light is impractical. Although acute biocompatibility has been assessed *in vitro* and *in vivo*, laboratory and animal model results may not translate to human outcomes due to differences in periodontal structure, microbial diversity, and disease progression. Meanwhile, to ensure efficient treatments, further investigation into the acute and long-term toxicity, biodegradability, *in vivo* distribution, and overall biosafety of biofilms-resistant biomaterials in both animals and humans is necessary.

In conclusion, biomaterials as anti-biofilm agents represent a promising approach for periodontitis treatment, with future strategies likely to incorporate multiple treatment modalities. This review has highlighted recent advances, ongoing challenges, and future directions in biomaterials-based treatments for mature subgingival plaque biofilms. With the rapid progress in nanotechnology and biotechnology, it is expected that increasingly effective biomaterials will soon be developed, enhancing clinical anti-biofilm therapies and providing more personalized, effective treatment options for periodontitis patients.

CRediT authorship contribution statement

Jiawen Tao: Writing – review & editing, Writing – original draft, Conceptualization. **Yirong Sun:** Writing – review & editing, Conceptualization. **Guoliang Wang:** Writing – review & editing. **Jingru Sun:** Writing – review & editing. **Shujun Dong:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Jianxun Ding:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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