



Smart dental materials for antimicrobial applications

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ABSTRACT

Smart biomaterials can sense and react to physiological or external environmental stimuli (e.g., mechanical, chemical, electrical, or magnetic signals). The last decades have seen exponential growth in the use and development of smart dental biomaterials for antimicrobial applications in dentistry. These biomaterial systems offer improved efficacy and controllable bio-functionalities to prevent infections and extend the longevity of dental devices. This review article presents the current state-of-the-art of design, evaluation, advantages, and limitations of bioactive and stimuli-responsive and autonomous dental materials for antimicrobial applications. First, the importance and classification of smart biomaterials are discussed. Second, the categories of bio-responsive antibacterial dental materials are systematically itemized based on different stimuli, including pH, enzymes, light, magnetic field, and vibrations. For each category, their antimicrobial mechanism, applications, and examples are discussed. Finally, we examined the limitations and obstacles required to develop clinically relevant applications of these appealing technologies.

1. Introduction

Teeth have limited self-regeneration capability, and thus we rely on dental materials to treat and improve oral health [1]. Enamel is acellular and does not self-regenerate. Unlike bone [2], dentin's self-regeneration capacity is limited and conditioned by the dental pulp stem cell pool [3]. For example, in response to caries, odontoblast cells deposit minerals and form reactionary dentin [4]. This produced tissue is a poorly organized with tubular structure and cells trapped within the matrix [5,6]. Dental materials are used to modify, prevent, diagnose, and alleviate oral and dental pathological conditions. For example, resin composites are commonly used to restore teeth function after infection by pathogens that destroyed the tissue [7]. At the same time, superparamagnetic iron oxide (SPIO)/colloidal gold nanoparticles (NPs) have been used as a theranostic agent for dental pulp capping showing improved magnetic resonance imaging and dentin regeneration capabilities [8]. Unfortunately, the incidence of major oral diseases remains high even though they could be largely preventable through a simple self-care

intervention [9]. For example, dental caries affects 92% of adults in the USA [10]. As a result, dental materials continue to be a fundamental tool in dentistry. The oral cavity is a harsh and hostile environment for dental materials. Bacteria can produce acids that demineralize hard tissues contributing to the failure of both direct and indirect restorations. They do this by interfering with esterase's from saliva causing hydrolytic degradation of dental resin adhesives [11–13]. An ideal dental material is required to fight pathogens, prevent hydrolytic degradation, promote remineralization, bond strongly to tissues, and regenerate dental tissues to treat a dental disease. Specifically, a compound that can withstand all these degradative insults for the duration of treatment. As of today, we still have not found the “holy grail” of dental materials for different dental treatments.

Recent advances in technology and manufacturing tools (e.g., additive manufacturing) are enabling the development of “smart” dental materials that offer multiple functionalities for different therapies. In general, “smart” biomaterials change one or more of their properties in response to a stimulus [14,15]. For example, enzymes produced during

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the progression of a disease can trigger a smart biomaterial to release specific drugs for treatment at the required moment. The definition of smart biomaterials is very broad, often misinterpreted, and non-inclusive hampering the identification and classification of biomaterials with different magnitudes of “smart” functions. To solve this dichotomy, Montoya et al. (2021) purposely classified smart biomaterials according to their level of smartness, which was determined by the degree of interaction between the biomaterial and the surroundings, and the precision to deliver a therapy [16]. Four levels of smart biomaterials were defined, including bioinert, bioactive, bioresponsive, and autonomous (Fig. 1).

Bioinert biomaterials cause minimal interaction with surrounding tissues and have minimal harm or toxicity to the surrounding tissues after implantation [17]. For example, polyetheretherketone (PEEK) is a safe, chemically inert biomaterial used for oral implants, crowns, bridges, endoposts, and denture frameworks [18]. Other bioinert dental materials include 316L stainless steels [19], titanium [20], and polymethyl methacrylate (PMMA) [21]. Active or bioactive materials induce a specific biological response at the material-tissue interface after implantation or contact with tissues, cells, or body fluids [22]. In this context, bioactive refers to materials that provide beneficial therapy (e.g., antibacterial, regeneration, drug delivery) and not a biomaterial that only provides remineralization [23]. These biomaterials release the therapy “uncontrollably” after being installed in the body. For example, fluoride-releasing compounds stabilize the tooth’s cyclic demineralization and remineralization processes [24]. When the saliva pH is less than 5, fluoride ions (F⁻) replace OH⁻ ions in the tooth hydroxyapatite (HAP), resulting in the formation of fluorapatite (FA) or fluorhydroxyapatite (FHA), compounds more resistant to changes in pH and therefore resistant to demineralization [25]. Moreover, fluoride is toxic to bacterial cells by inhibiting bacterial growth and interfering with its acidogenicity, acidurancy, and adherence to the tooth surface [26]. Bioinert dental materials can be upgraded to bioactive via surface coating or functionalization (see Section 3.1). *Responsive, bioresponsive, or stimuli-responsive biomaterials* can “sense” a specific stimulus (e.g., light, temperature, pH changes, electrical and magnetic fields, enzymes) to then “respond” by releasing a pre-programmed therapy [27]. They can react to in-body or out-body signals. For example, a dental composite is fabricated with pH-sensitive NPs that deliver antimicrobial agents under certain pH levels (acidic) to treat caries [28]. Finally, *autonomous* biomaterials can sense multiple stimuli and adjust their response accordingly to offer an appropriate response for each need at different time points. This class of biomaterials is the smartest. For example, magnetically driven nanobots loaded with antibacterial therapies are able to penetrate dentinal tubules in radicular dentin to sterilize and treat root canal infections [29]. Yet, dentistry has not fully harnessed these smart biomaterials’ potential for improving oral health.

The use of smart biomaterials in different areas of medicine has been

exponentially growing in recent years [30]. They have a wide range of applications such as drug delivery [31,32], biosensors [33,34], tissue engineering [35,36], antimicrobial [37], tissue regeneration [30], and remineralization [38], among many others. For example, smart piezoelectric scaffolds are being used in tissue engineering to conveniently generate electric signals analogous to native tissues for enabling physiological functions [39,40]. Dentistry is beginning to benefit from the smart functionality of these biomaterials. This article aims to compile how smart biomaterials are being applied to prevent and treat infections. Specifically, this article describes how active, bioresponsive, and autonomous biomaterials are designed and used for antimicrobial therapies in dentistry.

2. Oral environment and the need for antimicrobial dental materials

The oral cavity is the second most complex microbial community in the human body. It is comprised of bacteria, viruses, fungi, and protozoa [41]. More than 700 microbial species form biofilms within the oral cavity, such as teeth and dental materials [42,43]. Oral biofilms generally coexist in a symbiotic (balanced) state [42]. Under these conditions, the proliferation of pathogenic oral microorganisms is suppressed, preventing the progression of a disease [44]. For example, the positive interplay between the host’s immune system with its microbial symbionts (commensal species) prevents acute infections of the oral mucosa despite dense microbial colonization [45]. Dysbiosis occurs when the balance within the microbiome is disrupted. Generally, in this case, disease-associated pathogens increase in number while symbionts decrease. Factors driving oral dysbiosis include changes in saliva (flow/composition), poor oral hygiene, antibiotic treatment, and lifestyle choices (diet, smoking) [46]. For example, the interface between restoration and dental tissue harbors bacteria that are impossible to remove with conventional cleaning methods resulting in secondary caries and premature restoration failure [47]. In addition to biological factors, oral health involves social, economic, political, and cultural aspects (e.g., social structure and health beliefs) [48]. For example, socioeconomic inequalities (i.e., income and education access), as well as public policies and availability of services, influence the general health status of populations and the use of medical and dental services [49].

The harmful change in the microbiota’s natural balance may lead to oral diseases such as caries, periodontitis, root canal infections, peri-implantitis, pulpitis, candidiasis, denture stomatitis, and soft tissue infections [50] (Fig. 2). For example, in caries, an increase in sugar intake and a reduction in saliva flow results in the growth of acid-producing and acid-tolerating bacteria (e.g., *Streptococcus mutans*) that demineralizes hard tissues and inhibits the growth of commensal species [51]. If pathogenic biofilms are not controlled, oral infections can become chronic, causing loss of dental tissues and even resulting in

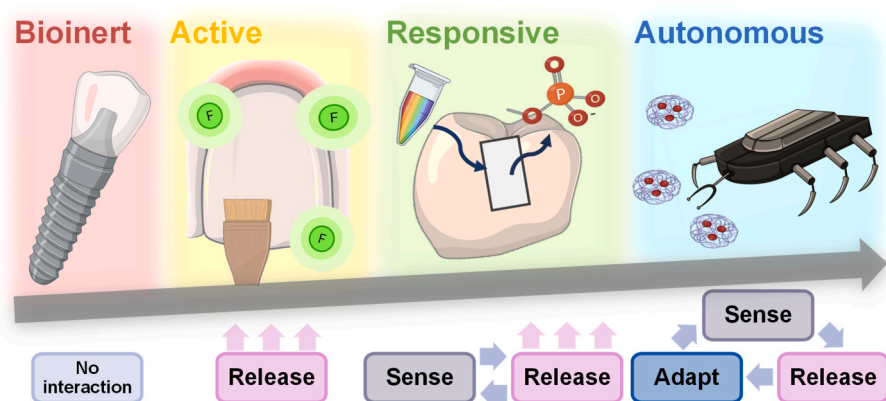


Fig. 1. Levels of smart biomaterials are classified as bioinert, bioactive, bioresponsive, or autonomous. Bioinert biomaterials cause minimal interaction with surrounding tissues and are the least smart. Bioactive materials release an active therapy after implantation to elicit a specific biological response at the material-tissue interface. Bioresponsive materials react to internal or external stimuli releasing specific agents for therapy. Finally, autonomous (or self-sufficient) materials respond holistically to the microenvironment complexity (adapting to changing conditions).

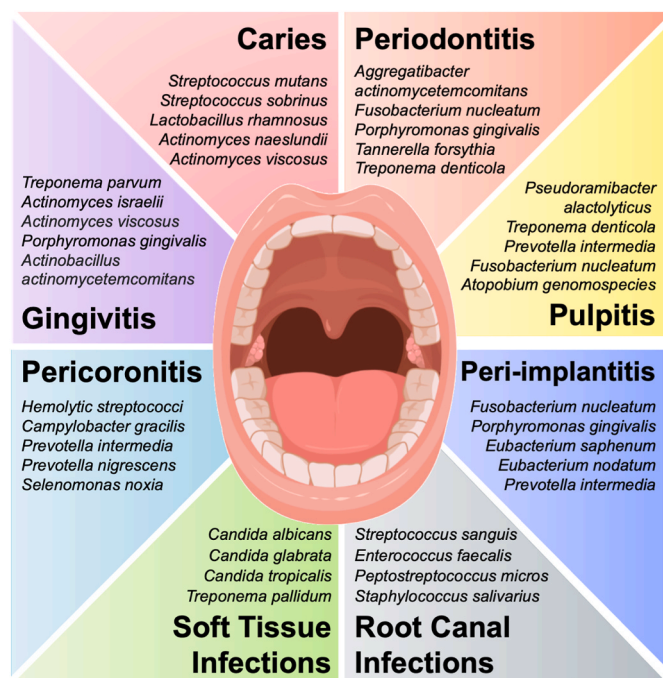


Fig. 2. Pathogen microorganisms associated to oral and systemic diseases.

tooth loss [52]. Therefore, developing dental materials offering antimicrobial therapies is necessary to prevent dental infections and early failure of treatments [53].

Although oral infections are generally polymicrobial in nature, specific pathogens have been associated with specific dental infections (Fig. 2). The primary strategy for developing antimicrobial biomaterials is to deter the growth or target of those pathogens. For example, *S. mutans* has been the primary pathogen associated with dental caries, while the excessive growth of *Candida albicans* is related to the development of candida-induced denture stomatitis [54,55]. Most anti-caries biomaterials are tested against only this pathogen. However, infections are usually polymicrobial. *S. mutans* does not act alone in caries development since there are interactions between different microorganisms. For example, *C. albicans* and *S. mutans* strongly interact during caries development [53]. Microbial products from this cross-kingdom interaction stimulate the accumulation of *S. mutans* within biofilms resulting in increased severity of disease and difficulty of treatment [53]. More sophisticated strategies to develop antimicrobial dental materials include targeting specific virulent genes related to a particular infection or interrupting the bacterial communication mechanisms (i.e., quorum quenching) via enzymatic degradation of signaling molecules, blocking signal generation, and blocking signal reception [56]. For example, the extracellular polymeric substance (EPS) is a protective layer where cells are embedded during biofilm development. Targeting the disruption of the EPS via enzymes (e.g., dispersin B) will offer antibiofilm therapies [57]. Quorum quenching via degradation and inhibition of autoinducers produces the suppression of quorum sensing and prevents density-dependent functions such as virulence and biofilm formation [58]. The main advantage of these approaches is preventing commensal organisms from eradicating. The ideal antimicrobial strategy would consider the combination of antibacterial agents (removal of pathogens) with capabilities for EPS disassembly and quorum quenching [57].

3. Smart dental materials for antimicrobial and antibiofilm therapies

The dental field has used a plethora of antimicrobial agents to treat different infections. A summary of the most common agents and their

mechanisms is presented in Table 1. Additional information regarding antimicrobial dental materials is found in recent reviews [59–72]. This review is not a presentation of the menu of all the antimicrobial agents used in dentistry. Yet, it's a novel review of the different strategies to deliver these antimicrobial agents classified based on the biomaterial's smartness level. For example, silver is a traditional antibacterial agent used to treat/prevent dental caries. A common delivery method of this agent is by applying a coating over a surface (e.g., SDF – silver diamine fluoride) [73]. However, since silver can now be fabricated in nano-sizes (NPs), it can be encapsulated or loaded in different vehicles or carriers for a “sophisticated” or “smart” delivery. In addition, the field has seen the development of dental materials offering multiple antimicrobial functions (e.g., killing pathogens and destroying the biofilm matrix) by combining different agents into a single carrier. For example, a dual antibacterial system consisting of NPs loaded with myricetin and farnesol can reduce biofilm acidogenicity and EPS synthesis since farnesol acts as a membrane-disrupting agent and Myricetin kills *S. mutans* biofilms [74]. This paper shows the different approaches used to deliver/release antimicrobial agents in dentistry, including bioactive, bioresponsive, and autonomous.

3.1. Bioactive antimicrobial therapies

Different antimicrobial agents are employed in bioactive therapies, including chemical compounds (e.g., antibiotics such as chlorhexidine (CHX), minocycline), cationic monomers [75,76] (e.g., quaternary ammonium methacrylate, MDPB), antimicrobial peptides (AMPs) [77], and metallic and non-metallic fillers (e.g., zinc oxide - ZnO) [78,79]. Bioactive technologies usually consist of the incorporation of these antimicrobial agents within a carrier (biomaterial) to deliver the therapy right after implantation. For example, leachable antibiotics such as CHX, tetracyclines, and metronidazole have been incorporated into adhesives [80], sealants [81], and dentures [82] preventing biofilm formation and suppressing microbial growth. Other carriers for antibacterial agents in the nano-space have been studied [83,84], including dendrimers [85], nanocapsules [86], core shells [87], liposomes [88], micelles [89], and nanofibers [90]. Due to their large contact surface, nanofibers are used as high-loading carriers [91], while micelles are preferred due to their easy manipulation and encapsulation of the agent [92]. The advantages of these nano-carriers are the improved control of agent release, pharmacokinetics (in the case of antibiotics), increased agent selectivity, and thus, treatment effectiveness [83,93]. Many of these bioactive antimicrobial formulations are already used in clinical practice. For example, Arestin® utilizes polylactide-glycolic acid copolymer (PLGA) microspheres that contain minocycline hydrochloride (antimicrobial agent) to treat periodontal disease [94]. A similar concept was developed by using microspheres of calcium polyphosphate glass loaded with minocycline for sustained release of effect [95].

Bioactive monomers are usually incorporated in dental resins (composites, primers, and adhesives) for antimicrobial therapies [96–98]. They have demonstrated superior antibacterial effects when unpolymerized but also offer contact inhibitory effects after polymerization. Antibacterial monomers can also be immobilized within the polymer chain but also free to act as a leachable compound [96]. Recent efforts have been focused on increasing the monomer concentration (up to 5%) to improve the antimicrobial effect without compromising biocompatibility, solvent sorption, mechanical properties, and curing performance [96]. These agents have been tested for various gram-positive and gram-negative bacteria, including caries- and endo-related pathogens. Commercially, MDPB has been added into a primer solution of a self-etching system (Clearfil Liner Bond 2, Kuraray Medical, Japan) and as an adhesive (Clearfil SE Protect), showing bactericidal effects against a broad range of caries-related pathogens [99].

Bioactive fillers have gained attention as a promising strategy to overcome the concerns regarding microbial resistance to antibiotics

Table 1
Conventional materials/agents used in the prevention and treatment of oral and systemic diseases and their antimicrobial mechanism [75,78,96,106].

Type	Antimicrobial Agent	Antimicrobial Mechanism	
Chemical agents	Chlorhexidine (CHX)	Binds to the bacterial cell wall interfering with the cell membrane transport systems causing cytoplasmic protein precipitation	
	Tetracycline (minocycline, doxycycline)	Attaches to the bacterial 30S ribosomal subunit preventing protein synthesis	
	Metronidazole	Inhibits protein synthesis by interacting with DNA	
	Triclosan (TCS)	Blocks bacterial fatty acid biosynthesis at the enoyl-acyl carrier protein reductase (FabI) step	
	Amphotericin-B	Induces ergosterol sequestration resulting in membrane stability disruption.	
	Quaternary ammonium compounds (cetyl pyridinium chloride, cetyl trimethyl ammonium bromide, octenidine, cetrimide)	Induces antibacterial action through attraction to the negatively charged bacterial membrane	
	Nitrous oxide (NO)	Produces reactive nitrogen oxide species (RNOS), causing oxidative and nitrosative damage by altering DNA, inhibiting enzyme function, and inducing lipid peroxidation	
	Sodium hypochlorite (NaOCl)	Interferes in the cytoplasmic membrane integrity causing enzymatic inhibition and biosynthetic alterations in the cellular metabolism	
	Natural agents and extracts	Catechins (Epigallocatechin-3-gallate (EGCG) and Gallic acid (GCG))	Binds to the bacterial cell wall interfering with its biosynthesis/reacts with dissolved oxygen in an aqueous solution, generating hydrogen peroxide/inhibits the bacterial type II fatty-acid synthase
		Coffea arabica or canephora	Inactivates cellular enzymes
Cranberry proanthocyanidins		Affects bacterial adhesion, coaggregation	
Alliin (diallyl thiosulfinate)		Inhibits sulfhydryl-dependent enzymes (alcohol dehydrogenase, thioredoxin reductase, and RNA polymerase)	
Isothiocyanates		Reacts with proteins that disturb bacterial biochemical processes	
Clove oil (Eugenol)		Damages and disrupts the bacterial cell membrane	
Citrus limonum/Citrus aurantium		Disrupts bacterial cytoplasmic membrane	
Punica granatum		Inhibits extracellular microbial enzyme and oxidative phosphorylation	
Propolis compounds (Farsenol)		Interferes with the permeability of the cellular membrane disrupting the membrane potential and adenosine triphosphate (ATP) production	
Cinnamomum zeylanicum		Destroys the membranes of bacterial cells	
Urushiol	Destroys bacterial morphology and structural		

Table 1 (continued)

Type	Antimicrobial Agent	Antimicrobial Mechanism
Compounds	Quaternary ammonium polymers (12-methacryloyloxy dodecylpyridinium bromide (MDPB), methacryloxyethyl cetyl dimethyl ammonium chloride (DMAE-CB), quaternary ammonium dimethacrylate (QADM), Dimethylaminohexadecyl methacrylate (DMAHDM), 2-(methacryloyloxy)-N-(2-(methacryloyloxy)ethyl)-N,N-dimethylethan-1-aminium bromide (IDMA1), N,N'-([1,1'-biphenyl]-2,2'-diylbis(methylene))bis(2-(methacryloyloxy)-N,N-dimethylethan-1-aminium) bromide (IDMA2), 2-Dimethyl-2-dodecyl-1-methacryloxyethyl ammonium iodine (DDMAI), dimethylaminododecyl methacrylate (DMADDM), dimethylaminohexadecyl methacrylate (DHAHAD))	integrity of the intracellular matrix Induces antibacterial action through attraction to the negatively charged bacterial membrane
	Zwitterionic polymers (Poly(2 (methacryloyloxy) ethyl phosphorylcholine) (PMPC), poly (carboxybetaine) (pCB), poly (sulfobetaine) (pSB), poly (carboxybetaine acrylamide) (pCBAA))	Forms a hydration layer via electrostatic interaction and hydrogen bonds that lead to a strong repulsion to protein adsorption and bacterial adhesion
	Chitosan	Binds to the bacterial cell wall altering the membrane permeability, causing inhibition of DNA replication and, subsequently, cell death
	Catechol derivatives (Polydopamine (PDA), L-3,4-dihydroxyphenylalanine (L-DOPA))	Produces hydrogen peroxide, which subsequently produces hydroxyl radicals
	Polyaniline (PANI)	ROS production that damage proteins and/or the cell membrane, resulting in cell lysis
	Polyamidoamine (PAMAM)	Binds to the cellular lipid membrane followed by insertion into the membrane, leading to effective bacterial death
	Silver (Ag)	Liberation of ions that adhere to the bacterial cell wall and cytoplasmic membrane leading to disruption of the bacterial envelope
	Magnesium oxide (MgO)	Damage of the outer and/or inner bacterial membrane/oxidative damage by ROS/inhibition of essential enzymes/degradation of DNA
	Copper (Cu)	
	Zinc oxide (ZnO)	
Titanium dioxide (TiO ₂)		
Copper iodide (CuI)		
Silicon dioxide (SiO ₂)/Mesoporous silica		
Iron oxide		
Silver oxide (Ag ₂ O)	DNA loses its replication ability, and the cell cycle halts at the G2/M phase owing to the DNA damage	
Graphene/Graphene oxide/Carbon	Oxidative stress, membrane stress, and electron transfer	
Zeolite	When loaded with biocidal cations, its antimicrobial efficiency is increased	
Peptides	GH12/GH12-M1/GH12-M2	

(continued on next page)

Table 1 (continued)

Type	Antimicrobial Agent	Antimicrobial Mechanism
	Dermaseptin K4-S4(1–15) KSL L-K6 ZXR-2 GL13K Dhvar4 Lys-a1 AMP17/AMP2 Nal-P-113 TNH19 PAC113	Disrupt the bacterial cell membrane and enter the bacterial cells. Later, bind to DNA, inhibiting enzymatic activity, protein synthesis, nucleic acid biosynthesis, and cell division
Enzymes	α -Amylase	Inhibits extracellular polymeric substances by preventing the adherence of the microbial cells
	Salivary peroxidases (sialoperoxidase) Lysozyme	Inhibits bacterial growth/ Induction of DNA damage Aggregates bacteria affecting their adherence
	Lactoferrin	Iron deprivation and membrane permeation
	Dextranase Mutanase	Degrades the biofilm extracellular matrix/ Disrupts biofilm formation by interfering with sucrose-dependent adhesion of bacteria
	Krillase Papain	Disrupts bacterial adhesion and coaggregation of microorganisms
	Deoxyribonuclease I (DNase I) Dispersin B (DspB)	Degrades extracellular DNA Hydrolyzes the biofilm poly-(beta-1,6)-N-acetylglucosamine exopolysaccharide

[100]. Generally, these fillers are inorganic (e.g., metals) and fabricated on the nano-scale from tens of nano-meters and in different shapes [78]. The most common fillers are nano-structures (silver, zinc oxide, titanium and copper compounds, glass, nanodiamonds), polymeric/organic (quaternary ammonium polyethyleneimine, chitosan), and AMPs [62]. To enable the antimicrobial therapy, fillers or their ions are released into the microenvironment to deter pathogens. The use of NPs as fillers offers a wide range of customization possibilities. For example, the antibacterial/antibiofilm response of NPs can be improved by varying the filler size, surface area-to-mass ratio, particle shapes, surface charge, dose, and NP coatings [101]. In addition, fillers can be modified to target specific pathogens with fewer side effects. Adsorption of (bio)molecules, addition of functional groups, and alteration of the filler surface charge induce antimicrobial selectivity toward certain bacteria [102]. In dental composites, the amount of filler influences the performance (structural, aesthetic, chemical, biological) of the material [103]. For example, adding ZnO NPs up to 7.5% into a standard dental adhesive promoted a substantial bacterial reduction of biofilms while maintaining an acceptable degree of conversion, flexural strength, and elastic modulus [104].

AMPs have broad-spectrum inhibitory activity against gram-positive and gram-negative bacteria, fungi, parasites, and viruses [105]. Their antimicrobial activity is associated with their conformation (α -helical, β -sheet) [105], net charge, and hydrophobicity [105]. AMPs are present in the saliva, gingival crevicular fluid (e.g., histatin-1,3 and 5), epithelium (e.g., adrenomedullin, β -defensins), and neutrophils (α -defensins) [106]. Natural AMPs act as a defense mechanism against the virulence factors of various microorganisms. For example, histatin acts as an antimicrobial agent to prevent secondary caries (*S. mutans*) [107], while mature α -defensin has antimicrobial activity against *Escherichia coli*, *Enterococcus faecalis*, and *C. albicans*. AMPs can be derived from natural (e.g., microorganisms, plants, insects, crustaceans, mammals) or synthetic sources (see Table 1). As antimicrobial agents, AMPs have been

incorporated into adhesive systems [108,109] and implant coatings [110,111]. For example, when added to dental adhesives, GH12, a peptide derived from bacterial and fungal sources, results in bacteria inhibition at the adhesive/dentin interface [112]. ϵ -Polylysine has also been added into resin systems and successfully tested against oral pathogens associated with periodontitis and caries [113]. The use of antimicrobial AMPs has also been extended to test the dentin-composite interfaces ex-vivo, showing selective antimicrobial potency against two crucial acidogenic initial colonizers as well as the most highly abundant taxa associated with failed composite restorations [114,115]. Research on AMPs has reached clinical trials with optimistic results to move commercially [116]. For instance, C16G2 strips, varnish, and gels with antibacterial effect against *S. mutans* are being evaluated to treat tooth decay [117,118]. To treat periodontitis, Nal-P-113 injected into the periodontal pocket showed decreased levels of *Fusobacterium nucleatum*, *Streptococcus gordonii*, *Treponema denticola*, and *Porphyrromonas gingivalis* in subgingival plaque of patients [119]. Finally, a PAC113 (a histatin analogue) mouth rinse that targets *C. albicans* is in the second evaluation phase to treat oral candidiasis in individuals with HIV [120]. The main advantages of AMPs are their minimal bacterial resistance [121], the rapid onset of action [122], and the less mammalian cellular toxicity compared to traditional antibiotics [123,124]. In addition, AMPs have the ability to target specific groups of bacteria [125]. There are still many significant challenges for AMPs, including the decrease in the antibacterial activity with the reduction of the spacer length, high hemolysis, high cost of extraction, short half-life (<37 h), and low stability in-vivo [126,127].

Antimicrobial coatings are also part of bioactive therapies. For implant dentistry, coatings prevent bacterial colonization and biofilm formation on implant surfaces and have successfully reduced peri-implant mucositis, peri-implantitis, and implant loss [128]. Strategies to create antimicrobial coatings include contact and release-killing surfaces [129]. Contact-killing surfaces are based on surface-attached antimicrobial elements such as quaternary ammonium compounds [130], AMPs [131,132], and antimicrobial enzymes (AMEs) [133]. For example, GL13K, an AMP derived from the human salivary protein BPIFA2, is used as a bioactive coating in implant surfaces to treat peri-implantitis [134]. A coat of titanium dioxide (TiO₂) nanotubes and GL13K showed antibacterial response against *F. nucleatum* and *P. gingivalis* and biocompatibility with preosteoblast and macrophage cells [135]. Release-killing coatings are usually based on drug delivery systems [136] and ion-releasing coatings such as Ag, Au, Zn, and Cu [137]. Antimicrobial coatings offer several advantages over the administration of antibiotics, especially in terms of their localized activity [138]. However, in some cases, when their maximum antibacterial properties are achieved, their biocompatibility and osseointegration can be compromised.

Anti-biofouling surfaces prevent microbial adhesion and biofilm formation and are created by altering the surface topography [139,140]. Some of these topographical changes are inspired by nature, mimicking the architecture of animal skin (i.e., shark, cicada, and dragonfly wings) and vegetal surfaces (i.e., lotus, rose petals) [141]. For example, Arango-Santander et al. (2020) modified the surface of orthodontic archwires, mimicking the surface of *Colocasia esculenta* leaves resulting in reduced adhesion and colonization of *S. mutans* compared to unmodified wires [142]. Another example are the mussel-inspired catechols (i.e., polydopamine (PDA) and dopamine) for surface functionalization and bonding in wet environments [143]. Catechol coatings prevent bacterial adhesion and proliferation by producing hydrogen peroxide (H₂O₂) and single oxygen (O₂) that cause oxidative stress to induce bacterial cell death [144]. Additionally, due to its antimicrobial properties, catechol has excellent biocompatibility and moist-resistant adhesion, making it suitable as a coating for dental implants [145,146]. For example, PEEK dental implants coated with graphene oxide (GO) and PDA showed a significant reduction in the number of *P. gingivalis*, *F. nucleatum*, and *S. mutans* attached to the surface of the

biomaterial compared to non-coated materials [147]. In addition, polymeric particles made of dopamine methacrylamide (DMA) and eugenyl methacrylate (EMA) used as a coating in titanium implants showed excellent antimicrobial activity (more than 90%) against *E. coli* [148]. In general, topographies at the micro-scale do not have bactericidal effects but may limit bacterial adhesion [149]. In contrast, nano-topographic features with high-aspect-ratio (width-to-height ratio between 0.2 and 2) cause high deformational stresses on the bacterial membrane leading to their rupture [150]. However, the antimicrobial efficiency of a patterned surface is also dependent on the microbe species [151]. Although multiple studies have evaluated the effectiveness of topographical changes against gram-positive and gram-negative bacterial species for orthopedics applications [152–154], advances in the dental field with in-vivo results are limited. A recent study etched surfaces of commercially pure titanium to form spikes that eliminated anaerobic dental pathogens [155].

Although some of these bioactive antimicrobial agents have been used commercially, some limitations remain. First, the long-term delivery of the antimicrobial therapy is problematic since it could cause antimicrobial resistance through horizontal gene transfer among bacteria [156,157]. These technologies begin to release the agent right after implantation leading to the quick exhaustion of the effect compared to the treatment duration (lifetime). Typically, the antimicrobial effect of a leachable agent is less than 1 year [158]. Once depleted, the agent could not be recharged. Second, the release of the antimicrobial agent could cause a change in the properties of the carrier. For example, dental composites, sealants, or adhesives with exhausted agents may be detrimental to the mechanical and physical properties compared with the same material without an antimicrobial agent [96]. Third, an uncontrolled release of antimicrobial agents challenges the delivery of an appropriate dose. This uncontrolled release can speed up the agent depletion or provide insufficient amount of agent for therapy. This has been circumvented to some degree by using nano-carriers. Fourth, the lack of targeting causes collateral damage (killing of commensal species) and a potential imbalance in the oral microbiota [159,160] since the therapy will “attack” everything it encounters in the microenvironment. Fifth, although the use of chemical compounds has some benefits, such as high efficacy, high cure rate, and minimally invasive procedures for its application [161], its use still raises concerns regarding the resistance of microbes to antibiotics [162]. In the case of antimicrobial polymers, although they overcome some drawbacks of the leachable chemical therapies such as long-term activity (no leaching or exhaustion of the antimicrobial compound), limited toxicity against mammalian cells, reduced antimicrobial resistance, and increased chemical stability [163]; significant limitations remain regarding the high selectivity against gram-positive strains and high cost of manufacturing [163]. Finally, although several clinical trials have successfully evaluated the use of NPs in different dental materials as antimicrobial agents [164–168], the wide use of NPs in clinical practice is limited due to concerns regarding the release of toxic ions that could cause inflammation, immunotoxicity, cytotoxicity, and genotoxicity in healthy cells. For example, titanium NPs released from implants after decontamination via ultrasonic tips and lasers cause a strong systemic immune response [169,170]. This takes more relevance since controlling the dispersion of NPs in a clinical setting remains a great challenge [171].

3.2. Bioresponsive antimicrobial therapies

Bio- or stimuli-responsive biomaterials are those capable of sensing a stimulus to then respond to it by releasing therapeutic agents [16,66,172]. Generally, the antimicrobial agent is incorporated into a carrier/vehicle (a biomaterial), designed to respond to the specific stimulus by changing its properties (e.g., degradation). To release the antimicrobial agent, some carriers may vary their structure or properties after responding to the stimulus [173]. Bioresponsive antimicrobial biomaterials have gained considerable attention due to their capacity to

overcome some of the limitations of bioactive antimicrobial therapies, including the target of individual pathogens and improvement of effectiveness, dosage, location, and duration of the therapy. In dentistry, these responsive antimicrobial technologies are triggered by different internal stimuli, including microenvironmental signals (salivary enzymes and low pH levels produced by pathogens), microbes’ metabolites (secreted enzymes), or by targeting specific peptides/proteins/genes on microbe’s surface. These responsive biomaterials are also triggered by external (out of the body) stimuli including light, magnetism, electrical fields, and masticatory loading. This section will describe the different bioresponsive antibacterial biomaterials used for dental applications.

pH-responsive biomaterials respond to the changes in the pH level of the surrounding medium or microenvironment. Depending on their design, biomaterials may expand, collapse, or change a specific property. For example, in an acidic environment, some hydrogels may expand (structural change) to release the drugs, while basic pH levels force the hydrogel’s collapse and the drugs remain protected and unreleased (Fig. 3) [174]. Designing biomaterials sensitive to different pH levels is highly attractive in dentistry. Many oral pathogens are

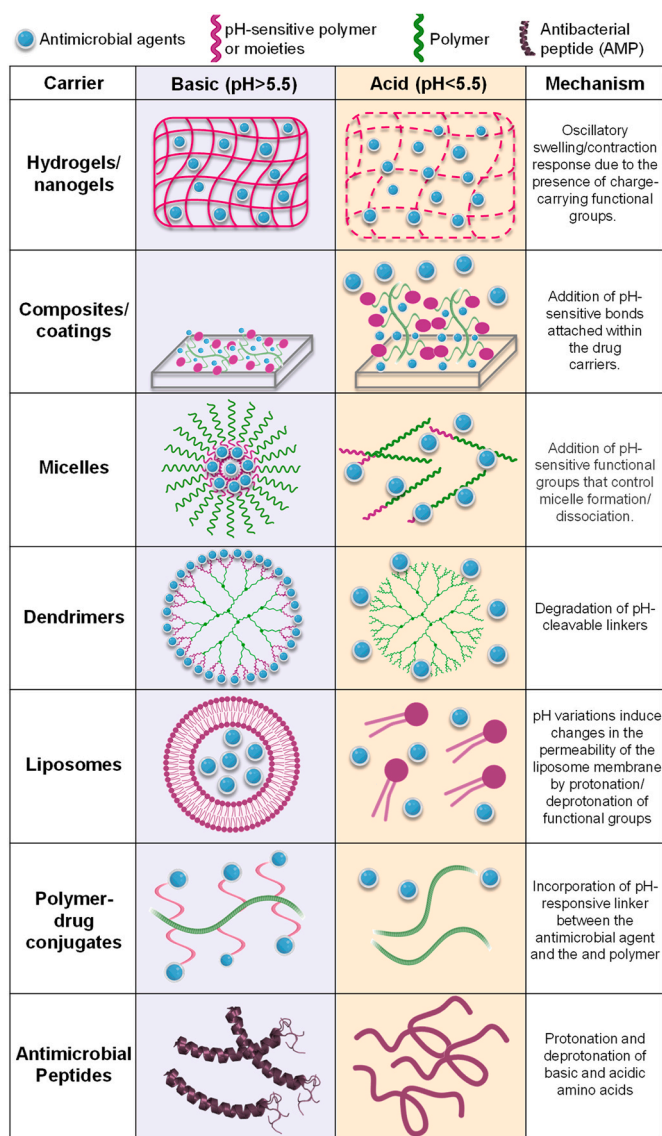


Fig. 3. Configurations used as pH-responsive carriers for the delivery of oral antimicrobial therapies. After degradation/cleavage of the pH-sensitive bonds/compounds, the carriers release their payloads, which can be in the form of antimicrobial compounds, nano-fillers, or antimicrobial peptides.

aciduric and acidogenic, significantly changing the pH levels of the microenvironment during the progression of the disease. For example, the pH range of the microenvironment of active dental caries is 4.5–5.5, while in physiological conditions, saliva has a normal pH range of 6.2–7.6. As a result, pH-responsive biomaterials have become an attractive choice to be used in the treatment of caries, periodontitis, and peri-implantitis [175].

In dentistry, resins (adhesives/sealants), hydrogels, and nanocarriers (micelles) have been used as the “smart” carrier/vehicle for pH-responsive antimicrobial technologies for the treatment of infections [176]. Generally, polymers with weak acid (e.g., carboxylic acid) or base (e.g., primary and tertiary amines) groups can cause changes in ionization, surface activity, chain conformation, solubility, and configuration at the desired pH level [177]. For example, dodecylmethylaminoethyl methacrylate (DMAEM) is a tertiary amine (TA) resin used as a pH-responsive resin in dentistry [178]. DMAEM has reversible protonation and deprotonation reactions in response to changes in pH levels behaving as cationic polymers (antibacterial agent) under acidic conditions by forming quaternary ammonium monomers [178]. Liang et al. (2020) incorporated DMAEM into a dental adhesive resin (at 5%), providing antibacterial effects in the presence of an acidic medium (pH < 6) [28]. This reversible pH-responsive and non-drug release dental adhesive could achieve long-term anticaries effect without disturbing the oral microecological balance. In a recent follow-up study, the team successfully translated the use of DMAEM into resin-based sealants to prevent long-term microleakage [178]. pH-responsive hydrogels that release antibacterial agents have also been used in dentistry. A recent work designed a N-dimethylaminoethyl methacrylate (DMAEMA)-co-2-hydroxyethyl methacrylate (HEMA) (poly(DMAEMA-co-HEMA) hydrogel capable of releasing CHX in response to pH levels to prevent and treat dental caries [179]. This bioresponsive biomaterial inhibited the development of *S. mutans* biofilm and regulated the oral microecosystem. In another study, nanoporous silica NPs containing CHX (antimicrobial agent) were mixed with a poly(4-vinylpyridine) hydrogel [180]. At acidic pH values (~4.0), the polymer became protonated and released the antimicrobial agent. At physiological pH values (7.0), the polymer served as a gatekeeper, preventing the release of agents. This system was successfully tested against cariogenic pathogens (*S. mutans*). The hydrogel swells/collapses in response to the pH level to control the release and containment of the drug. A recent work used a pH-responsive hydrogel as an antifouling-bactericidal coating [181]. The growth of cariogenic bacteria decreased pH levels over the hydrogel surface, which triggered a shift in the surface charge. After attracting the pathogens, the loaded octapeptides were released for antibacterial effects. Overall, pH-sensitive hydrogels have shown stability, cytocompatibility, and appropriate mechanical properties for dental applications.

pH-responsive nanocarriers such as nanogels, micelles, polymer-drug conjugates, core-shell NPs, and nanospheres have been used as vehicles for these types of biomaterials [182]. Generally, these compounds are fabricated with pH degradable linkages, pH cleavable crosslinking, or the inclusion of charge-shifting polymers that, when activated with the stimuli, release their payload to the environment [183] (Fig. 3). pH-responsive nanocarriers protect the encapsulated agent from degradation and can release their cargo in a controlled manner. Additionally, the localized release of the agent increases therapy efficacy due to increased penetration within biofilms and improved agent stability and solubility [184]. For example, pH-responsive micelles are used to encapsulate and release farnesol for caries treatment [89]. To reduce dental caries, Yu et al. (2020) used polymeric micelles loaded with farnesol and pyrophosphate, which adhere to dental enamel and release the farnesol in acidic conditions, avoiding bacterial proliferation [89]. In-vivo experiments showed that farnesol reduced the severity of smooth and sulcal surface caries in rats infected with *S. mutans* [89]. Similar results were observed in pH-responsive micelles fabricated with methoxypolyethylene glycol-b-poly-2-(diisopropylamino) ethyl methacrylate (mPEG-b-PDPA)

loaded with bedaquiline [184]. Antimicrobial fillers have also been encapsulated into these pH-responsive carriers. To treat periodontitis, one study encapsulated metronidazole and N-phenacylthiazolium bromide (PTB) –as host modulator– into PLGA and chitosan nanospheres [185]. Chang et al. (2017) fabricated an injectable hydrogel with amphipathic carboxymethyl-hexanoyl chitosan (CHC), β -glycerol phosphate (β -GP), and glycerol carrying naringin (antimicrobial agent) [186]. In both studies, at a pH of 5.5, the agents were released from their carriers, reducing periodontal bone loss and inflammatory cell infiltration [185, 186]. In addition, a recent study fabricated pH responding NPs of quaternary ammonium chitosan-liposome to combat biofilms and treat periodontitis [187]. The agent showed accepted cytotoxicity and inhibited gingival inflammation and alveolar bone loss in-vivo. Several studies have reported the development of a series of pH-responsive NPs, including dextran-iron oxide [188], farnesol-DMAEMA [189], catalytic-iron oxide NPs [190], and ferumoxytol NPs for treatment against dental caries both in-vitro and in-vivo [191]. Overall, the NPs showed no adverse effects on oral microbiota diversity and mucosal and gingival tissues. In another study, quaternary pyridinium salt (QPS) exhibited pH-controlled antibacterial activity, selectively inhibiting the growth of acid-producing bacteria (*Streptococcus* spp) at low pH levels (4.1) [192]. Cariogenic biofilms are also inhibited when pH-sensitive nanocarriers are fabricated with poly(DMAEMA-co-HEMA) [179] and poly(ethylene glycol)-block-poly(2-((2-aminoethyl)carbamoyloxy)ethyl methacrylate) (PEG-b-PAE-COEMA) [193] loaded with CHX. Some limitations associated with using these nanocarriers include low transfection efficiency, batch-to-batch variation, reduced drug capacity and entrapment, and particle-particle aggregation [194].

pH-responsive AMPs have recently opened new opportunities to develop oral antimicrobial technologies with higher bacteria selectivity. An innovative approach is to combine the antibacterial capabilities of AMPs and the tunability of pH-responsive nanocarriers by encapsulating AMPs into these nanocarriers. The encapsulation and delivery of AMPs is a promising strategy to protect the peptides from enzymatic degradation. The encapsulation can also selectively target their antimicrobial activity to the sites of infection with abnormal pH values while avoiding off-target side effects [195]. The development of pH-responsive AMPs usually involves the protonation and deprotonation of basic and acidic amino acids [196]. For example, modifying the amphipathic α -helical GH12 with histidine, increases the peptide membrane penetrating property and lytic activity at acidic pH [197]. The resulting pH-responsive peptide has strong bactericidal effects on both planktonic and biofilms at pH 5.5 compared to a 7.2 environment [197]. A similar response is observed by the His-rich peptide C18G-His against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *E. coli* [198]. For example, a pH-responsive coat for dental materials made of carboxybetaine methacrylate-dimethylaminoethyl methacrylate copolymer P(CBMA-co-DMAEMA) when in contact with low pH, releases octapeptides that attract and kill cariogenic bacteria (i.e., *S. mutans*) [181]. The development of an adhesive tissue membrane fabricated with pH-responsive chitosan and loaded with D-GL13K and IDR-1018 resulted in antimicrobial action comparable to CHX against oral streptococci [199]. The addition of oxidized pectin as a membrane coating resulted in increased mucoadhesion to soft and hard tissues to treat periodontitis, peri-implantitis, and caries. A recent work developed dual-sensitive AMP NPs (pHly-1 isolated from a spider's venom) for treating dental caries [200]. The peptide adopted a random coil conformation under acidic conditions (pH = 5.5-4.5) to form NPs. In contrast, exposure to neutral pH leads to a conformational transition to form β -sheets and nanofibers, providing low toxicity to oral microbes and mucosal tissues and the deactivation of antimicrobial effects. However, the encapsulation of AMPs into nanostructures remains challenging due to their low penetration efficiency, short-lasting bioactivity, and high cost of production [201].

Enzyme-responsive: Enzymes are catalysts that accelerate biochemical reactions. Salivary and bacterial enzymes have been used as

a trigger (or signal) to release antimicrobial agents (antibiotics, AMPs, NPs) for treatments. Bacteria and fungi secrete various enzymes, including lipase, esterase, phosphatase, urease, gelatinase, and many more [202,203]. Some of these enzymes have been established as the marker to indicate active stage of disease, which is when a therapy is needed (See Table 2). For example, a bacterial by-product in chronic periodontitis is the enzyme matrix metalloproteinase-8 (MMP-8), which triggers the host immune response [204]. This enzyme has been used as a stimulus in bioresponsive delivery systems for managing periodontitis. The study by Guo et al. (2019) encapsulated minocycline hydrochloride and antimicrobial peptide in a poly(ethylene glycol) (PEG) hydrogel that was biodegradable in response to MMP-8 for periodontal disease treatment [205]. Activation using MMP-8 has also been used in a hydrogel made of gelatin methacrylate (GelMA) loaded with CHX and aluminosilicate nanotubes. The presence of MMP-8 degrades the hydrogel in 20 days and provides a sustained release of CHX for dental infection ablation [206]. The work by Ribeiro et al. (2020) relied on the biodegradation of GelMA triggered by MMPs to release CHX, halloysite aluminosilicate nanotubes, clindamycin, metronidazole, and ciprofloxacin for periapical infections [206,207]. This enzyme-response system showed antimicrobial effects against *C. albicans* and *E. faecalis* in-vitro, in addition to appropriate biocompatibility and minimum inflammatory response in-vivo.

Generally, enzyme-responsive biomaterials could be programmed to respond to different enzymes, including bacterial (i.e., esterase, phosphatase, phospholipase, β -lactamases, and gelatinase), cell surface enzymes (i.e., MMPs) and salivary (i.e., lipase, protease, esterase, alpha-amylase, anhydrase, lysozyme, and lactoperoxidase) [208] (Fig. 4). In this class of biomaterials, enzymatic reactions have high efficacy during catalysis and high selectivity and specificity, avoiding the limitations of traditional antimicrobial therapies that kill bacteria indiscriminately [209]. In enzyme-responsive systems, the antimicrobial agent is released after the degradation of a degradable carrier (e.g., poly(ethylene succinate) (PES), polycaprolactone (PCL), hyaluronic acid, PEG) via exposure to enzymatic activity [210]. Enzymes may cause hydrolysis, swelling, backbone cleavage, degradation, disassembly, phosphorylation, and dephosphorylation in the carrier leading to agent release at the target site [208]. For example, Wang et al. (2022) fabricated a lipase-responsive nanocarrier formed by 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine-PEG (DSPE-PEG) loaded with alpha-lipoic acid (ALA); and a hydrophilic shell comprising a poly (amidoamine) dendrimer (PAMAM) that electrostatically adsorbed minocycline hydrochloride to treat periodontitis in diabetic rats [209]. When activated by

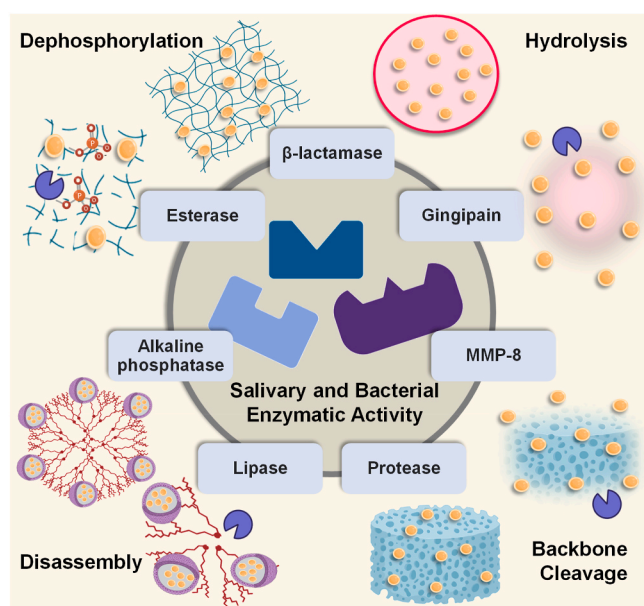


Fig. 4. Schematic representation of the typical drug delivery mechanisms used by enzyme-responsive antimicrobial dental materials. The listed salivary and bacterial enzymes activate enzyme-responsive materials such as membranes, nanocarriers (liposomes, dendrimers), nano-hydrogels, or polymer composites to release antimicrobial therapies such as antimicrobial compounds, nano-fillers, or antimicrobial peptides.

lipase secreted from periodontal pathogens, the release of minocycline hydrochloride inhibits the formation of subgingival microbial colonies. Compared to other responsive biomaterials, biomaterials activated by enzymatic levels are one step closer to becoming autonomous. Since enzyme levels are an endogenous stimulus, the biomaterial activation does not require external stimuli, therefore, the host “modulates” the release of the agent.

Gingipain is a protease secreted by *P. gingivalis* that degrades cytokines and hydrolyzes proteins to downregulate the host response during periodontitis [211]. A recent work used this protease to activate the release of an antibacterial agent (a peptide) from a polyethylene glycol diacrylate (PEGDA) hydrogel [212]. The enzyme-responsive biomaterial was successfully tested in-vitro and in-vivo for periodontal disease treatment with accepted biocompatibility. Another enzyme-responsive

Table 2

Bacterial and oral enzymes used as biomarkers for oral diseases and its contribution to the prevention/progression of the disease [202,203,210].

Disease	Enzyme	Mechanism
Caries	Proteinase 3	Degrade extracellular matrix/Cleavage of inflammatory mediators/Induction of endothelial cell apoptosis
Caries/ Periodontitis	Carbonic anhydrase	Maintain pH homeostasis by supporting neutralization of acid produced by bacteria
	Matrix metalloproteinases (MMPs) (Collagenases, Geletinases, Stromelysins, Matrilysin)	Degrade extracellular matrix, cytokines, and chemokines
	Alpha-amylase	Measures caries and periodontal disease severity and progression/Regulates bacterial colonization and adds glucose for biofilm formation.
	Cysteine proteases/thiol proteases (Gingipain)	Destroy organic matrices/Cause cytokine degradation
Periodontitis	Cathepsin D, G, B	Destruction of both epithelium and connective tissue/Hydrolyze collagen laminin, fibronectin
	Lysozyme	Its production is stimulated by the presence of caries/Contribute to the formation of pocket by its detrimental effect on epithelial cells
	Aryl sulfatase	Degradation of glycosaminoglycans
	β -glucuronidase	
	Elastase	Degrade collagenous and non-collagenous extracellular matrix proteins
	Aspartate aminotransferase (AST)	Release by dead or dying cells during periodontal tissue destruction
	Lactate dehydrogenase	
Secondary Caries	Dentilisin	Degrade fibronectin, laminin, and type IV collagen
	Alkaline phosphatase (ALP)	Measure the inflammatory activity in periodontal tissues
	β -lactamases	Degrade penicillins and its derivatives
	Pseudocholesterase	Catalyze the hydrolysis of ester bonds
	Esterase	

biomaterial to treat periodontal disease includes an alkaline phosphatase (released from polymorphonuclear leukocytes during inflammation) responsive to a chitosan membrane containing polyphosphoester and minocycline hydrochloride that reduces gingival inflammation and bacteria proliferation [213].

Esterases (hydrolase enzyme) present in the oral cavity, from both saliva and bacterial origin, degrade dental resins by cleaving ester bonds in monomers [13]. A responsive antimicrobial adhesive was designed to utilize this “degradation” mechanism for the release of antimicrobial agents for caries treatment. Silica particles were loaded with octenidine dihydrochloride into a total-etch commercial adhesive [171]. The release of the drug was modulated by the oral environment (esterase-catalyzed biodegradation of the polymer resin matrix) with successful prevention of *S. mutans* biofilm formation without toxicity on human gingival fibroblasts. However, the stability of the adhesive with time and its effect on the dentin/composite interface bond require further investigation. A major limitation in the use of enzyme-responsive biomaterials is related to an early release of the therapy when there are chemically related enzymes (i.e., esterase and lipase) [214]. Additionally, the treatment of diseases in which the enzymatic response is related to the disease stage and age of the host requires the development of custom-built materials.

Photo-responsive: These antimicrobial biomaterials combat pathogens after being excited with light [215]. Many outstanding photo-responsive antimicrobial biomaterials have been developed, including photocatalysts, photosensitizers (PS), and photothermal. Specifically, antimicrobial photodynamic therapy (aPDT) utilizes harmless light to activate non- or minimal-toxic PS to generate cytotoxic species (e.g., Reactive Oxygen Species (ROS)) for pathogen eradication. The generation of ROS (O_2 , H_2O_2 , hydroxyl radical ($\cdot OH$)) causes damage to the bacterial membranes and cell walls, destruction of lipids, proteins, and ion channels, removal of critical metabolic enzymes, cell agglutination, and direct inhibition of exogenous virulence factors such as lipopolysaccharide, collagenase, and protease [216].

aPDT is a non-invasive technique with advantages over traditional therapies. Such advantages include a reduced antimicrobial resistance, accelerated antimicrobial elimination without high PS concentrations, localized effect without affecting underlying structures and tissues, on/off trigger, and a broad antimicrobial spectrum against both gram-positive and gram-negative bacterial pathogens [216]. This technique has been used increasingly in dentistry to treat dental caries, candidiasis, periodontitis, endodontic diseases, and peri-implantitis due to its antimicrobial effect on various oral microbial pathogens [217]. For example, aPDT has high efficacy in eradicating cariogenic biofilms (i.e., *S. mutans*) when methylene blue, toluidine blue, aluminium-chloride-phthalocyanine, Fotoenticine®, Photoditazine®, chlorophyllin-phycocyanin, emodin, curcumin, diacetylcurcumin, chlorella, Fagopyrin F and erythrosine were used as PS [218–229]. A summary of the more common PS utilized to eradicate dental pathogens is presented in Table 3. The antimicrobial effects of aPDT with Fotoenticine® are greater than methylene blue in the control of *S. mutans* [230]. Recently, Fotoenticine® and toluidine blue O were effective against the heterogeneous (multispecies) biofilms of dental caries [230, 231]. Toluidine blue has also been successfully evaluated against *E. faecalis* for disinfection of root canals [232,233].

Photodynamic therapy has also been explored for the treatment of peri-implant diseases using similar PSs (toluidine blue, phenothiazine chloride) [234,235]. Different periodontal pathogens are also inactivated with aPDT using Toluidine Blue O as PS [236]. aPDT and antibiotics provided equal clinical improvements in the treatment of periodontitis and peri-implantitis [237,238]. Many of the studies have been conducted in-vitro, with few in clinical studies [239,240]. Toluidine blue, toluidine blue O, and natural products such as hypericin, riboflavin, or curcumin have been associated with reducing *C. albicans* biofilms when there is a superficial infection [241–243]. The cationic porphyrin PS has also been shown to inactivate *Candida* biofilms [244].

Table 3

Typical photosensitizers used in Antibacterial Photodynamic therapy (aPDT) against oral bacteria [215,216].

Photosensitizer (PS)	Wavelength (nm)	Bacteria
Phenothiazinium (Toluidine blue, Toluidine blue O, Methylene blue)	620–660	<i>Streptococcus mutans</i> , <i>Enterococcus faecalis</i> , <i>Candida</i> spp, <i>Porphyromonas gingivalis</i> , <i>Actinobacillus actinomycetemcomitans</i> , <i>Fusobacterium nucleatum</i>
Tetra-pyrrole structures (Porphyrin, Rose Bengal)	500–632	<i>Candida albicans</i> , <i>Enterococcus faecalis</i> , <i>Porphyromonas gingivalis</i> , <i>Prevotella</i> spp, <i>Aggregatibacter actinomycetemcomitans</i> , <i>Streptococcus mutans</i>
Chlorophyll derivatives (Chlorin e6 (Ce6), Fotoenticine®, Photoditazine®, Zn(II) Ce6 methyl ester (Zn(II)e6Me)	645–675	<i>Streptococcus sanguinis</i> , <i>Porphyromonas gingivalis</i> , <i>Fusobacterium nucleatum</i> , <i>Candida albicans</i> , <i>Actinomyces viscosus</i> , <i>Enterococcus faecalis</i> , <i>Streptococcus mutans</i>
Curcumin	405–435	<i>Streptococcus mutans</i> , <i>Candida albicans</i> , <i>Lactobacillus acidophilus</i> , <i>Aggregatibacter actinomycetemcomitans</i> , <i>Porphyromonas gingivalis</i> , <i>Fusobacterium nucleatum</i> , <i>Prevotella intermedia</i>
Safranin O	620–660	<i>Streptococcus gordonii</i> , <i>Streptococcus mutans</i> , <i>Fusobacterium nucleatum</i> , <i>Aggregatibacter actinomycetemcomitans</i> , <i>Porphyromonas gingivalis</i> , subgingival plaque samples
Riboflavin	300–600	<i>Aggregatibacter actinomycetemcomitans</i> , <i>Candida albicans</i> , <i>Enterococcus faecalis</i> , <i>Porphyromonas gingivalis</i> , <i>Prevotella intermedia</i> , <i>Fusobacterium nucleatum</i> , <i>Streptococcus gordonii</i>
Phthalocyanines (Zinc phthalocyanine, Aluminum disulphonated phthalocyanine (ALPcS2))	600–700	<i>Streptococcus mutans</i> , <i>Porphyromonas gingivalis</i> , <i>Candida albicans</i>
Triarylmethane (Malachite green, Crystal violet, Victoria Blue)	560–610	<i>Streptococcus mutans</i> , <i>Actinobacillus actinomycetemcomitans</i>
Chlorella	405–682	<i>Streptococcus mutans</i> , <i>Enterococcus faecalis</i>
Anthraquinones (Aloe-emodin, Purpurin)	400–780	<i>Streptococcus mutans</i> , <i>Candida albicans</i>
Coumarin 6 (C6)	630	<i>Streptococcus sanguinis</i> , <i>Porphyromonas gingivalis</i> , and <i>Fusobacterium nucleatum</i>
Photogem	455–630	<i>Streptococcus mutans</i> , <i>Lactobacillus acidophilus</i> , <i>Candida</i> spp
Indocyanine green	810	<i>Enterococcus faecalis</i> , <i>Porphyromonas gingivalis</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Streptococcus salivarius</i> , <i>Streptococcus mutans</i> , <i>Lactobacillus acidophilus</i>
Erythrosine	500–550	<i>Streptococcus mutans</i>
Hypericin	590	<i>Candida albicans</i> , <i>Streptococcus mutans</i> , <i>Streptococcus sobrinus</i> , <i>Lactobacilli mutans</i>
Fagopyrin F	450	<i>Streptococcus mutans</i>

Most PSs are activated by red light between 620 and 700 nm corresponding to a light penetration depth between 0.5 and 1.5 cm [245]. For example, Zn(II)chlorin e6 methyl ester (Zn(II)e6Me) activated by red light is able to remove around 60% of *E. faecalis* and *C. albicans* biofilms, suggesting its potential to be used as endodontic disinfection [246]. A

convenient strategy for increasing the therapeutic effect is to load PSs with photocatalysts [215]. Different light sources are used in aPDT, including lasers of helium-neon, gallium-aluminum-arsenide diode, argon, and non-laser light sources such as light-emitting diodes (LED) [247]. Titanium implants have been coated with chitosan-modified molybdenum disulfide loaded with Ag-NPs, which were able to kill bacteria under visible light due to photocatalytic activity and excessive production of ROS [248].

As a strategy to improve antimicrobial efficacy, NPs have been used as carriers of PS to avoid aggregation of PS and antimicrobial resistance and to enhance their penetration into the biofilm matrix and bacterial cell wall [249]. NPs such as fullerenes, graphene, graphene oxide, carbon nanotubes, and metal oxides NPs (i.e., ZnO, TiO₂, Au, Ag) are preferred to be used as PS due to their high stability, ability to generate ROS, thermal, optical, and biocompatible properties [250,251]. Sun et al. (2019) fabricated iron oxide (Fe₃O₄) NPs containing Chlorin e6 (Ce6) and Coumarin 6 (C6) as PS. Using NPs in combination with PS improved penetration of the PS into the biofilm matrix providing strong antibacterial against *Streptococcus sanguinis*, *P. gingivalis*, and *F. nucleatum* biofilms compared to control groups (4–5 log reductions) [252].

The fabrication of biodegradable hydrogels, micelles, liposomes, and polymeric NPs as PS nanocarriers allow the localized release of PS at the site of infection, reduces the risk of side effects, and increases the efficacy of the therapy. These nanocarriers are “doubly smart” since the release of the PS occurs after degradation of the carriers due to hydrolytic, chemical, or enzymatic cues. Moreover, irradiation induces antimicrobial therapy once the PS is released at the site of infection. For example, Lopes Dos Santos et al. (2021) encapsulated curcumin into polymeric micelles to eradicate *S. mutans* and *C. albicans* biofilms. Irradiation of the micelles with blue light for 1 min resulted in a significant reduction in the number of bacteria (~3 logs) compared to the same micelles without light irradiation [253]. Nano-GO was used as an indocyanine green (PS) carrier to enhance its antimicrobial effect against *E. faecalis* biofilms for root infections [254–256]. Moreover, aluminum phthalocyanine chloride was encapsulated in chitosan NPs to inactivate multispecies cariogenic biofilms [257]. Chitosan-gold NPs with curcumin conjugates were prepared to enhance curcumin’s dispersibility and stability and provide a pH-responsive behavior that allows a controlled antibacterial effect against gram-positive and -negative species [258].

Enhanced antimicrobial activity was obtained through the combination of aPDT and low-frequency ultrasonic irradiation [259]. Ultrasound irradiation bears a deeper penetration in human tissues than light and, sequentially, can promote drug delivery through the cavitation effect. The work by Zhang et al. (2019) combined the Ce6 (PS) with upconversion NPs (NaYF₄:Yb,Er) to overcome the limited tissue penetration depth and increase the luminescence for the enhancement of antimicrobial against periodontal pathogens [260]. In another work, emodin-chitosan NPs were designed as PS in aPDT therapy against *S. mutans* biofilm on the enamel surface ex-vivo [223]. To improve the antimicrobial specificity and selectivity, stimuli-responsive nanoplat-forms have been proposed to enhance the delivery of PS [261]. Different signals from pH levels, enzymes, redox, magnetic, and electric have been used and reviewed here [261]. For example, in dentistry, magnetic fields have been used in the targeted delivery of magnetic materials. Ce6 (PS) was loaded in NPs of Fe₃O₄ (magnetic), and under the magnetically driven force, the carrier increased the penetration of the PS into biofilms for improved efficacy [252].

The use of light to kill oral pathogens has been suggested as an adjunct for some dental treatments (i.e., caries, tooth decay, peri-implantitis) and as local disinfection therapy (i.e., root canal disinfection). For example, to treat tooth decay, a dental coating fabricated by mixing ZnO, fluorine-modified nano-silica, and polydimethylsiloxane (PDMS) effectively resists bacterial and protein adhesion when sprayed on the surface of the tooth [262]. However, its antimicrobial activity can

be enhanced when under irradiation with yellow light the ZnO acts as PS increasing the production of ROS [262]. Recent work has designed a hydrogel with NPs to simultaneously achieve local tooth whitening and biofilm removal through a photodynamic dental therapy process since ROS can be used for tooth whitening (the produced H₂O₂ cleans pigmentation via oxidation) [263].

Inflammatory periodontal pockets are known to be hypoxic influencing vascular response. A near-infrared light (NIR)-responsive nano-system was developed to scavenge oral biofilms and prevent dental caries [264]. A PEG NP penetrated biofilms to deliver ciprofloxacin under acidic conditions. NIR irradiation provided augmented potency in oral biofilm penetration and disruption compared with drugs alone. The antibacterial effect in hypoxic microenvironments is hindered due to continuous oxygen consumption and poor excitation in light penetration depth. To overcome these challenges, oxygen-self-generation (O₂), carbon monoxide (CO), and nitric oxide (NO) biomaterials systems have been proposed. For example, Ce6 and C6 (as PS) were encapsulated in Fe₃O₄ NPs covered with a layer of magnesium dioxide (MnO₂) [265]. Rising oxygen levels in the periodontal pocket effectively relieved the hypoxia and enhanced ROS production boosting the aPDT efficacy against pathogens. In a different study, a nanoplat-form was created by combining up-conversion NPs and partially oxidized tin disulfide (SnS₂) nanosheets and indocyanine green stimulated with NIR to produce both O₂ and CO [266]. The antibacterial activity and anti-inflammation of the light-responsive system were demonstrated in-vitro (against oral pathogens) and in-vivo. The NO nanogenerator provided dual functions (aPDT and photothermal therapy-PTT), and the NO production modulates the inflammatory responses by reducing the level of pro-inflammatory cytokines for periodontal disease treatment [267]. In a slightly different approach, an injectable anti-periodontitis ointment with the catalytic activity of a modified platinum nanocluster was designed. The system was activated with mild ultraviolet irradiation and was able to produce ROS in the dark without the generation of gases [267].

Recent trends have proposed using MOF (metallic organic frameworks) as antibacterial agents [268–271]. MOFs are novel materials consisting of metal clusters, metal ions, and organic linkers. PSs have been added to the building blocks of MOFs to improve the antibacterial effect. For example, a photo-responsive ointment comprised of a 2D porphyrinic MOF (CuTCPP) system incorporated into a PEG matrix was developed [272]. The biocompatible/biodegradable system showed broad-spectrum antimicrobial activity (>99%) against diverse oral pathogens by the synergistic effect of ROS and released ions both in-vitro and in-vivo. The toxicity of MOFs can be significant and controlled by several factors, such as their dose, composition, structural stability, particle size, shape, and surface chemistry.

Limitations in photo-responsive materials include the low antimicrobial activity against gram-negative bacteria, high cost, and tooth staining/discoloration when the tissues are in contact with specific types of light sources (i.e., methylene blue) [269]. In addition, reduction in bond strength due to dentin impregnation with PS, and in some cases, excessive temperature during the therapy can produce tissue trauma and damage [270]. Reduction in cell viability after application of aPDT need further studies [218].

Electrical stimulation: The effect of electrical charges (i.e., currents) on microbial biofilms has been studied for several years as an alternative to chemical therapy without leading to antibiotic resistance or as an adjunct treatment to enhance the effectiveness of conventional therapies. Advantages of this approach are the high spatial cover and time controllability, rapid action, and minimal invasion [273]. The capacity of electrical charges to destroy pathogens depends not only on the bacterial strain but the electrical charge magnitude, density, and polarity [274]. Against oral pathogens, electric charges have shown antimicrobial response against *P. gingivalis* [275,276], *S. mutans* [277,278], *E. faecalis* [279], *C. albicans* [280,281], among others [282,283]. Typically, low current levels <30 mA for less than 30 min have been

evaluated [284]. Several mechanisms are proposed to explain the killing ability of electrical charges. These mechanisms include the direct contact theory, in which the electric current directly results in bacterial death by disrupting the integrity of the cell membrane [284]. The indirect killing theories are explained by the production of reactive toxic substances (i.e., ROS, reactive nitrogen species (RNS)) [285], pH and temperature changes, and galvanotaxis [284]. However, high concentrations of ROS can influence general inflammatory signaling and/or can induce mutations in bacteria, making them less susceptible to treatment [286].

The concept of using electrical current as an antibacterial mechanism has been mostly tested in metallic implants [287]. Electrically polarized materials possess electrical charges at the surface due to polar or electric properties [288]. The use of polarized substrates such as HAP has antibacterial activity against gram-positive and gram-negative bacterial strains and with different polarization directions (positive vs. negative), allowing tunability of the material response [289,290]. A similar response was obtained for bioactive glasses (BGs) combined with polarized ceramics ($\text{Na}_{0.5}\text{K}_{0.5}\text{NbO}_3$); the antimicrobial mechanism is attributed to increased superoxide production compared to commercial BGs [291]. A benefit of this technology is that electricity slows the spread of antibiotic-resistant infections. In a different approach, Liu et al. (2018) proposed a system that uses electricity to excite PS to generate ROS and then kill pathogens. This novel strategy avoids the employment of an external light source and was tested against *C. albicans* [292]. Improving bacterial selectivity and studying the long-term effects of using electrical currents (i.e., continuous or intermittent) on microbial cells and surrounding tissues remains challenging [284].

Magnetic-responsive: Static and pulsed magnetic fields are clinically used for healing bone fractures and promoting bone formation [293]. In the dental field, magnetic-responsive NPs have been used to treat infections and hypersensitivity, improve bond strength, targeted drug delivery, tissue engineering, and caries risk assessment [294]. In antimicrobial applications, magnetic NPs have been used mainly for positioning or moving the antibacterial agent closer to the infection site. This is highly attractive in dentistry since infected sites are usually deep within tissues and inaccessible to treatment. For example, a urethane dimethacrylate (UDMA)-HEMA system filled with CHX loaded with magnetite Fe_3O_4 NPs showed a significant antimicrobial effect against *P. gingivalis* for periodontal disease treatment [295]. Under a magnetic field, the CHX/ Fe_3O_4 compounds not only can move to the site of infection, but the movement releases the CHX to the targeted place [295]. Magnetic NPs can also interact with biofilm and planktonic microbes, adhering to the cell wall and disrupting the membrane through direct contact. Tokajuk et al. (2017) developed a nanosystem with magnetic NPs coated with aminosilane and CHX for antifungal effects against *Candida* biofilms [296]. Chitosan-coated Fe_3O_4 NPs have also been used as CHX carriers to remove *S. mutans*, *C. albicans* biofilms, and others [252,297–299].

Recent work combined PS for aPDT and magnetic NPs for positioning the PS to develop a multifunctional material with strong anti-biofilm activity against periodontitis-related pathogens, with acceptable biocompatibility, real-time monitoring, and magnetically targeting capacities [252,300]. The magnetic response aided in positioning the PS inside deep locations of the periodontal pocket for effective removal of the pathogens. Using a similar approach, Balhaddad et al. (2021) fabricated a microemulsion by mixing toluidine blue O and SPIONs [301]. In the presence of an external magnetic field, the microemulsion can be driven to penetrate deep sites inside the biofilms, resulting in an improved antimicrobial activity against *S. mutans* and saliva-derived multispecies biofilm compared with only photodynamic disinfection [301]. The transport of PEG/ Fe_3O_4 NPs inside the dental tubules via an external magnetic field showed successful results in occluding dentinal tubules to treat dental hypersensitivity [302]. The SPION was also employed in adhesive dentistry for bonding optimization. This approach

is promising to enhance the resin-tooth bond, strengthen tooth structures, and suppress secondary caries at the restoration margins. SPIONs enhanced penetrability into etched dentin guided by magnetic fields and provided antibacterial effects at the bonded interface [303]. The team showed improvement in the bond strength after using SPIONs and antibacterial effect against *S. mutans* biofilms. Another work embedded magnetic NPs into an adhesive with dimethylaminohexadecyl methacrylate (DMAHDM) and amorphous calcium phosphate NPs (ACP) [304]. The novel adhesive yielded greater dentin bond strength than commercial control, in addition, to reducing biofilm viability and increasing the biofilm pH from a cariogenic to a noncariogenic. To treat caries related biofilms, toluidine blue O was combined with SPIONs. The magnetic field and increasing concentration of the magnetic NPs enhanced the antibacterial reduction. For endodontic infections, glucose oxidase-modified magnetic NPs were developed, showing effective antibacterial activity against *E. faecalis* and *C. albicans* biofilms [305]. There are some limitations when working with magnetic NPs, including the tendency of agglomeration, toxicity levels, concerns on long-term stability and the limited directionality of positioning when using single magnets.

Mastication/vibrations-responsive: The oral environment can highly benefit from the forces provided during daily biomechanical movements through mastication to enable antibacterial therapies. Piezoelectric materials produce electrical charges in response to forces [306]. Recently, it was showed that these electrical charges enable antimicrobial therapy against oral pathogens [307]. For example, the addition of piezoelectric NPs (i.e., barium titanate - BaTiO_3) into dental composites [278] and dentures [281] showed antimicrobial response against *S. mutans* and *C. albicans* biofilms only when the materials are mechanically stimulated (charge generation). The antibacterial mechanism of piezoelectric charges is explained by increased levels of intracellular ROS produced by the cells, which is indicative of oxidative stress [308]. Additional studies regarding the distribution of the piezoelectric charges around the dental composites and dentures are required to guarantee a homogeneous antimicrobial effect. BaTiO_3 has also been proposed as discs with combined antibiofilm and energy-harvestable functions [309]. In addition, questions regarding the pathogen selectivity and the effect of polarization direction (positive versus negative) still need to be answered.

Other stimuli: Other different types of stimuli have also been proposed with less exploration and research. Glucose-responsive biomaterial systems have been developed for dental applications. For example, chitosan glucose-responsive hydrogels can detect glucose levels using immobilized glucose oxidase (GOx) on predesigned pH-responsive hydrogels. That is because immobilized GOx can oxidize ambient glucose to gluconic acid depending on the sensed glucose levels. The hydrogels release controlled doses of metronidazole as antimicrobial therapy against *P. gingivalis* [310,311]. A different approach used a glucose-sensitive antibacterial and anti-inflammatory chitosan hydrogel film with controlled release of tannic acid [312]. The addition of tannic acid increased the mechanical properties of the film and demonstrated adequate biocompatibility with inhibition of nitrite, interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) for anti-inflammatory application.

Sonodynamic therapy (SDT) is an emerging approach to eradicate tumors and infections [313]. After ultrasound exposure, sonosensitizers (akin to PS) produce ROS to eliminate bacteria. Advantages of SDT include deep penetration into the tissues, generation of cavitation to enhance the permeability of sonosensitizers into the biofilm, non-invasion, high selection spatiotemporally, and no bacterial resistance. For example, hematoporphyrin monomethyl ether was used as a sonosensitizer for antibacterial effects against *P. gingivalis* in-vitro [314]. The simultaneous use of aPDT and SDT was conducted using chitosan-iodocyanine green as a sensitizer against periodontal pathogens [315]. The work showed the synergistic effect of both therapies and envisioned the technology for decontamination of dental implant surfaces. A combination between SDT and chemodynamic therapy was

proposed after using a nano-sonosensitizer prepared by growing titanium oxide on dendritic silica [316]. The solution was placed in a periodontal pocket in-vivo to treat periodontal disease. Ultrasound irradiation significantly inhibited cell viability of *P. gingivalis* and effectively suppressed alveolar bone resorption and alleviated inflammatory responses.

3.3. Autonomous antimicrobial therapies

Autonomous biomaterials can sense, respond to different therapies, and adapt to different forms of stimulus. Their natural feedback allows complete integration of the biomaterial with the biological system [317]. For example, hydrogels can be programmed to perform complex computations based on inputs provided exclusively by their local environment [318]. The confluence of different areas of expertise (e.g., control theory, computer science, material science, medicine) has permitted the development of a new generation of autonomous materials. Recently, the development of micro/nanobots has been employed as a mean to treat infections. Using micro/nanobots in medicine and dentistry provides a new futuristic alternative for disease treatment. Micro/nanobots are machines at the micro- and nano-scale that can perform multiple specific tasks such as sensing, diagnostic, delivery, and detoxification through autonomous or external-powered propulsion [319,320]. Micro/nanobots have been evaluated successfully for drug targeting delivery [321], diagnosis [322], imaging [323], and cancer detection [324]. The design of micro/nanobots focuses on mimicking the behavior of biological organisms such as bacteria or cells. For example, microbivores are biomimetic nanorobots similar to white cells that can digest microbial pathogens in the bloodstream through phagocytosis [325]. Micro/nanobots have multiple advantages compared to other smart systems, such as the possibility of delivering information in real-time for proper diagnosis and treatment, encapsulation of functional elements (i.e., antimicrobial agents, growth factors), non-invasive intervention, and reduced side effects [326,327]. As antimicrobial therapy, micro/nanorobots can deliver antimicrobial agents in specific locations, offer targeted treatment, and enhance penetration of antibacterial agents into the targeted site or biofilms, thus showing great promise in emerging as an attractive alternative to conventional antibacterial therapies [319]. For example, Arqu e et al. (2022) created silica-based robots loaded with cationic AMPs (i.e., LL-37 and K7-Pol) for biofilm eradication [328]. The proposed robot, which can be driven to the infection site by the catalysis of the enzyme urease, showed bactericidal activity against gram-positive (*S. aureus*) and gram-negative (i.e., *P. aeruginosa* and *E. coli*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*) pathogenic bacteria [328]. Yet, the application of micro/nanobots in the dental field is limited to some proof of concepts.

Self-driven and externally powered micro/nanobots have been developed to eradicate dental biofilms. Self-driven micro/nanobots use chemical fuels by enabling the decomposition of H_2O_2 into O_2 and HO_2 , which source for bubble propulsion of the nanobots [329]. Other micro/nanobots are powered by external physical forces such as magnetic [330] and electrical fields [331] or ultrasound [332]. To eradicate dental plaque, a self-driven microbot was created by Villa et al. (2020) fabricated with TiO_2 NPs to produce microbubbles that allow the locomotion of the microrobot and the *in situ* formation of ROS, such as hydroxyl radicals, on the dental plaque surface, producing an antimicrobial effect [333]. In-vitro evaluation of the antimicrobial potential showed that using the microbot with 1% of H_2O_2 reduces by 95% the viability of a dental biofilm composed of *S. gordonii*, *Veillonella parvula*, and *F. nucleatum* [333]. Hwang et al. (2019) designed a catalytic antimicrobial robot using iron NPs that killed bacteria using ROS, produced rupture of the EPS, and removed the debris of the dental biofilm by forming a biofilm-removing plow [334]. These nanobots can be driven to the infection site by an external magnetic field and completely removed *S. mutans* biofilms in a study with a human tooth model [334]. In a recent follow-up study, the team created a magnetic field-directed

nanobot named STARS to remove and kill bacterial biofilms and diagnostic sampling of disease-causing biofilms [335]. STARS is fabricated with Fe_3O_4 NPs (IONPs) that dynamically assemble to form magnetic bristles under a magnetic field. Guided by the magnetic field, the bristles can modify their shape, length, and stiffness to remove the biofilm, while a catalytic reaction of the IONPs produces ROS as an antibacterial mechanism [335]. Finally, varying the length of the bristles allow the biofilm removal for external diagnosis. The concept was validated using *S. mutans* and *C. albicans* biofilms growth on materials with similar morphological properties as enamel. After biofilm sample collection, traces of bacteria, fungi, and EPS were found within the bristles [335]. The sensibility of catalytic NPs to environmental changes such as pH and temperature difficult the translation of this technology for clinical applications [188,336]. More research is required to develop coatings to increase the NPs stability, provide long circulation times in biological media, and control the locomotion of the nano/microbots [336,337].

4. Outlook future work

The last 20 years have witnessed a transformative evolution of antimicrobial dental materials. The field is switching from offering “passive” treatments to “smart” antimicrobial biomaterials that are triggered by different internal and external stimuli to deliver “on-demand” therapies with improved control of dosage, location, duration, and efficacy. Most of the contemporary antimicrobial biomaterial systems were noted in the bioresponsive or stimuli-responsive approach, using one stimulus to trigger the effect. Upcoming technologies aim to improve the antimicrobial efficacy and duration by offering multiple antimicrobial/antibiofilm effects. For example, bioresponsive antibacterial biomaterials target the pathogen for a killing action and target biofilm processes by disrupting the EPS production or inactivating quorum sensing. These systems offer dual action using antibacterial mechanisms that do not raise a concern about bacterial resistance.

Moreover, novel approaches of these bioresponsive antimicrobial systems are being designed to perform additional biofunctionalities, including tissue regeneration, remineralization, and anti-inflammatory. These multifunctional biomaterials can combine several abilities and respond to multiple stimuli in the oral cavity for synergistic effects. For example, in the dental field, dental resin adhesives with antibacterial and remineralization capabilities can be used to kill pathogens and regenerate tissue at the bonded interface. This system may decrease the incidence of secondary caries and extend the durability of a restoration [278,338]. Most multifunctional dental materials are fabricated by mixing multiple agents, each with one specific function. This design approach could add complexity to the formulation and difficult the tunability of physical properties for the application. Additional challenges of multifunctional biomaterials are to program the delivery of the specific therapy at the appropriate time (e.g., first antimicrobial, then regeneration) and to prevent the overproduction of ROS that can cause tissue injury, trigger an inflammatory response, and cellular damage [339–341]. Testing the multiple functionalities in-vitro is challenging since, traditionally, each effect is tested separately, which can hinder potential effects in-vivo.

Theranostics combines diagnosis and therapeutic actions into a single system. Nowadays, the diagnosis of pathogens and therapy are independent processes. Applying a theranostic approach for antimicrobial applications in dentistry may facilitate timely interventions at the early stage of infection before biofilm formation and disease progression. Theranostics has been used extensively for cancer diagnostics. Yet, dentistry still needs to exploit this sophisticated approach. For example, 5-aminolevulinic acid was used as a theranostic agent to kill cariogenic bacteria and to identify dental caries via aPDT [342]. Theranostics based on responding to microbial metabolites [343] can achieve detection and infection treatment without complicated interventions. The application of bioresponsive materials in theranostics is another step toward the development of intelligent dentistry. Furthermore, developing

biomaterials that diagnose and treat microbes in-vivo is the future direction of “smart” research.

The interactions between microbes and biomaterials have a significant degree of complexity [344]. Understanding the mechanisms of microbe interaction with biomaterial surfaces is essential for controlling adhesion and biofilm formation, especially for smart antibacterial biomaterial systems where additional interactions are necessary to prevent infection. There are many widely accepted standardized methods to evaluate the properties (physical, mechanical, biocompatibility) of dental materials [345,346]. However, there is no consensus to evaluate the biofilm-dental material interactions [347–349]. In fact, the International Organization for Standardization (ISO) is currently developing a standard (ISO 3990) for testing the antibacterial properties of dental restorative materials [350]. This standard proposes defining the basic requirements for sample preparation, selection of strains, in-vitro test methods and assessment, and reporting results. These standardized methods will enable us to effectively compare outcomes between studies, prevent dubious conclusions, and offer solid predictors for clinical efficacy of the antibacterial technology. Moreover, in-vivo models for mimicking oral biofilm formation and development have been used due to the acceptable representation of human pathology (i.e., similar anatomies, healing processes, and immune response), the possibility of establishing lineages that provide animals with the same genetic background, and the study of complex interactions (i.e., genetic/environmental factor) [351]. However, in-vivo models to specifically study the interactions between the biomaterials and biofilms are limited, which hinders the comparison of outcomes between studies [347]. Directing efforts in this area could facilitate the translation of technologies to the clinic, reduce the number of animals used for in-vivo evaluation, minimize the costs of in-vivo pre-clinical studies, and foster the development of organs on-a-chip technologies [352].

Summary

This review article presented the state-of-the-art of different bioactive, bioresponsive (or stimuli-responsive), and autonomous dental materials for antimicrobial applications. In the first section, we described the different levels of smartness available in dental materials to clarify potential misconceptions about the strategies used by these biomaterials to provide the effect. In the second section, we briefly described different bioactive antimicrobial technologies providing various examples and antibacterial mechanisms. In the third section of the manuscript, we described the different external and internal stimuli used by these smart dental materials to provide an antimicrobial effect. We described systems that responded to pH levels, enzymes, magnetism, electricity, and vibrations to deliver the antibacterial effect. Autonomous microrobots were also covered, showing how this disruptive approach can provide antimicrobial therapy. The outlook section of the manuscript described how multifunctional dental materials and theranostics can open avenues for new research and concepts.

Ethics approval and consent

N/A.

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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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