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Smart Dental Materials and their Antimicrobial Applications: An Updated Review

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Abstract:

Background: Dental materials are crucial for treating and improving oral health as teeth have limited regenerative capabilities. The structure of enamel and dentin poses challenges in oral health restoration, and traditional materials such as resin composites and colloidal nanoparticles have been explored for their regenerative potential. Despite advances, common oral diseases, including dental caries, remain widespread due to factors like bacterial infection. Additionally, the oral cavity presents a harsh environment for dental materials, where acids from bacteria can cause degradation. The ideal dental material should resist infection, promote remineralization, and regenerate dental tissues.

Aim: This review aims to explore the design and applications of smart dental materials, particularly their antimicrobial capabilities, in addressing oral health challenges. These materials include bioactive, bioresponsive, and autonomous biomaterials that can respond to environmental stimuli to enhance treatment outcomes.

Methods: The review examines various dental materials, categorized by their “smartness,” including bioinert, bioactive, bioresponsive, and autonomous. It discusses their use in antimicrobial therapy, specifically for the prevention and treatment of oral infections such as dental caries and periodontitis. Key materials and mechanisms, including antimicrobial agents such as silver and nanoparticles, are highlighted, along with innovative strategies for their delivery.

Results: Smart dental materials exhibit diverse functionalities, such as pathogen eradication and biofilm disruption. The integration of antimicrobial agents into dental materials allows for sophisticated delivery mechanisms that can release therapeutic compounds in response to environmental stimuli. For example, nanoparticles incorporated with agents like myricetin and farnesol offer enhanced biofilm control, targeting specific pathogens like *Streptococcus mutans*.

Conclusion: The development of smart dental materials represents a promising frontier in oral health. These materials offer more effective and sustainable solutions for preventing and treating infections, reducing the risk of restoration failure, and promoting tissue regeneration. However, further research is needed to fully realize their potential in clinical settings.

Key Words: Smart dental materials, antimicrobial agents, bioactive, bioresponsive, biofilm, dental caries, tissue regeneration, nanoparticles, and antimicrobial therapy.

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Introduction:

Because teeth have a limited ability to regenerate themselves, dental materials are required in order to treat and improve oral health [1]. Since enamel is a cellular, it cannot regenerate, whereas the stem cell pool in the tooth pulp limits and influences the regenerative capability of dentin [3]. For example, odontoblasts produce reactive dentin by secreting minerals in response to carious lesions [4]. Cells are embedded in the matrix of this freshly produced tissue, which has an atubular, disordered structure [5,6]. In order to treat, diagnose, prevent, and alleviate oral and dental pathological problems, dental materials are essential. For instance, resin composites are widely utilized to restore tooth function after pathogenic infection-induced tissue damage [7]. Furthermore, colloidal gold nanoparticles (NPs) and superparamagnetic iron oxide (SPIO) have been investigated as theranostic agents for dental pulp capping, exhibiting improved dentin regeneration and magnetic resonance imaging capabilities [8]. Significant oral diseases are nonetheless common despite the availability of preventive methods, despite the fact that they might be significantly reduced with basic self-care practices [9]. Dental caries, which affects 92% of individuals in the US, is one example [10]. As a result, dental supplies continue to be essential in the profession. For dental materials, the mouth cavity is an especially harsh and difficult environment. Both direct and indirect restorations may fail as a result of the acids produced by oral bacteria that demineralize hard tissues. Salivary esterase disruption causes this, hastening the hydrolytic breakdown of dental resin adhesives [[11], [12], [13]]. To effectively treat dental disorders, the perfect dental material should have the ability to fight off infections, stop hydrolytic degradation, encourage remineralization, form a strong link with tissues, and regenerate dental tissues. In particular, during treatment, such a material must withstand these degradative difficulties. The "holy grail" of dental materials that can fully meet these standards has not yet been found, despite continuous research.

The creation of "smart" dental materials—materials with numerous functions for a range of therapeutic applications—is being made possible by technological and manufacturing advancements, including additive manufacturing. "Smart" biomaterials are typically made to change one or more of their characteristics in reaction to outside stimuli [14,15]. Enzymes generated over the course of a disease, for instance, can cause a smart biomaterial to release particular therapeutic compounds at the exact time needed for therapy. However, it is difficult to categorize and identify biomaterials with different levels of "smart" capability because the term "smart biomaterials" is vague and frequently misunderstood. A classification system for smart biomaterials was proposed by Montoya et al. (2021) to address this problem. This system is based on the biomaterial's degree of "smartness," which is based on how well it delivers therapeutic interventions and how much it interacts with its surroundings [16]. Bioinert, bioactive, bioresponsive, and autonomous are the four types they distinguished.

Following implantation, bioinert biomaterials present little risk of damage or toxicity and interact with surrounding tissues very little [17]. One prominent example is polyetheretherketone (PEEK), a chemically inert substance frequently found in denture frames, endoposts, crowns, bridges, and oral implants [18]. Polymethyl methacrylate (PMMA) [21], titanium [20], and 316L stainless steel [19] are further bioinert materials. On the other hand, after being implanted or coming into touch with cells, tissues, or bodily fluids, bioactive materials are made to trigger a particular biological reaction at the interface between the material and tissue [22]. Rather than materials that only aid in remineralization, the term "bioactive" here refers to compounds that have therapeutic benefits, such as antibacterial activities, regenerative characteristics, or drug delivery [23]. Once implanted, these biomaterials release therapeutic chemicals in an uncontrollable way. Fluoride-releasing substances, for instance, aid in maintaining the tooth's normal cycles of demineralization and remineralization [24]. More acid-resistant fluorapatite (FA) or fluorohydroxyapatite (FHA) compounds are formed when the pH of saliva falls below 5 because fluoride ions (F-) take the place of hydroxide ions (OH-) in the tooth's hydroxyapatite (HAp) [25]. Moreover, fluoride is toxic to bacteria by preventing their growth and preventing them from generating acids, surviving in acidic conditions, and adhering to tooth surfaces [26]. Bioinert dental materials can be transformed into bioactive forms by surface coating or functionalization

Bioresponsive or stimulus-responsive biomaterials can release pre-programmed therapeutic compounds in response to certain environmental stimuli, such as light, temperature, pH changes, magnetic fields, or enzymes [27]. Both internal and external impulses can cause these materials to react. To cure caries, for example, a dental composite may include pH-sensitive nanoparticles (NPs) that, when exposed to acidic environments, release antimicrobial agents [28]. Autonomous biomaterials, the most sophisticated type, are able to detect various stimuli and modify their reactions, accordingly, providing customized interventions at particular periods. In order to sterilize and cure root canal infections, magnetically driven nanobots that are equipped with antibacterial treatments can enter dentinal tubules in radicular dentin [29]. Nevertheless, the promise of these intelligent biomaterials to improve oral health has not yet been completely realized in dentistry.

Across a range of medical specialties, the application of smart biomaterials has grown dramatically in recent years [30]. Drug delivery [31,32], biosensing [33,34], tissue engineering [35,36], antibacterial therapies [37], tissue regeneration [30], and remineralization [38] are just a few of the many uses for these materials. In tissue engineering, for example, intelligent piezoelectric scaffolds are used to produce electrical signals that replicate the physiological processes of tissues [39, 40]. The multifunctional properties of these biomaterials are steadily helping dentistry, especially in the treatment and prevention of infections. The purpose of this article is to give a general overview of the design and use of active, bioresponsive, and autonomous biomaterials for antimicrobial therapy in dental applications.

Oral Environment::

Bacteria, viruses, fungi, and protozoa are all found in the oral cavity, which is the second most complex microbial ecosystem in the human body [41]. In the oral cavity, more than 700 bacteria species, especially on teeth and dental materials, produce biofilms [42, 43]. These oral biofilms typically maintain a symbiotic, balanced relationship that inhibits the growth of pathogenic microbes, hence halting the progression of disease [44]. For example, in spite of intense microbial colonization, the immune system works in concert with commensal species to avoid acute infections of the oral mucosa [45]. When this equilibrium is upset, a condition known as dysbiosis takes place, which usually results in an overabundance of harmful microbes at the expense of helpful ones. Changes in the content and flow of saliva, inadequate dental hygiene, antibiotic treatments, and lifestyle choices including smoking and eating habits are all contributing factors to oral dysbiosis [46]. For instance, germs that are difficult to eradicate using standard cleaning techniques may be present at the interface between dental restorations and tooth tissue, leading to secondary caries and early restoration failure [47]. Furthermore, the general health and oral care habits of communities are greatly influenced by elements like socioeconomic disparities, public health regulations, and dental care accessibility [49].

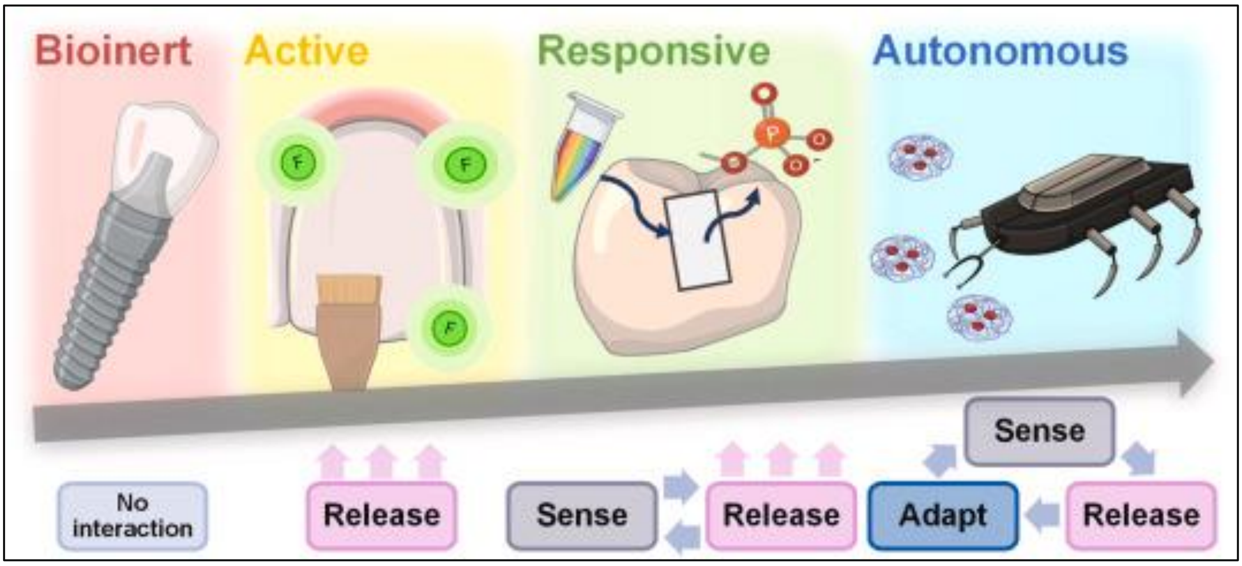

Figure 1: Levels of Smart Biomaterials.

Caries, periodontitis, root canal infections, peri-implantitis, pulpitis, candidiasis, denture stomatitis, and soft tissue infections are among the oral disorders that can result from upsetting the normal equilibrium of the oral microbiome [50]. Increased sugar intake and decreased salivary flow in caries lead to the formation of acid-producing bacteria such as Streptococcus mutans, which demineralize tooth tissues and prevent commensal species from growing [51]. Pathogenic biofilms can cause persistent oral infections that cause dental tissue loss and possibly tooth loss if they are not controlled [52]. To avoid these infections and lessen the likelihood that dental procedures may fail too soon, antimicrobial dental materials must be developed [53].

Although oral infections typically exhibit polymicrobial characteristics, certain pathogens are commonly linked to specific dental conditions. The primary approach in the development of antimicrobial biomaterials is to inhibit the proliferation or target these specific pathogens. For instance, *Streptococcus mutans* is the predominant pathogen associated with dental caries, while an overgrowth of *Candida albicans* is implicated in the onset of denture stomatitis induced by Candida [54,55]. Most anti-caries biomaterials are evaluated primarily against this pathogen. However, dental infections are often polymicrobial. *S. mutans* does not act in isolation in the development of caries, as interactions with other microorganisms are evident. For example, *C. albicans* and *S. mutans* engage in a synergistic interaction during caries formation [53]. Microbial products from this cross-kingdom interaction promote the accumulation of *S. mutans* within biofilms, exacerbating the disease's severity and complicating treatment [53]. More advanced strategies in the design of antimicrobial dental materials focus on targeting specific virulence-associated genes pertinent to particular infections or disrupting bacterial communication systems (e.g., quorum sensing), via enzymatic degradation of signaling molecules, blocking signal production, or impeding signal reception [56]. A notable example includes the extracellular polymeric substance (EPS), which forms a protective matrix for cells during biofilm development. Disrupting the EPS, for instance, by utilizing enzymes such as dispersin B, offers a promising avenue for antibiofilm therapy [57]. Furthermore, quorum quenching, which involves the degradation or inhibition of autoinducers, suppresses quorum sensing and inhibits density-dependent functions such as virulence and biofilm formation [58]. The primary advantage of these approaches lies in preventing the elimination of commensal organisms. The optimal antimicrobial strategy would integrate antibacterial agents (for pathogen removal) with capabilities for EPS disassembly and quorum quenching [57].

3. Smart Dental Materials for Antimicrobial and Antibiofilm Therapies

The dental sector has employed a wide range of antimicrobial agents to address various infections. Additional details on antimicrobial dental materials are available in recent reviews

[59,60,61,62,63,64,65,66,67,68,69,70,71,72]. This review does not provide an exhaustive list of all antimicrobial agents used in dentistry. Instead, it presents a novel examination of the diverse strategies for delivering these agents, categorized by the level of sophistication of the biomaterials. For example, silver, a traditional antibacterial agent employed in the treatment and prevention of dental caries, is commonly delivered through surface coatings such as silver diamine fluoride (SDF) [73]. However, with the advent of nanoscale silver particles (NPs), these can be encapsulated or incorporated into various vehicles or carriers, thus facilitating a more "sophisticated" or "smart" delivery system. Additionally, the field has witnessed the emergence of dental materials that offer multiple antimicrobial functionalities, such as pathogen eradication and biofilm matrix disruption, by integrating various agents into a single carrier. A notable example is a dual antibacterial system comprising NPs loaded with myricetin and farnesol. This combination reduces biofilm acidogenicity and EPS synthesis, with farnesol serving as a membrane-disrupting agent, while myricetin targets and eradicates *S. mutans* biofilms [74]. This paper highlights the various approaches used to deliver and release antimicrobial agents in dental applications, including bioactive, bioresponsive, and autonomous systems. Conventional materials and agents employed in the prevention and treatment of oral and systemic diseases, along with their respective antimicrobial mechanisms [75,78,96,106].

- **Chemical Agents**
  - *Chlorhexidine (CHX)*: Binds to bacterial cell walls, disrupting membrane transport systems and causing cytoplasmic protein precipitation.
  - *Tetracycline (minocycline, doxycycline)*: Binds to the bacterial 30S ribosomal subunit, inhibiting protein synthesis.
  - *Metronidazole*: Interferes with protein synthesis by interacting with DNA.
  - *Triclosan (TCS)*: Blocks bacterial fatty acid biosynthesis at the FabI step of the enoyl-acyl carrier protein reductase pathway.
  - *Amphotericin-B*: Disrupts membrane stability by sequestering ergosterol.
  - *Quaternary Ammonium Compounds*: Induce antibacterial action through attraction to the negatively charged bacterial membrane.
  - *Nitrous Oxide (NO)*: Generates reactive nitrogen oxide species (RNOS), causing oxidative and nitrosative damage to DNA, enzymes, and lipids.
  - *Sodium Hypochlorite (NaOCl)*: Disrupts cytoplasmic membrane integrity, causing enzymatic inhibition and metabolic alterations.
- **Natural Agents and Extracts**
  - *Catechins (EGCG, GCG)*: Bind to bacterial cell walls, disrupting biosynthesis, or generate hydrogen peroxide through reactions with dissolved oxygen.
  - *Coffea arabica/canephora*: Inactivate cellular enzymes.
  - *Cranberry Proanthocyanidins*: Inhibit bacterial adhesion and coaggregation.
  - *Allicin*: Inhibits sulfhydryl-dependent enzymes like alcohol dehydrogenase.
  - *Isothiocyanates*: React with proteins, disrupting bacterial biochemical processes.
  - *Clove Oil (Eugenol)*: Damages the bacterial cell membrane.
  - *Citrus limonum/Citrus aurantium*: Disrupt bacterial cytoplasmic membranes.
  - *Punica granatum*: Inhibits microbial extracellular enzymes and oxidative phosphorylation.
- **Compounds**

  - *Quaternary Ammonium Polymers*: Attract to the bacterial membrane, inducing antibacterial effects.
  - *Zwitterionic Polymers*: Form hydration layers that strongly repel bacterial adhesion via electrostatic interactions.
  - *Chitosan*: Binds to bacterial cell walls, altering membrane permeability and inhibiting DNA replication.
  - *Catechol Derivatives*: Produce hydrogen peroxide, which generates hydroxyl radicals damaging bacterial structures.
  - *Polyaniline (PANI)*: Produces reactive oxygen species (ROS), damaging proteins and membranes.
  - *Polyamidoamine (PAMAM)*: Binds to lipid membranes, leading to bacterial cell death.
  - *Silver (Ag)*: Releases ions that disrupt bacterial membranes and cytoplasmic integrity.
- **Enzymes**
  - *α-Amylase*: Prevents microbial adherence by inhibiting extracellular polymeric substances.
  - *Salivary Peroxidases*: Induces DNA damage and inhibits bacterial growth.
  - *Lysozyme*: Aggregates bacteria, affecting their adherence.
  - *Lactoferrin*: Disrupts bacterial membranes and deprives them of iron.
  - *Dextranase*: Disrupts biofilm formation by interfering with sucrose-dependent bacterial adhesion.
  - *Mutanase, Krillase*: Disrupt bacterial adhesion and coaggregation.
  - *Dispersin B (DspB)*: Hydrolyzes biofilm exopolysaccharides, disrupting biofilm integrity.

Bioactive Antimicrobial Therapies

To counteract microbial activity, bioactive antimicrobial treatments use a variety of substances. These consist of chemical substances such antimicrobial peptides (AMPs) [77], cationic monomers [75,76] (like quaternary ammonium methacrylate, MDPB), antibiotics (like chlorhexidine (CHX) and minocycline), and both metallic and non-metallic fillers (like zinc oxide, or ZnO) [78,79]. These technologies usually provide the medication right after implantation by combining antimicrobial chemicals into a carrier (biomaterial). Leachable antibiotics, such as CHX, tetracyclines, and metronidazole, for example, are used in adhesives [80], sealants [81], and dentures [82] to limit microbial growth and stop biofilm development. Other nanospace carriers of antibacterial drugs, including dendrimers [85], nanocapsules [86], core-shell structures [87], liposomes [88], micelles [89], and nanofibers [90], have been investigated [83,84]. Micelles are preferred for their ease of manipulation and capacity to encapsulate agents [92], but nanofibers are high-loading carriers because of their large surface area [91]. Enhanced control over agent release, better pharmacokinetics (particularly for antibiotics), and higher selectivity are just a few advantages that these nano-carriers provide, all of which contribute to improved therapeutic success [83,93]. Numerous formulations of bioactive antimicrobials are now being used in therapeutic settings. For instance, Arestin® treats periodontal disease by using polylactide-glycolic acid copolymer (PLGA) microspheres that contain minocycline hydrochloride [94]. For sustained-release treatment, a similar idea was used with calcium polyphosphate glass microspheres loaded with minocycline [95].

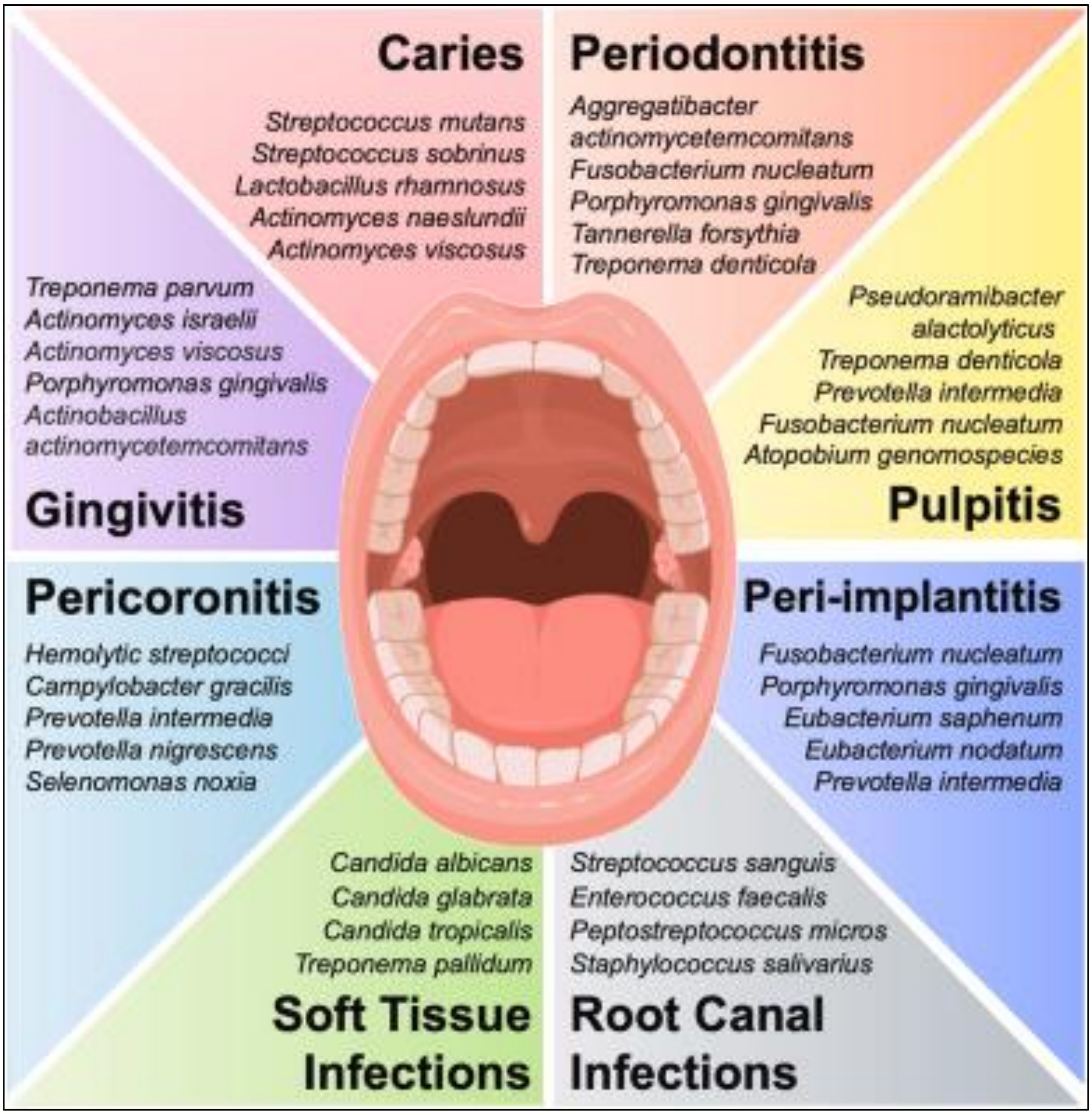

Figure 2: Pathogen Microorganisms associated to oral environment.

For antimicrobial treatments, bioactive monomers are commonly added to dental resins (such as composites, primers, and adhesives) [[96], [97], [98]]. When left unpolymerized, these monomers have strong antibacterial qualities; once polymerized, they also impede contact. Moreover, antibacterial monomers may remain leachable as free compounds or become trapped within the polymer chain [96]. In order to improve antimicrobial effects while preserving mechanical qualities, solvent sorption, biocompatibility, and curing efficiency, recent studies have concentrated on raising the monomer concentration to 5% [96]. Both gram-positive and gram-negative bacteria, including those linked to caries and endodontic problems, have been tested against these substances. MDPB has demonstrated bactericidal action against a wide range of caries-related bacteria when added commercially to primer solutions of self-etching systems (Clearfil Liner Bond 2, Kuraray Medical, Japan) and adhesives (Clearfil SE Protect) [99].

Concerns regarding microbial resistance to antibiotics may be resolved with the help of bioactive fillers [100]. These fillers, which are usually inorganic, are made at the nanoscale and come in a variety of forms [78]. The most widely used fillers include AMPs, polymeric/organic fillers (such as quaternary ammonium polyethyleneimine, chitosan), and nano-structures (such as silver, zinc oxide, titanium, copper compounds, glass, and nanodiamonds) [62]. These fillers or their ions are released into the surrounding microenvironment to inhibit infections in order to have an antibacterial effect. Nanoparticles (NPs) provide a great deal of customizing potential when used as fillers. For instance, by modifying the size, surface area-to-mass ratio, particle shape, surface charge, dosage, and coatings, NPs' antibacterial and antibiofilm response can be maximized [101]. Furthermore, fillers with fewer adverse effects can be altered to target particular infections. The antibacterial selectivity towards certain bacteria is improved by methods such surface charge modification, functional group addition, and molecule adsorption [102]. The filler content in dental composites affects the material's chemical, biological, structural, and cosmetic properties [103]. For instance, adding up to 7.5% ZnO NPs to a typical dental adhesive led to a notable decrease in bacteria in biofilms while preserving a respectable level of conversion, flexural strength, and elastic modulus [104].

Gram-positive and gram-negative bacteria, fungi, parasites, and viruses are among the many pathogens that AMPs have broad-spectrum inhibitory effect against [105]. Their shape (e.g., α-helical, β-sheet), hydrophobicity, and net charge are associated with their antibacterial activity [105]. Saliva, gingival crevicular fluid (e.g., histatin-1,3, and 5), the epithelium (e.g., adrenomedullin, β-defensins), and neutrophils (e.g., α-defensins) are natural sources of AMPs [106]. When it comes to protecting against the virulence factors of bacteria, AMPs are essential. For example, mature α-defensin has antibacterial activity against Escherichia coli, Enterococcus faecalis, and Candida albicans, while histatin functions as an antimicrobial agent to prevent secondary caries induced by Streptococcus mutans [107]. Both manufactured and natural sources, such as bacteria, plants, insects, crustaceans, and mammals, can produce AMPs. AMPs have been included into implant coatings [110,111] and adhesive systems [108,109] as antibacterial agents. For instance, when added to dental adhesives, the peptide GH12, which comes from both bacterial and fungal origins, suppresses microorganisms at the adhesive/dentin interface [112]. Additionally, ε-Polylysine has been evaluated against oral pathogens associated with periodontitis and caries and added to resin systems [113]. The use of AMPs has expanded to ex vivo testing at dentin-composite interfaces, where they have shown selective antibacterial action against the most common taxa linked to failed composite restorations as well as two important acidogenic colonizers [114,115]. Clinical research on AMPs have shown encouraging results, and products like C16G2 strips, varnish, and gels are being tested for their antibacterial properties against S. mutans in the treatment of dental decay [117,118]. Furthermore, it has been demonstrated that injecting Nal-P-113 into the periodontal pocket lowers the amounts of Porphyromonas gingivalis, Treponema denticola, Streptococcus gordonii, and Fusobacterium nucleatum in patient subgingival plaque [119]. For the treatment of oral candidiasis in HIV-positive people, a PAC113 (histatin analogue) mouthwash that targets Candida albicans is presently undergoing phase two evaluation [120]. The main benefits of AMPs over conventional antibiotics are their low cellular toxicity [123,124], quick beginning of action [122], and poor bacterial resistance [121]. Additionally, certain bacterial groups can be targeted by AMPs [125]. However, problems still exist, including low stability in vivo, excessive hemolysis, short half-lives (less than 37 hours), short spacer lengths that impair antibacterial activity, and expensive extraction procedures [126,127].

Because they stop germs from colonizing and forming biofilms on implant surfaces, antimicrobial coatings are essential parts of bioactive therapies, especially in implant dentistry. It has been demonstrated that these coatings lower the risk of implant failure, peri-implantitis, and peri-implant mucositis [128]. Both contact-killing and release-killing surfaces are used in antimicrobial coating techniques [129]. Antimicrobial components affixed to the surface, such as quaternary ammonium compounds [130], AMPs [131,132], and antimicrobial enzymes (AMEs) [133], are essential for contact-killing surfaces. For instance, peri-implantitis is treated using implant surface coatings that include GL13K, an AMP that is generated from the human salivary protein BPIFA2 [134]. When paired with GL13K, a titanium dioxide (TiO2) nanotube coating demonstrated antibacterial action against Porphyromonas gingivalis and Fusobacterium nucleatum, along with biocompatibility with macrophage and preosteoblast cells [135]. Drug delivery methods [136] or ion-releasing coatings like copper (Cu), zinc (Zn), silver (Ag), and gold (Au) [137] are commonly used in release-killing coatings. Although their optimum antibacterial potency may occasionally jeopardize biocompatibility and osseointegration, these antimicrobial coatings provide localized activity advantages over systemic antibiotic administration [138].

By changing the surface topography, anti-biofouling surfaces stop microorganisms from adhering and forming biofilms [139, 140]. Some of these topographical changes are modeled after the structure of plant surfaces (like lotus or rose petals) and animal skins (like shark, cicada, or dragonfly wings) [141]. In contrast to unaltered wires, Arango-Santander et al. (2020) reduced the adherence and colonization of S. mutans by altering orthodontic archwires to resemble the surface of Colocasia esculenta leaves [142]. In wet conditions, catechols inspired by mussels, like dopamine and polydopamine (PDA), are used for surface bonding and functionalization [143]. By generating hydrogen peroxide (H2O2) and singlet oxygen (O2), catechol coatings prevent bacterial adherence and growth and cause oxidative stress, which kills bacteria [144]. Catechols are good for dental implant coatings because of their antibacterial qualities, as well as their high biocompatibility and moisture resistance [145,146]. For instance, when compared to uncoated implants, PEEK dental implants coated with graphene oxide (GO) and PDA shown a notable decrease in bacterial attachment from Porphyromonas gingivalis, Fusobacterium nucleatum, and S. mutans [147]. Furthermore, dopamine methacrylate-based polymeric particles can be added to hydroxyapatite (HA) coating to create a strong bond and increase surface roughness, which would increase antibacterial activity [148].

Polymeric particles composed of dopamine methacrylamide (DMA) and eugenyl methacrylate (EMA), utilized as coatings on titanium implants, demonstrated exceptional antimicrobial efficacy (over 90%) against *Escherichia coli* [148]. Typically, micro-scale topographies lack bactericidal properties but may reduce bacterial adhesion [149]. In contrast, nano-scale topographical features with high aspect ratios (ranging from 0.2 to 2 in width-to-height ratio) induce significant deformational stress on bacterial membranes, leading to rupture [150]. However, the antimicrobial effectiveness of patterned surfaces is also influenced by the specific microbial species [151]. While several studies have explored the impact of topographical modifications on both gram-positive and gram-negative bacteria in orthopedic applications [[152], [153], [154]], the advancement of such approaches in dental applications, particularly those involving in-vivo results, remains limited. A recent study involved etching commercially pure titanium to form spiked surfaces, effectively eliminating anaerobic dental pathogens [155].

Despite the commercial use of several bioactive antimicrobial agents, certain limitations persist. A primary challenge is the long-term delivery of antimicrobial therapies, which could lead to antimicrobial resistance through horizontal gene transfer among bacteria [156,157]. These technologies typically release antimicrobial agents immediately after implantation, leading to rapid depletion and insufficient therapeutic duration (often less than one year) [158]. Once exhausted, the agents cannot be replenished. Additionally, the release of antimicrobial agents may alter the properties of the carrier. For instance, dental composites, sealants, or adhesives with depleted antimicrobial agents may exhibit diminished mechanical and physical properties compared to their counterparts without such agents [96]. Uncontrolled release further complicates the delivery of an adequate dosage, potentially accelerating agent depletion or providing insufficient amounts for effective therapy. This issue has been somewhat mitigated by employing nano-carriers. Furthermore, the lack of specificity in targeting pathogens can lead to collateral damage, disrupting the balance of the oral microbiota and harming commensal species [159,160], as the therapy indiscriminately affects all microorganisms in the microenvironment. Despite the advantages of chemical compounds—such as high efficacy, elevated cure rates, and minimally invasive applications—concerns about microbial resistance to antibiotics persist [161,162]. Antimicrobial polymers, while overcoming some drawbacks of leachable agents (e.g., prolonged activity without leaching, minimal toxicity to mammalian cells, reduced resistance, and enhanced chemical stability) [163], face challenges, including limited efficacy against gram-positive strains and high production costs [163]. Moreover, although several clinical trials have successfully tested the use of nanoparticles in dental materials as antimicrobial agents [[164], [165], [166], [167], [168]], the widespread clinical adoption of these nanoparticles is hindered by concerns over the release of toxic ions, which can trigger inflammation, immunotoxicity, cytotoxicity, and genotoxicity in healthy cells. For example, titanium nanoparticles released from implants during decontamination procedures, such as ultrasonic cleaning and laser treatment, can provoke a pronounced systemic immune response [169,170]. The challenge of controlling nanoparticle dispersion in clinical settings remains a significant concern [171].

Bioresponsive Antimicrobial Therapies

Materials that can recognize particular stimuli and react by releasing therapeutic substances are known as bioresponsive or stimulus-responsive biomaterials [16,66,172]. These materials are frequently made to include antimicrobial compounds in carriers, which alter their characteristics (such as deterioration) in reaction to stimuli, allowing the agent to be released in a controlled manner [173]. Because they overcome some of the drawbacks of traditional bioactive antimicrobial treatments, bioresponsive antimicrobial biomaterials hold great promise. These materials improve the efficacy, dose, localization, and duration of therapy while providing better targeting of certain infections. These responsive technologies in dentistry are triggered by a variety of internal stimuli, including microbial metabolites (like secreted enzymes), microenvironmental signals (like salivary enzymes or low pH levels caused by pathogens), or by targeting particular peptides, proteins, or genes on the microbial surface. These biomaterials can also be activated by extrinsic stimuli like as electrical fields, light, magnetism, and masticatory strain. The several bioresponsive antimicrobial biomaterials utilized in dental applications are examined in this section.

One important subset of biomaterials in this field are pH-responsive biomaterials, which react to variations in the pH of the surrounding medium. Depending on the pH, these materials may expand, collapse, or change other characteristics. For example, certain hydrogels alter structurally in an acidic environment, expanding to release therapeutic drugs, and collapsing to retain the medication in a basic environment [174]. In dentistry, where many oral infections are aciduric and acidogenic and cause major changes in the pH of the microenvironment during the course of disease, the development of pH-sensitive biomaterials is extremely beneficial. For instance, normal saliva has a pH range of 6.2–7.6, whereas the microenvironment pH falls to between 4.5 and 5.5 with active dental caries. As a result, pH-responsive biomaterials are now the go-to option for treating peri-implantitis, periodontitis, and dental cavities [175]. Hydrogels, resins (adhesives and sealants), and nanocarriers (such micelles) have all been used as the "smart" vehicles for pH-responsive antimicrobial technologies in dental applications. When exposed to particular pH values, polymers with weak acid groups (like carboxylic acids) or base groups (like primary and tertiary amines) alter in ionization, solubility, surface activity, and configuration, which makes them useful for therapeutic applications [177]. In dentistry, for instance, the tertiary amine resin dodecylmethylaminoethyl methacrylate (DMAEM) serves as a pH-responsive agent [178]. DMAEM functions as a cationic polymer in acidic environments, generating quaternary ammonium monomers that release antibacterial agents [178]. DMAEM has recently been added to dental adhesive resins, which have antimicrobial properties in acidic conditions ($pH < 6$) and provide long-term antimicrobial benefits without upsetting the equilibrium of the oral microbiota. The application of DMAEM to resin-based sealants has been effectively expanded by additional study, improving their resistance to microleakage [178]. In dentistry, caries has also been treated with pH-responsive hydrogels that release antibacterial compounds. In order to prevent dental caries, one study created a hydrogel made of N-dimethylaminoethyl methacrylate (DMAEMA) and 2-hydroxyethyl methacrylate (HEMA) that effectively produced chlorhexidine (CHX) in response to acidic pH levels [179].

Furthermore, antimicrobial compounds have been encapsulated and released in response to pH variations using pH-responsive nanocarriers, such as core-shell nanoparticles, micelles, and nanogels. These nanocarriers usually consist of charge-shifting polymers or pH-degradable links that release their payload in a regulated way when exposed to acidic environments [182]. By enhancing agent stability, solubility, and penetration within biofilms, this tailored release boosts therapeutic efficacy [184]. For example, in animal models, farnesol-loaded pH-responsive micelles have been demonstrated to lessen the severity of dental caries [89]. Similarly, it was discovered that farnesol and pyrophosphate-containing polymeric micelles adhered to dental enamel and released farnesol in acidic environments, preventing the growth of germs [89]. antibacterial drugs including metronidazole and N-phenacylthiazolium bromide (PTB) have been encapsulated in PLGA and chitosan nanospheres for the treatment of periodontitis, and when released in response to low pH, they exhibit effective antibacterial activity [185]. In order to combat biofilms and avoid periodontal damage, quaternary ammonium chitosan-liposome complexes have been included into formulations of pH-responsive nanoparticles for dental caries treatment [187]. In in vivo investigations, these nanoparticles showed good cytotoxicity profiles, preventing alveolar bone loss and inflammation. Notwithstanding the encouraging possibilities of these nanocarriers, problems including particle aggregation, batch-to-batch variability, and low transfection effectiveness continue to be major obstacles [194]. Oral antibacterial technologies with enhanced bacterial selectivity are now possible because to the combination of pH-responsive nanocarriers with antimicrobial peptides (AMPs). A promising tactic for targeted antimicrobial therapy is the encapsulation of AMPs in these sensitive carriers, which provides improved protection against enzymatic degradation.

Enzyme-Responsive Systems in Antimicrobial Therapy:

Certain bacterial and salivary enzymes have been used as triggers to release antimicrobial agents (antibiotics, antimicrobial peptides [AMPs], and nanoparticles [NPs]) for therapeutic purposes. Enzymes operate as biological catalysts and are essential for speeding up biochemical reactions. Numerous enzymes secreted by bacteria and fungi, such as lipase, esterase, phosphatase, urease, gelatinase, and others, have been found to be biomarkers for identifying disease phases that are active and require intervention [202,203]. For example, during chronic periodontitis, bacteria secrete a by-product called matrix metalloproteinase-8 (MMP-8), which triggers the host immunological response [204]. In bioresponsive delivery systems intended to treat periodontal disease, MMP-8 has been used as a stimulus. Guo et al. (2019) treated periodontal diseases by encapsulating minocycline hydrochloride and antimicrobial peptides in a biodegradable poly(ethylene glycol) (PEG) hydrogel that reacted to MMP-8 [205]. Likewise, under MMP-8 activity, a hydrogel made of gelatin methacrylate (GelMA) loaded with aluminosilicate nanotubes and chlorhexidine (CHX) was demonstrated to break down in 20 days, allowing for prolonged CHX release to treat dental infections [206]. In order to treat periapical infections, Ribeiro et al. (2020) also used MMP-mediated biodegradation of GelMA to release CHX, halloysite aluminosilicate nanotubes, clindamycin, metronidazole, and ciprofloxacin. They showed notable antimicrobial effects against Candida albicans and Enterococcus faecalis in vitro, as well as acceptable biocompatibility and low inflammatory responses in vivo [206,207].

By signaling when treatment is necessary, bacterial and oral enzymes function as biomarkers for the development and prevention of oral illnesses, aiding in clinical management. Degradation of extracellular matrix components, control of pH homeostasis, and modulation of cytokine and chemokine activity by enzymes such matrix metalloproteinases (MMPs), carbonic anhydrase, and proteinase 3 are some of the mechanisms implicated in different disorders [202,203,210]. As demonstrated by alpha-amylase in periodontal disease and cavities, these enzymes also help determine the severity of the disease [210]. Furthermore, enzymes such as cathepsins and cysteine proteases aid in the production of biofilms and tissue degradation, both of which are essential steps in the pathophysiology of illness. By breaking down different extracellular matrix proteins and antibiotics, aryl sulfatase, elastase, and β-lactamases further affect the course of the disease, especially in periodontitis [210]. Understanding disease processes and developing customized treatment plans depend heavily on these enzymatic reactions.

Bacterial enzymes (including esterase, phosphatase, phospholipase, β-lactamases, and gelatinase), cell-surface enzymes (like MMPs), and salivary enzymes (like lipase, protease, alpha-amylase, lysozyme, and lactoperoxidase) can all be specifically targeted by enzyme-responsive biomaterials [208]. By eliminating the non-specificity connected with conventional antimicrobial treatments, these systems provide great efficacy and selectivity during catalysis. Enzymatic activity triggers the enzymatic destruction of degradable carriers, including poly(ethylene succinate) (PES), polycaprolactone (PCL), hyaluronic acid, and PEG, which results in the release of antimicrobial compounds in enzyme-responsive systems [210]. The targeted release of medicines at illness locations is made possible by enzymatic reactions that can cause hydrolysis, swelling, backbone cleavage, or degradation. For instance, Wang et al. (2022) used 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-PEG (DSPE-PEG) to create a lipase-responsive nanocarrier that was loaded with minocycline hydrochloride and alpha-lipoic acid (ALA). The lipase released by periodontal pathogens activated the nanocarrier. In diabetic rats with periodontal infections, the activated nanocarrier successfully prevented the growth of microbial colonies [209]. Since endogenous enzyme levels function as triggers and do not require external activation, enzyme-responsive biomaterials are a step toward autonomous systems.

Photodynamic Therapy in Antimicrobial Treatment:

Using light to activate non-toxic or minimally toxic photosensitizers (PS), photodynamic antimicrobial therapy (aPDT) eliminates microorganisms by producing reactive oxygen species (ROS) like singlet oxygen (O2), hydrogen peroxide (H2O2), and hydroxyl radicals (·OH). In addition to impairing external virulence factors like collagenase and lipopolysaccharides, this method damages bacterial membranes and cell walls by interfering with lipids, proteins, ion channels, and vital metabolic enzymes [216]. Reduced antimicrobial resistance, quicker pathogen removal with lower PS concentrations, localized effects without causing tissue damage, and a broad antimicrobial spectrum that targets both gram-positive and gram-negative bacteria are just a few of the benefits that aPDT offers over conventional antimicrobial treatments. The method has been widely used in dentistry to treat a variety of oral microbial pathogens that cause conditions such peri-implantitis, endodontic infections, periodontitis, dental caries, and candidiasis [217].

For instance, when employing PS agents like methylene blue, toluidine blue, aluminum chloride-phthalocyanine, and chlorophyll derivatives, aPDT has proven to be very successful in removing cariogenic biofilms, especially Streptococcus mutans [218][219][220][221][222][223]. In comparison to methylene blue, fotoenticine® has shown higher efficacy in controlling S. mutans. It has been proven efficient against multispecies biofilms linked to dental caries [230]. Additionally, Enterococcus faecalis has been successfully eradicated from root canals using toluidine blue O [232,233]. Because aPDT may treat a wide range of oral disorders with minimal negative effects on surrounding tissues, its usage has become more popular.

Conclusion:

The integration of smart materials into dentistry is a transformative approach to improving oral health. Traditional dental materials often fail due to the harsh and dynamic conditions in the oral cavity, such as bacterial presence and acidic environments. These conditions challenge the longevity and effectiveness of dental restorations, necessitating materials that can resist degradation and promote tissue regeneration. Smart dental materials, which respond to environmental stimuli such as pH changes, light, or temperature, are emerging as a promising solution to address these challenges. This review highlights various categories of smart dental materials, each designed to provide specific therapeutic benefits. Bioactive materials, for instance, release fluoride or antimicrobial agents to aid in remineralization and combat infections. Bioresponsive materials can release therapeutic compounds when triggered by environmental stimuli, offering more targeted and timely treatment. Autonomous materials, the most advanced, adapt to changing conditions and can even perform complex functions such as detecting pathogens or releasing drugs on demand. These capabilities significantly enhance the potential of dental materials to prevent, treat, and even reverse the effects of common oral diseases like dental caries and periodontitis. The incorporation of nanoparticles into dental materials further enhances their functionality, offering controlled release of antimicrobial agents like silver and myricetin. Such innovations not only improve the treatment of infections but also tackle biofilm formation, a key factor in the persistence of oral diseases. The dual functionality of these materials, targeting both pathogens and biofilm matrices, offers a sophisticated approach to oral health management. Despite these advancements, the full potential of smart dental materials has yet to be realized. Challenges in achieving optimal performance and long-term clinical success remain, but ongoing research is likely to overcome these hurdles. As these materials evolve, they hold the promise of significantly improving the effectiveness and durability of dental treatments, paving the way for more personalized, efficient, and sustainable dental care.

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لمواد السنية الذكية وتطبيقاتها المضادة للميكروبات: مراجعة محدثة

الملخص:

الخلفية :تعد المواد السنية أساسية في علاج وتحسين صحة الفم حيث إن الأسنان تتمتع بقدرات تجديد محدودة. يشكل هيكل المينا والعاج تحديات في استعادة صحة الفم، وقد تم استكشاف المواد التقليدية مثل المركبات الراتنجية والجسيمات النانوية الغروية لإمكاناتها التجديدية. على الرغم من التقدم، لا تزال الأمراض الفموية الشائعة، بما في ذلك تسوس الأسنان، منتشرة بسبب عوامل مثل العدوى البكتيرية. علاوة على ذلك، يقدم التجويف الفمي بيئة قاسية للمواد السنية، حيث يمكن للأحماض الناتجة عن البكتيريا أن تسبب التدهور. يجب أن تقاوم المادة السنية المثالية العدوى، وتعزز التمعدن من جديد، وتعيد تجديد الأنسجة السنية.

الهدف :تهدف هذه المراجعة إلى استكشاف تصميم وتطبيقات المواد السنية الذكية، خصوصاً قدراتها المضادة للميكروبات، في مواجهة تحديات صحة الفم. تشمل هذه المواد البيولوجية النشطة، والبيولوجية المستجيبة، والمواد الحيوية المستقلة التي يمكنها الاستجابة للمحفزات البيئية لتحسين نتائج العلاج.

الطرق :تستعرض المراجعة مختلف المواد السنية، مصنفة حسب "ذكائها"، بما في ذلك المواد البيولوجية غير التفاعلية، والبيولوجية النشطة، والبيولوجية المستجيبة، والمستقلة. تناقش استخداماتها في العلاج المضاد للميكروبات، وخاصة للوقاية من وعلاج الالتهابات الفموية مثل تسوس الأسنان والتهاب اللثة. يتم تسليط الضوء على المواد والآليات الرئيسية، بما في ذلك العوامل المضادة للميكروبات مثل الفضة والجسيمات النانوية، بالإضافة إلى استراتيجيات مبتكرة لتوصيلها.

النتائج :تتمتع المواد السنية الذكية بوظائف متنوعة، مثل القضاء على مسببات الأمراض وتعطيل الأغشية الحيوية. يسمح دمج العوامل المضادة للميكروبات في المواد السنية بآليات توصيل متطورة يمكنها إفراز المركبات العلاجية استجابة للمحفزات البيئية. على سبيل المثال، توفر الجسيمات النانوية المدمجة بعوامل مثل الميريستين والفارنيسول تحكماً معززاً في الأغشية الحيوية، مستهدفة مسببات الأمراض المحددة مثل *Streptococcus mutans.*

الخاتمة :يمثل تطوير المواد السنية الذكية آفاقاً واعدة في صحة الفم. توفر هذه المواد حلولاً أكثر فعالية واستدامة للوقاية من وعلاج الالتهابات، وتقليل خطر فشل الترميم، وتعزيز تجديد الأنسجة. ومع ذلك، فإن مزيداً من البحث مطلوب لتحقيق إمكاناتها بالكامل في الأوساط السريرية.

الكلمات المفتاحية :المواد السنية الذكية، العوامل المضادة للميكروبات، البيولوجية النشطة، البيولوجية المستجيبة، الأغشية الحيوية، تسوس الأسنان، تجديد الأنسجة، الجسيمات النانوية، والعلاج المضاد للميكروبات.