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An introduction to antibacterial materials in composite restorations

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Abstract

The longevity of direct esthetic restorations is severely compromised because of, among other things, a loss of function that comes from their susceptibility to biofilm-mediated secondary caries, with *Streptococcus mutans* being the most prevalent associated pathogen. Strategies to combat biofilms range from dental compounds that can disrupt multispecies biofilms in the oral cavity to approaches that specifically target caries-causing bacteria such as *S mutans*. One strategy is to include those antibacterial compounds directly in the material so they can be available long-term in the oral cavity and localized at the margin of the restorations, in which many of the failures initiate. Many antibacterial compounds have already been proposed for use in dental materials, including but not limited to phenolic compounds, antimicrobial peptides, quaternary ammonium compounds, and nanoparticles. In general, the goal of incorporating them directly into the material is to increase their availability in the oral cavity past the fleeting effect they would otherwise have in mouth rinses. This review focuses specifically on natural compounds, of which polyphenols are the most abundant category. The authors examined attempts at using these either as pretreatment or incorporated directly into restorative material as a step toward fulfilling a long-recognized need for restorations that can combat or prevent secondary caries formation. Repeatedly restoring failed restorations comes with the loss of more tooth structure along with increasingly complex and costly dental procedures, which is detrimental to not only oral health but also systemic health.

Graphical Abstract

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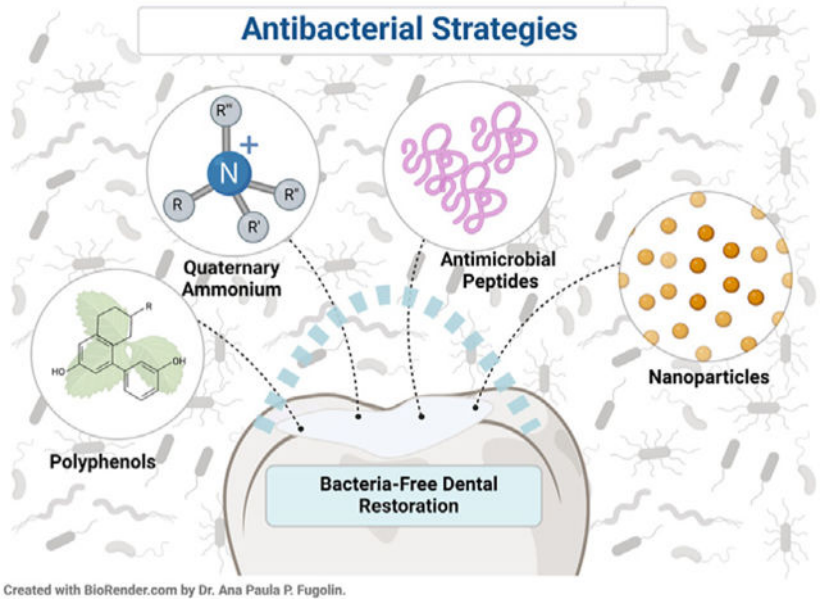
Disclaimer. Carmem S. Pfeifer serves as an editorial board member for JADA FS. Dr Pfeifer was not involved in decisions about the article she wrote, and peer review was handled independently.



Keywords

Caries; antimicrobial compounds; dental materials; restorative dentistry

Introduction

The World Health Organization's Global Burden of Disease 2019 study estimated that approximately 3.5 billion people worldwide are affected by oral diseases, of which caries is the most common condition.[1] The oral cavity is one the most heavily colonized parts of the body, being a dynamic home to more than 700 bacterial species.[2] Microbial symbiosis in the oral cavity, which ensures that heterogeneous communities work together to protect the body from external infections, is affected by changes in diet, local pH, lifestyle, stress, and other systemic conditions.[3] When the ecosystem is no longer in balance, bacterial biofilms in the oral cavity become cariogenic; such infections lead to loss of minerals on the tooth structure, which in turn contributes to loss of function as well as pain and distress.[3] Ordinarily, oral biofilms may colonize any surface in the mouth, including natural teeth and restorative materials, albeit with different efficiencies.[4] Colonization is mediated by a proteinaceous layer known as an acquired pellicle, which immediately coats hard surfaces on contact with saliva.[5] Early colonizers, mostly commensal bacteria, attach first, with species diversification following suit. Depending on hygiene and dietary habits, the ecology of the biofilm might evolve to have a prevalence of caries-forming bacteria.[6] A plethora of different antibacterial compounds are available on the market to either prevent formation or aid in the removal of cariogenic biofilms, mainly as adjuvants to mechanical removal (brushing, high-pressure water sprays), including mouthrinses and short-term varnish coatings.[7] Though effective in compliant patients, these products offer only transient contact with the bacteria, with long-term effectiveness being dependent on dentist visit recall.[7] Alternatively, it has been proposed that antimicrobial agents be added

to restorative materials, with the aim of providing sustained availability of the antimicrobial agent, although not without challenge.[8]

The most commonly used materials to restore lost tooth structure are dental composites, with an average longevity of only 7 through 10 years,[9] which has prompted significant efforts for improvements in resistance to degradation,[10] increase in mechanical properties,[11] and inclusion of some antimicrobial function.[12] In fact, with the improvements in the mechanical properties of materials, attention has shifted to biological interactions of said materials in the oral environment. As expected, a small percentage of the experimental materials proposed have made their way into commercial products, and this has indeed contributed to a steady increase in longevity over the years.[9] One of the main reasons for restoration replacement, which accounts for up to 60% of all restorative work done in dentistry, is secondary caries or recurrent caries caused by the presence of bacteria at the adhesive-dentin interfaces.[13] The composition of adhesives themselves has improved, but the hybrid layer formed with dentin, in particular, continues to be susceptible to degradation. Other than attempts to reinforce the collagen network[14] or the adhesive material itself,[10] there are at least 2 commercial materials that incorporate antibacterial compounds to address microbial colonization at the interface directly.[15] These are based on quaternary ammonium compounds, a broad-spectrum antibiotic whose killing mechanism is still not completely understood in materials.[16] The rise of antibiotic-resistant strains of bacteria has also created an urgent need for strategies that go beyond conventional antibiotic strategies, with an emphasis on preserving the symbiotic biofilm composition.[17,18] The most commonly used types of antimicrobial compounds proposed for use in dentistry are shown in Figure 1.

One consideration when designing additives is how they affect material properties and, in turn, how the bioavailability of the compound is affected by being embedded into the material. In general, antimicrobial compounds can be incorporated by mixing the unfunctionalized molecule directly or sequestered into nanocarriers, implying that the antibacterial effect would be dependent on the compound leaching out of the material, or by tethering the antimicrobial functionality to the material via copolymerization or prefunctionalization of particle surfaces. In the unfunctionalized approach, the advantage is that the antimicrobial compound retains its original structure, and it is expected to be effective, provided that it can diffuse out of the material. The disadvantage is that the leaching intrinsically affects the structure of the material, so it is common for mechanical properties to deteriorate over time. However, several studies combined quaternary ammonium compounds with polyethylenimine nanoparticles and reported an antimicrobial effect against *Streptococcus mutans* that was sustained for at least 1 month without prejudice to mechanical properties.[22–24] In addition, the antibacterial effect might be limited to the original loading of the drug, which supposedly reduces substantivity after the initial burst release of the drug.[25] The use of nanocarriers somewhat ameliorates this.[24,25] Conversely, if the antibacterial compound is tethered to the material, it intrinsically loses mobility and, therefore, requires contact with the microorganism or extrinsic enzyme to work.[25] Specifically for the oral biofilm, the surface of the material is always covered by a proteinaceous layer (the acquired pellicle), which may decrease the substantivity of this antimicrobial agent.[26] In addition, even if the early colonizers are killed, there is a

possibility that the biofilm will still form using the dead but adhered bacteria as an anchor (Figure 2), which is a common criticism for antimicrobial material design.[17]

Although antibacterial additives such as chlorhexidine and quaternary ammonium compounds continue to be pursued by the field for their broad-spectrum antibacterial effects, this review focuses on the mechanism of action, advancements, and translational barriers in dental materials using natural compounds, of which polyphenols are the most prominent examples.[27] Antimicrobial peptides (AMPs) make up another class of natural and synthetic compounds that have garnered attention in the past few years as antimicrobials against bacterial activity.[7,28] Even though the focus here lies on natural compounds, it is acknowledged that other synthetic alternatives are also being investigated. The main goal of this review is to recognize the pitfalls and potential strategies for the incorporation of antibacterial compounds in materials with broad applications in dentistry (ie, direct and indirect restorations, sealants, and oral appliances), to potentially increase their substantivity beyond that shown when they are used in solution.

Polyphenol Compounds

General introduction

In plants, polyphenol compounds (PC) occur in abundance and have multiple functions, including offering protection from ultraviolet rays, serving as intermediaries in attracting pollinators, and providing defenses against microbial invasions.[29] These compounds, of which there are more than 10,000 different types, have shown ubiquitous antibacterial activity against gram-positive and gram-negative bacteria and fungi, including oral-relevant species. All these compounds share a common structural feature: at least 1 aromatic ring with 1 or more hydroxyl group. Depending on the number and arrangement of those phenolic rings, they can be divided into 6 major categories: benzoic acids,[30] cinnamic acids, coumarins, stilbenes, flavonoids, and hydrolyzable tannins, in increasing order or molecular weights.[31] Other simpler classifications include 4 major categories: benzoic acids, stilbenes, flavonoids, and lignans (Figure 3), again in increasing order or molecular weights, and each with slightly differing antibacterial mechanisms and minimal inhibitory concentrations.[32] In nature, they also occur in conjugate form with monosaccharides or polysaccharides to form esters and methyl esters functional glycol-derivatives. For general biomedical applications, flavonoids or hydrolyzable tannins were shown to be the most effective against clinical isolates.[31] Among hydrolyzable tannins, ellagitannins are the most abundant in plant extracts and have been most commonly tested against clinical samples.[31] Specifically for the oral health application, multiple studies of PC have looked at the mechanism of action for their antibacterial properties,[33] with catechin being effective against *S mutans*.[34] Fewer studies have focused on incorporating PC within dental restoratives and examining the challenges in the translation potential of this technology, such as sustaining antimicrobial activity without compromising the mechanical integrity of the material. One study has shown that when incorporated into a hydrophilic, slowly degrading coating, proanthocyanidins from grape seeds were able to reduce bacterial colonization and infiltration at the margin of restorations exposed to simulated, high-caries conditions.[35]

Mechanism of action

PCs exert their antibacterial effect through several mechanisms, including reduction of biofilm formation via inhibition of glucosyltransferase (GTF) or of other virulence factors such as enzymes and toxins.[36] GTFs convert sucrose into a sticky extracellular polymer glucan layer that drives biofilm buildup via cellular attachment to surfaces. PCs can also interact with proteins and bacterial cell walls, alter cytoplasmic functions and membrane permeability, and inhibit energy metabolism.[37] For example, for oral bacteria, catechins, and proanthocyanidins have shown inhibition of the cariogenic early colonizer *S mutans* by modulating the expressions of GTF genes at the transcriptional level.[38–40] In another example, epigallocatechin gallate was shown to not only inhibit GTF enzymatic activities but also its secretion from the cells through dissipating proton motive force across the cell membrane, altering membrane permeability.[41]

The minimum inhibitory concentrations at which these phenolic compounds have shown significant antimicrobial potential (as shown by a decrease in biofilm biomass of at least 2 orders of magnitude[42]) are relatively high for all compounds. For example, 1 study showed a reduction in acid production in a *S mutans* monoculture with 1 mg/mL,[34] whereas other authors reported minimal inhibitory concentration of 0.4 mg/mL.[27] These values are much higher than the typical maximum dose for toxicity at 10 μM (as defined by inhibition of the CYP450 enzyme), used as a benchmark in medicinal chemistry to develop new drugs.[42] This is relevant because to reach this concentration in the leachable components, the overall concentration in the material will likely be much higher, and this might be prohibitive in terms of handling and final mechanical properties of this material.

Toxicity considerations

As plant extracts, PC is broadly considered safe and beneficial for humans. Rats fed about 240 times the estimated daily proanthocyanidin intake by humans showed no observed adverse effects during a 90-day study.[43] Grape seed polyphenolic extracts were also deemed safe after rodents were fed with chow, and extract for 90 days showed no observed adverse effects, even when doses were increased from 200 to 2,150 mg/kg/d.[44] However, contradictory results from other oral toxicity studies have added to PC safety concerns, and in such studies, high doses of PC have shown carcinogenicity, thyroid toxicity, and interactions with pharmaceuticals in animal models.[45] The interaction with pharmaceuticals is of concern as specific PC have also been shown to alter drug bioavailability and pharmacokinetics of compounds using common drug metabolizing enzyme pathways, which can lead to drug accumulation and unintentional overdose.[45,46] There is a need for more detailed safety and efficacy studies regarding PC to determine the optimal concentrations that are safe for human exposure and consumption before they can be used confidently in dental materials.

Material considerations

PCs are relatively hydrophilic, water-dispersible molecules that are not easily incorporated within more hydrophobic formulations, such as restorative composites. Moreover, the relatively high molecular weight, especially for PCs, makes outward diffusion challenging, which may explain why a lot of the materials containing PC are used to produce thin

antimicrobial coatings, such as in implants to prevent *Candida albicans* infections,[47] to serve as antioxidants to prevent onset of periodontal disease and reduce osteoclastic activity,[48,49] or in hydrophilic coatings over dental restorations against anticariogenic biofilms, as already mentioned.[35] Several alternatives to directly dispersing these compounds in materials are available, including the use of drug delivery strategies such as encapsulation of PC in hollow mesoporous silica,[50] chitosan,[51] polycaprolactone,[52] and alginate-based nanoparticles.[53] Albeit commonly used as local delivery agents in mouthrinses or hydrogels, fewer studies have incorporated them directly into restorative materials.[54] As with any additive, these drug delivery systems, as well as the phenolic compounds themselves, have the potential to negatively impact the degree of conversion and mechanical properties, which is a serious concern considering the mechanical demands of occlusal forces,[55] and may at least partially explain why no commercial materials exist that incorporate such strategies. The effect of natural antimicrobial compounds on the mechanical properties of materials can vary depending on several factors: type and concentration of antimicrobial compound, interaction with matrix material, processing conditions, and testing conditions and evaluation times.[56] Although natural antimicrobial compounds are generally added in small amounts to materials, their impact on mechanical properties needs to be evaluated on a case-by-case basis.[57] However, at least 1 study has shown that quercetin and gallic acid had much lower free-radical inhibition potential than hydroxybutyl toluene, a common stabilizer used in commercial dental materials.[58] In addition, in the intrinsically hydrophilic, low-viscosity adhesive formulations, which are not subjected to significant mechanical demands, the feasibility of adding PC increases substantially. In fact, given that secondary caries form by definition at the interface, the addition of antibiofilm agents in the adhesive is a logical step. When used with the intent of reinforcing the collagen substrate, different PCs were shown to enhance bond strength and durability in fifth-generation adhesives.[59,60] Even at relatively high concentrations, these compounds did not seem to impair material properties.[60] Specifically for the antimicrobial effect, the PC epigallocatechin-3-gallate was incorporated into adhesives and was shown to inhibit *S mutans* and *Enterococcus faecalis* growth, enhance the microtensile bond strength (microtensile bond strength) of the formulation and showed better long-term push-out bond strength after thermocycling 5,000 times than the control group.[55,61] Similarly, adhesives doped with quercetin showed inhibition of *S mutans* biofilm growth and reduction of cariogenic gene expression.[62] Again, the limitations of these studies were that the concentrations of PC were relatively high, the materials were tested in monoculture (which does not take into account synergistic ecological interactions with other microorganisms[18]), and the follow-up times were relatively short. Although these studies are an imperative first step and highlight progress in understanding the mechanisms of action of PC, further research is needed to incorporate PC within restorative materials for translation into the clinic.

Other Natural Antimicrobials: Antibacterial Peptides

General introduction

As a host defense against infections, AMPs can be antibacterial, antiviral, or antifungal and are typically made up of 12 through 50 amino acids.[63] AMPs tend to be unstructured in free solution, folding into their final configurations on interaction with biological membranes.[64]

The amino acid backbone, size, and the ability of AMPs to attach to bacterial cell walls all contribute to their function as antibacterial agents. AMPs are classified based on their origin, activity, constituents, and structure (Figure 4). An in-depth literature review on AMPs in preventive dentistry identified 7 natural and 43 synthetic AMPs that have been studied for the prevention and treatment of caries.[65]

Mechanism of action

AMPs are typically small, cationic, and amphipathic, all factors that help them attach to and insert themselves within membranes to penetrate cells, including bacteria.[66] Bacterial cell surfaces contain negatively charged molecules such as *O*-glycosylated mucins and heparin sulfates, allowing cationic AMPs to attach and distort the membranes.[67] The amphipathic character of AMPs is necessary for membrane helix transitions and cell lysis, in which the arrangement of amino acid units provides a gradient in hydrophobicity to drive the formation of a membrane-active α-helix, resulting in cell death.[68] AMPs can also directly interact with other molecules, such as DNA, RNA, and enzymes, to interfere with protein and cell wall synthesis.[69] AMPs can also engage the host's innate resistance to infections by inhibiting lipopolysaccharide-induced proinflammatory cytokine production, altering host gene expression, inducing chemokine production or acting as chemokines, and modulating adaptive immune responses.[70] Even though these peptides present significant antimicrobial activity and inhibition of biofilms, rapid enzymatic degradation in the oral cavity, loss of target specificity in solution, especially with dissolution in saliva, and anionic protein adsorption reduce their effectiveness.[71–73] Research on materials containing AMPs in dentistry is relatively limited compared with other types of antimicrobial agents like quaternary ammonium compounds or metal ions, but this topic has seen significantly growing interest over the past decade for the potentially targeted action against cariogenic bacteria.[8,74]

Toxicity considerations

The mechanism of action of AMPs largely involves the inhibition of cell growth and proliferation by inducing cell lysis via cell membrane permeabilization and the prevention of essential nutrients to cells. As a result, AMPs act with varying levels of potency and are not exclusively selective to bacteria, which have the potential to affect host cells. A modified histidine AMP, temporin-GHa, was developed using database-assisted design and optimized for its antimicrobial activity against planktonic *S mutans* by changing the number of positive surface charges on the peptide.[75] However, the authors found that antimicrobial activity was compromised when structural changes were made to reduce its toxicity to human oral epithelial cells, indicating there is a balance between anticariogenic properties and cytotoxicity that needs to be maintained. Other groups have shown that it is possible to design AMPs with low toxicity, such as the GL13Ks enantiomers, and similar ongoing studies to design high-performance AMPs with low toxicity are promising.[76]

Material considerations

As a protein-rich film on the tooth surface, the acquired enamel pellicle (AEP) regulates the receptors presented for bacterial attachment. In dentistry, AMPs have been proposed to alter the AEP, with effects ranging from reduction of demineralization, reduction of

biomass and disorganization of biofilm structure,[77] inhibition of colonization by virulent species such as *S mutans*, as well as inhibition of matrix metalloproteinases and consequent collagen degradation.[28] In 1 in vitro study, the supplementation of the storage media with statherins led to a reduction in biofilm-derived demineralization.[77] Dual-function AMPs (antimicrobial and remineralizing) have also been investigated, specifically for phospherine-grafted-histatin 5 for better hydroxyapatite binding.[78] The cationic amino acids in this peptide elicit antibacterial activity via membrane disruption and intracellular DNA damage, with the adjunct function of adsorbing to the tooth surface, forming an antifouling coating that can also lead to remineralization of incipient caries lesions.[78] Several strategies for the delivery of these peptides have been investigated, including incorporation in liquid crystal systems.[79] For example, β-defensin-3 peptide fragment was used in conjunction with liquid crystal systems and showed antibiofilm activity with no cytotoxicity shown against epithelial cells.[80]

More specifically, immobilization and conjugation strategies have been attempted in materials applications.[8] For example, coating titanium surfaces with an AMP and a matrix metalloproteinase-9-responsive peptide showed potent antibiofilm activity while enabling osteoblast and fibroblast proliferation, as well as collagen preservation.[28] In dentin, amphipathic and AMPs were added to dental adhesives and showed structure-dependent antibiofilm properties, ascribed partially to the formation of a hydrophobic layer but also to the adsorption on the mineral phase of dentin.[81] Covalently-conjugated peptides, such as GH-12-derived, were made polymerizable and added to adhesives, with substantial inhibitory effects on the formation of *S mutans* biofilms.[75] Other methacrylate polypeptides have been studied via ring-opening polymerization of *N*-carboxyanhydride copolymerized with polydopamine resulting in a coating with polymer brushes featuring cationic AMP and antifouling polysarcosine, with antibacterial and antifouling activity against multispecies biofilms, including *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa,* and *C albicans*, at no cost to fibroblast survival in a mouse model[82]. One additional study reported on star-shaped polymers with similar effectiveness.[83] However, 1 concern with this strategy is that it is unlikely to be generalizable to all peptides because of the potential for structural constraints to the AMP.[84] To mitigate this concern, amphipathic, dual-function peptides (GL13K) have been proposed as adhesive additives, simultaneously acting as antimicrobials and collagen reinforcers.[85] In addition, nanofiber membranes composed of chitosan and pectin derivatives have been developed for pH-controlled delivery of AMPs to be used as antibacterial adhesive gingival grafts and membranes for guided bone regeneration in periodontal disease.[86] Although exciting, the strategies proposed in these in vitro studies still face the same challenges for translation as described for the phenolic compounds.

Conclusions

There continues to be intense research activity in antibacterial dental materials, including synthetic and natural compounds. With the growing knowledge of the oral microbiome and the ecological interactions among species,[18] the focus has shifted from identifying broad-spectrum antibiotics to more targeted approaches.[87] Whatever type of compound is selected, factors relating to the material itself cannot be ignored. For example, the simple

elution of antibacterial molecules and compounds as leachable from composites or adhesives does not significantly affect the original structure and antibacterial efficacy of the bioactive agent.[88] However, this approach is limited by concentration and solubility considerations, as well as the toxicity of the released compounds in the oral cavity.[88] Moreover, in the case of leachable antibacterial agents, once their action is depleted, bacteria are seen to attach and proliferate on the restoration.[17] Finally, 1 drawback of using antibacterial agents whose action is dependent on release from the material is the potential deleterious effect on the material's integrity and mechanical properties.[24] This is 1 of the reasons why most studies incorporating high molecular weight or hydrophilic agents such as phenolic compounds and peptides focus on adhesive and coating-type materials,[55] in which mechanical demands are not as high, rather than bulk restorative composites. Another reason for the higher antibacterial efficacy in adhesives is their direct contact with the tooth structure and the bonded interface.

Even when tethered to the material, the deposition of the AEP on the tooth surface and the subsequent bacterial load encountered often compromises the efficacy of the antibacterial restoration in the oral cavity.[17] Even if contact with the surface may kill the first series of bacteria, adaptive mechanisms allow them to attach to the dead early colonizers instead of directly onto the surface.[17] In addition, it has been shown that stress growth conditions can even trigger in situ remodeling by *S mutans* to create a highly resilient biofilm. Such resilient mechanisms from microbes further emphasize the need to continuously disrupt bacterial-derived mechanisms, such as the inhibition of enzymes responsible for the production of biofilm-enabling glucans[20] or the periodic disruption of biofilms via light-responsive coatings on composites.[89,90]

In the coming years, there will be advancements that improve the understanding of the interaction of antibacterial compounds and the mechanisms by which antibiofilm materials can be designed to affect restoration longevity. We predict that the future of dental restorations will rely on combining antibacterial compounds or patterned surfaces with materials capable of responding to environmental cues in real time.[91] For example, the use of materials that can respond to changes in the local pH to switch between antimicrobial and antifouling,[92] or the use of materials that can read the microbial environment and respond by maintaining microbial symbiosis,[93] are not too distant in the future.

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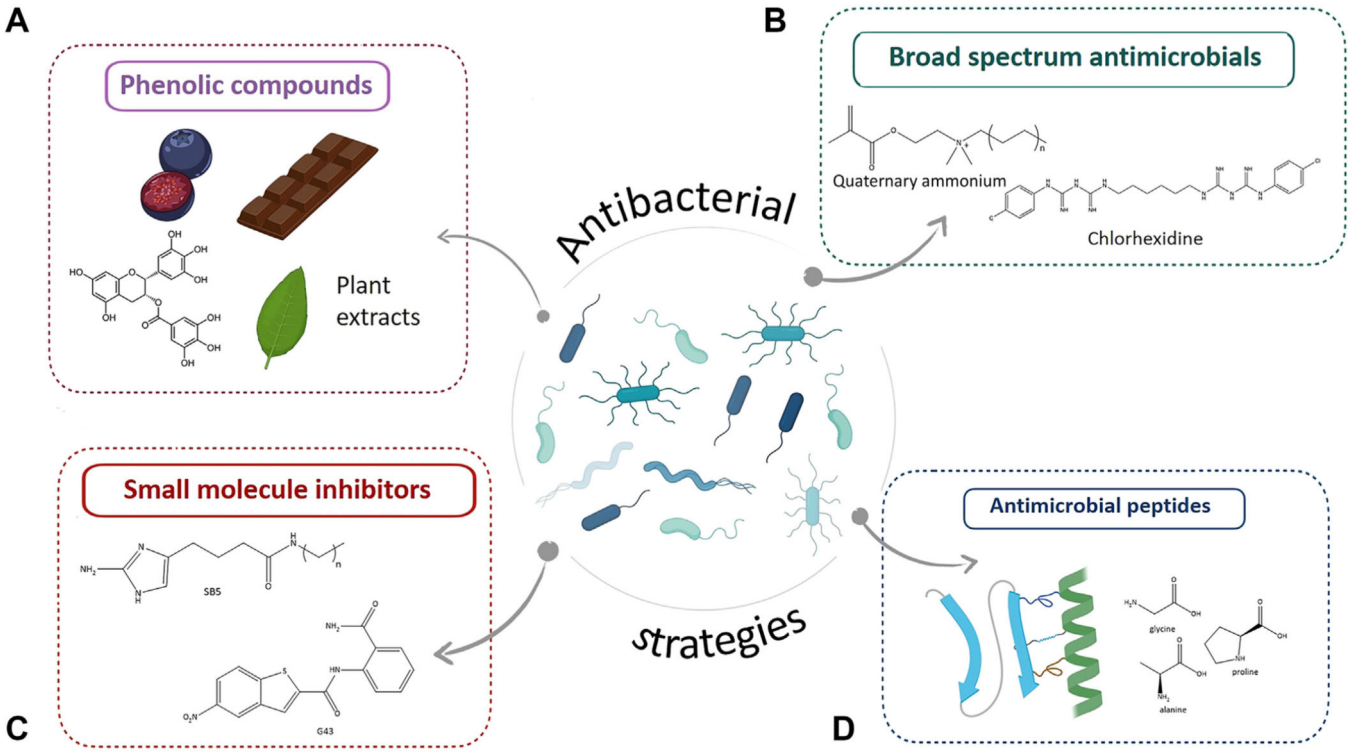

Figure 1.

Main classes of antimicrobial strategies proposed for use in dental materials. **A.** Phenolic compounds (more details in Figure 3). **B.** Quaternary ammonium compounds and broad-spectrum antibiotics; these can be added directly or copolymerized with the material to prevent leaching.[19] **C.** Small molecule inhibitors with targeted activity against virulent species. G43 and SB5 are specific against glucan-producing glucosyltransferases from *Streptococcus mutans*.[20,21] **D.** Antimicrobial peptides (more details in Figure 4). C: Carbon. Cl: Chlorine. H: Hydrogen. N: Nitrogen. O: Oxygen. S: Sulfur.

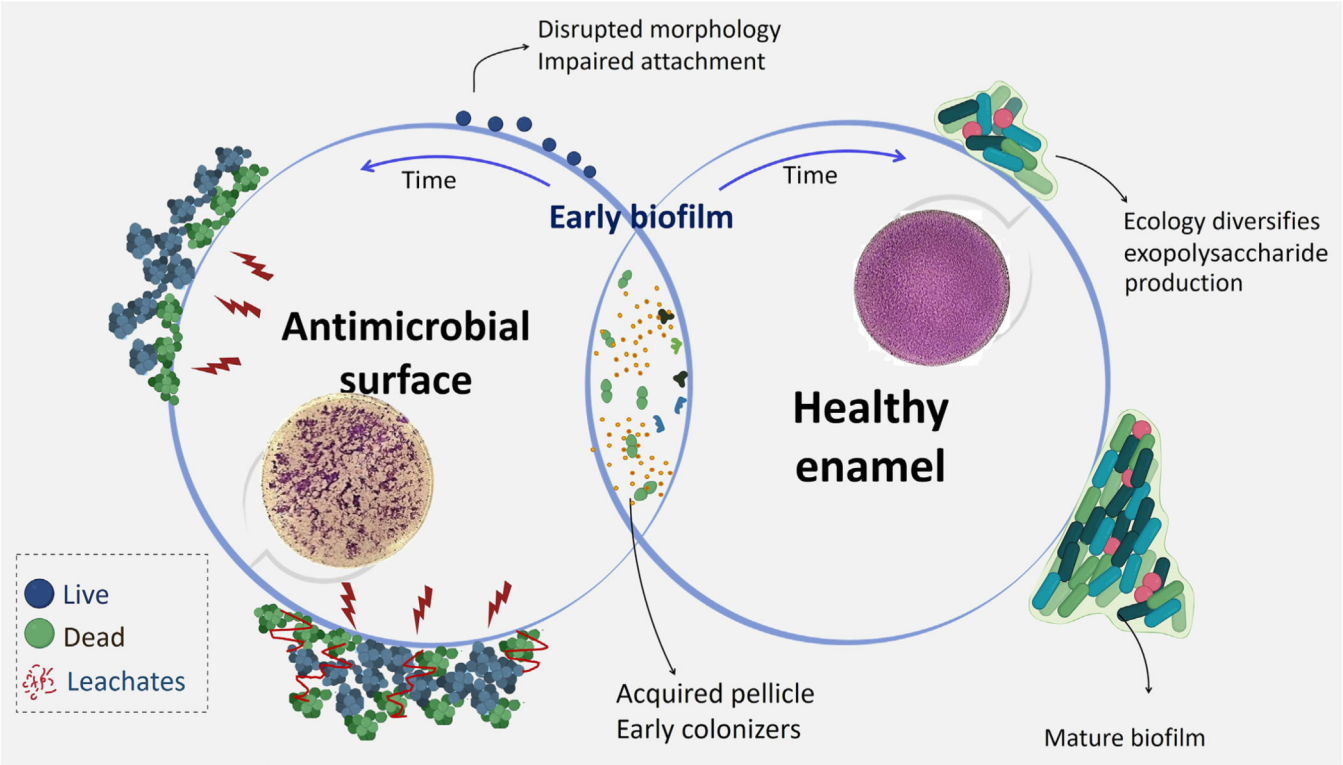

Figure 2.

Sequence of biofilm formation on the surface of enamel and antimicrobial materials. On healthy enamel, after the acquired pellicle is formed and the early colonizers get established, exopolysaccharide production leads to biofilm maturation and ecology modification. The result is a homogeneous coverage of the surface. On the surface of antimicrobial materials, the acquired pellicle may reduce the antibiofilm efficacy, but the early colonization still gets disrupted to different degrees depending on the class of antimicrobial. However, oral bacteria have redundant virulence mechanisms that allow them to attach to dead bacteria on the surface. If the material leaches antimicrobial compounds, there is a chance of distance killing of the bacteria. Either way, the result is either no biofilm or a biofilm with altered morphology and weaker attachment.[17]

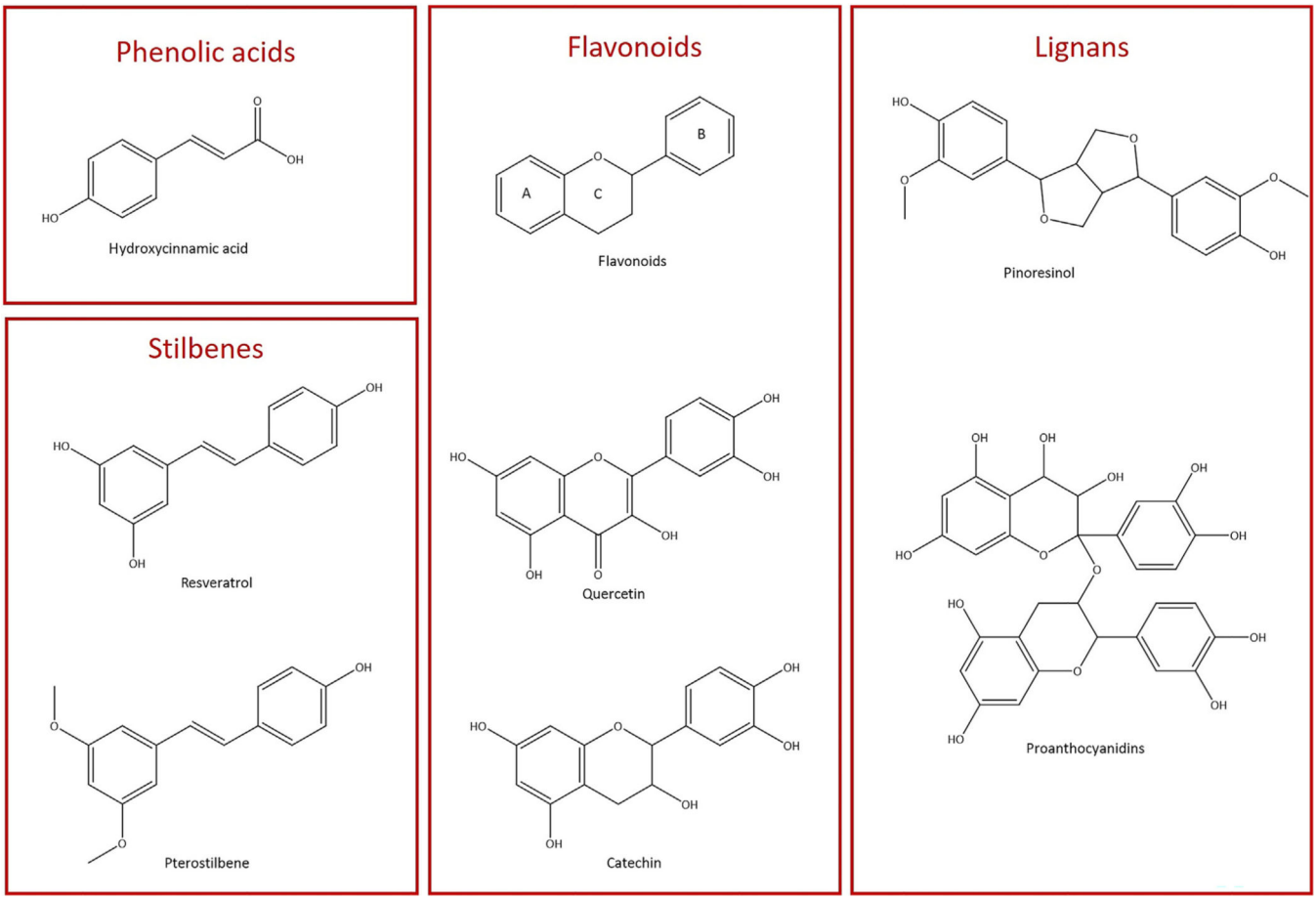

Figure 3.

Phenolic compounds are classified based on the number of phenol rings in the molecule and the structural elements that bind these rings to one another. One classification includes phenolic acids, stilbenes, flavonoids (with core structure containing rings A, B, and C), and lignans. H: Hydrogen. O: Oxygen.

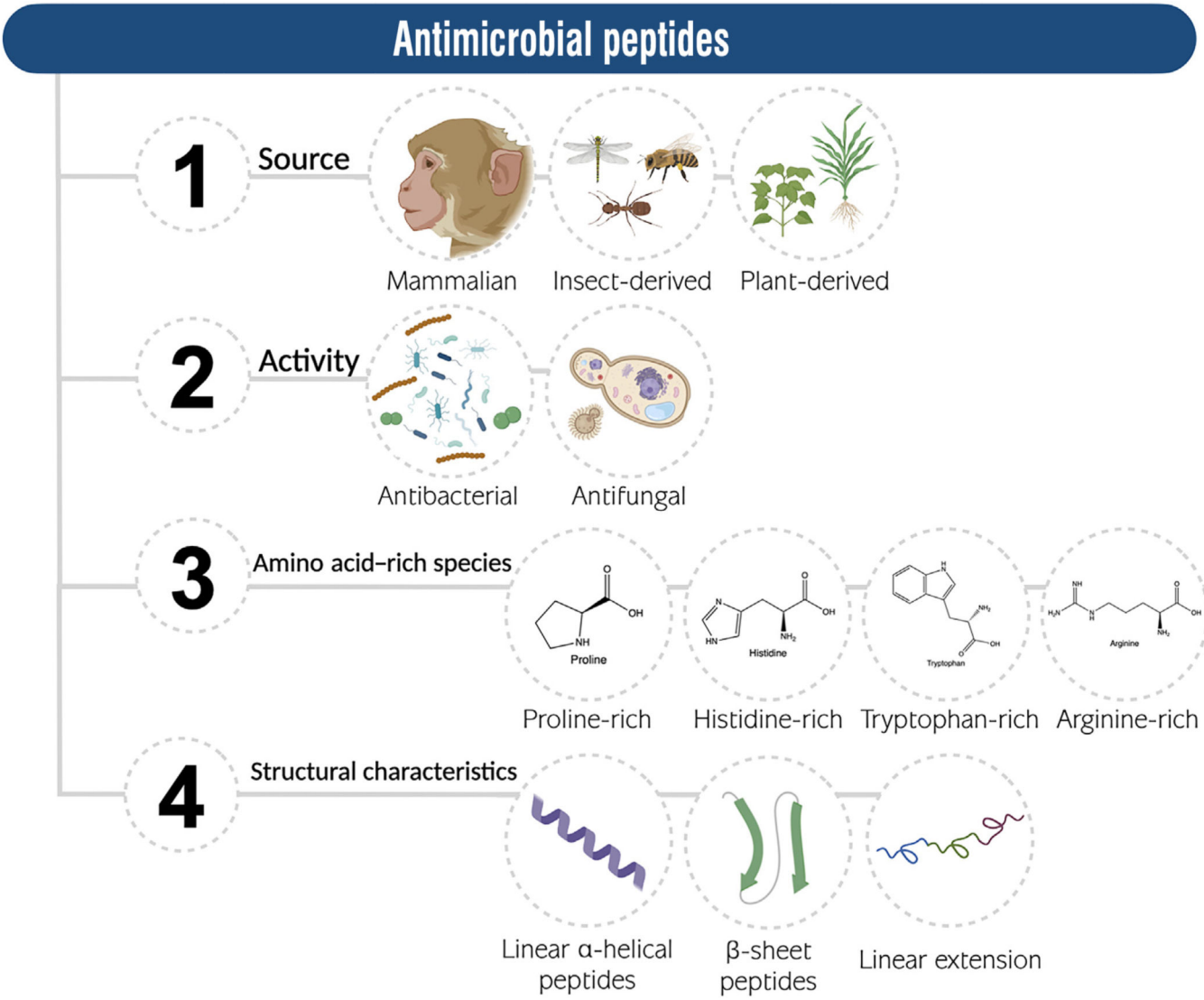

Figure 4.

Antimicrobial peptides are classified based on source (eg, mammalian, insect-derived, or plant-derived), activity (eg, antibacterial and antifungal peptides), amino acid–rich species (eg, proline-rich peptides, histidine-rich peptides, tryptophan, and arginine-rich antimicrobial peptides) and structural characteristics (eg, linear α-helical peptides, β-sheet peptides, and combination of both α-helix and β-sheet peptides and linear extension structure). H: Hydrogen. N: Nitrogen. O: Oxygen.