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REVIEW ARTICLE

Chemical Plaque Control Strategies in the Prevention of Biofilm-associated Oral Diseases

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ABSTRACT

Dental plaque is a biofilm that forms naturally on the surfaces of exposed teeth and other areas of the oral cavity. It is the primary etiological factor for the most frequently occurring oral diseases, such as dental caries and periodontal diseases. Specific, nonspecific, and ecologic plaque hypothesis explains the causation of dental and associated diseases. Adequate control of biofilm accumulation on teeth has been the cornerstone of prevention of periodontitis and dental caries. Mechanical plaque control is the mainstay for prevention of oral diseases, but it requires patient cooperation and motivation; therefore, chemical plaque control agents act as useful adjuvants for achieving the desired results. Hence, it is imperative for the clinicians to update their knowledge in chemical antiplaque agents and other developments for the effective management of plaque biofilm-associated diseases. This article explores the critical analysis of various chemical plaque control strategies and the current trends in the control and prevention of dental plaque biofilm.

Keywords: Bacteria, Chemical plaque control, Dental biofilm, Dental plaque.

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INTRODUCTION

Oral cavity is a single large microbial ecosystem consisting of oral fluid, immunoglobulin, agglutinins, antimicrobial enzymes, glycosyltransferase, proteins, carbohydrates, and millions of microorganisms. An estimated 1 ml of saliva consists about 200 million bacteria, and 1 mm^3 of dental plaque contains about the same number of bacteria. The density of microorganisms is about 1,000 times more in dental plaque than in saliva.[1] Dental plaque is a microbial biofilm defined as "matrix-enclosed bacterial population's adherent to each other and/or to surface or interfaces."[2] Biofilms are surface-associated communities of microorganisms embedded in an extracellular polymeric substance, which upon contact with the host may affect tissue hemostasis and result in disease.[3] Periodontitis and caries are infectious diseases of the oral cavity in which oral biofilms play a causative role. The presence of microorganisms in the oral cavity and their virulence decide the occurrence of a particular disease.[4]

The role of bacterial plaque is the primary etiological factor and can be classified as supragingival plaque and subgingival plaque or as tooth-associated or tissue-associated plaque.

The three main hypotheses that explain the disease occurrence in oral cavity are as follows:

1. *Specific plaque hypothesis*: In contrast to the above, this suggests the importance of individual bacterial species within dental plaque as causative of disease.[5]
2. *Nonspecific plaque hypothesis*: The bacterial dental plaque that accumulates around teeth is a relatively homogenous mass that causes periodontal disease when it accumulates to the point of overwhelming the host's defense mechanism.[6]

3. *Ecologic plaque hypothesis*: Based on the theory that unique local environment influences the composition of oral microflora, any disturbance in this balance may lead to increase in pathogenic microflora over harmless normal oral microflora.[7]

Even though the dental biofilm cannot be eliminated, it can be controlled with comprehensive mechanical and oral hygiene practices. Routine tooth brushing and other mechanical aids are widely recognized as the mainstay for the prevention of oral biofilm-associated dental diseases.[8] Due to the lack of effective use of mechanical plaque control, patients could explore additional benefits from chemotherapeutic antiplaque agents. The antiplaque agents can decrease the rate of new plaque accumulation, decrease or remove existing plaque, suppress the growth of pathogenic microflora, or inhibit the production of virulence factors.[9] The present article is an overview of the various chemical plaque control agents used for the prevention of biofilm-associated oral diseases.

Several classification systems exist in the literature and are compiled in Table 1. With the current understanding, several modifications have been added and one of the reliable methods is to evaluate the agents based on their mechanism of action, which is summarized in Table 2.

Table 1: Classification of chemical plaque control agents (different classification systems for the chemical plaque control agents)

1. Generations[78,79]
   - a First-generation agents – effective *in vitro* but lack substantivity and are not as effective *in vivo*
   - b Second-generation agents – substantive and effective *in vivo*
   - c Third-generation agents – block microbial colonization
2. Based on the chemical composition of the agents[78]
   - Bisbiguanides – chlorhexidine, alexidine
   - Bispyridines – octenidine hydrochloride
   - Halogens – iodine, iodophores, fluorides
   - Heavy metal salts – silver, mercury, zinc, copper, tin
   - Herbal extracts – sanguinaria extract
   - Oxygenating agents – peroxides, perborate
   - Phenolic compounds – phenol, thymol, triclosan, 2-phenylphenol, hexylresorcinol, Listerine
   - Pyrimidines – hexetidine
   - Quaternary ammonium compounds – cetylpyridinium chloride, benzethonium chloride, domiphen bromide
3. Classification by Mandel[79]
   - a Antiplaque enzymes
     Amyloglucosidase, glucose oxidase, dextranase, fungal enzymes, mucinase, mutanase, pancreatin, proteinase-amylase, zendium
   - b Plaque – modifying agents
     Ascoxal (astra zeneca), urea peroxide
4. Based on chemical composition
   - a Cationic
   - b Anionic
   - c Nonionic
   - d Other combinations

MECHANISM OF ACTION OF CHEMICAL PLAQUE CONTROL AGENTS

Dental plaque gets accumulated at clean areas of the teeth, making these sites susceptible to disease. Patient motivation is of utmost importance in mechanical plaque control. Chemical plaque control agents act as adjuncts to conventional mechanical plaque control and interfere with biofilm composition and metabolism. Antiplaque agents function by removing or disrupting biofilms, or by preventing the formation of new biofilm. Antimicrobial agents may be bacteriostatic or bactericidal.[10,11] These agents may be narrow spectrum or broad spectrum based on their target group of microorganisms. The action of antimicrobial agents is proportional to their concentration and the contact time. Over time, the oral biofilm microorganisms develop resistance to the antimicrobial agents in use. Moreover, a major requirement of the chemical antiplaque agents is to deliver sufficient

Table 2: The mechanism of action of antiplaque or antimicrobial agents in mouthwashes and dentifrices[10,39,73]

Class of inhibitor	*Example*	*Mechanism of action*
Bisbiguanide	Chlorhexidine	Inhibits sugar transport, acid production, amino acid uptake, polysaccharide synthesis, bacterial membrane functions, protease activity
Enzymes	Mutanase, dextranase, amyloglucosidase-glucose oxidase	Inhibit plaque biofilm matrix formation by degradation of bacterial polysaccharides, bacterial glycolysis by boosting salivary peroxidase system
Essential oil extracts	Menthol, thymol, eucalyptol, methyl salicylate	Inhibit acid production, bacterial growth reduces lipopolysaccharide
Metal salts	Zinc, copper, stannous ions	Inhibit sugar transport, acid production, protease activity
Quaternary ammonium compounds	Cetylpyridinium chloride	Damage cell membranes, inhibit bacterial enzymes
Phenols	Triclosan	Inhibit sugar transport, acid production, protease activity
Natural molecules	Plant extracts (e.g., apigenin, tt-farnesol)	Inhibit acid production, polysaccharide synthesis
Surfactants	Sodium lauryl sulfate, delmopinol	Damage cell membranes, inhibit bacterial enzymes

concentration of the active ingredients in a short period or the formulation should have high retentiveness so that they can be released over time for maximum benefit. There are only short periods where the agent is present in a high concentration followed by longer periods where the agent is present at sublethal levels. These limitations significantly affect the effectiveness of these agents.[12] Many agents that have been effective against the oral pathogens *in vitro* lack substantivity and are not as effective *in vivo*.[13] Also, organisms reported to have an apparent similar sensitivity to an antimicrobial agent can vary markedly in their susceptibility when exposed to the agent for only relatively short periods, as occurs during routine oral use. For instance, Gram-negative obligate anaerobes are more susceptible to agents like triclosan than the Gram-positive bacteria.[14] Many chemical plaque control agents also inhibit other metabolic functions of oral pathogens like sugar transport mechanisms, acid production, extracellular polysaccharide synthesis, and protease activity, thereby rendering aid in plaque control.[10,11] It takes about 2 days for the plaque biofilms to mature and reach the critical pH.[15] Thus, the appropriate use of plaque control agents can help to maintain oral health and prevent dental diseases.

Chlorhexidine (CHX)

Chlorhexidine is the most well-known antiplaque agent. Its molecules inhibit bacterial adhesion, bacterial growth, and biofilm formation, and are bactericidal at high concentration as they damage the bacterial cell membrane.[16-20] Chlorhexidine is available in the form of rinses, gels, and varnishes. Concentrations of 0.12 or 0.2% CHX mouthwash significantly reduce plaque and gingivitis.[21-23] The antibacterial properties of these products have been demonstrated *in vitro* as well as *in vivo*.[24,25] The studies comparing CHX with other active agents such essential oils, sanguinarine, and delmopinol provide enough evidence on the superiority of CHX.[24-30]

Listerine

Listerine®, an essential oil mouth rinse, is a combination of thymol and eucalyptol mixed with menthol and methyl salicylate in a hydroalcoholic vehicle. The antiplaque and antigingivitis effects as well as safety have been well documented.[31,32] The recommended use is twice daily following tooth brushing. In these studies, plaque and gingivitis reductions *vs* placebo have been demonstrated.[26,27,33-35] When compared with CHX mouth rinses, all studies seem to agree that the plaque/gingivitis-reducing efficacy of Listerine® is inferior.[26,27,33]

Cetylpyridinium Chloride (CPC)

Cetylpyridinium chloride is a cationic quaternary ammonium compound. It has been shown to be effective in reducing dental plaque and reducing gingivitis.[36,37] It may cause brown stains between the teeth and on the surface of the teeth. It has a relatively high substantivity owing to its cationic properties; however, it may interact with negatively charged particles found in other mouth rinses, dentifrices, serum, lipids, phospholipids, and proteins, leading to lowering CPC's biological activity, thereby affecting its efficacy.[38,39]

Triclosan

Triclosan is a bisphenol as well as a nonionic germicide with both antibacterial and antiinflammatory properties.[40] Its proposed mechanism of action is cytoplasmic membrane disruption of the bacterial cell and the inhibition of the oxygenase/lipoxygenase pathway. Studies[39-42] report 23 to 28% reduction in plaque when compared to placebo.[41-44] The various triclosan formulations have displayed antigingivitis and antiplaque when compared with placebo; however, there are contrasting views in the literature regarding the superiority of triclosan + copolymer over triclosan + zinc citrate.[45]

Delmopinol

Delmopinol is amino-alcohol with documented antibacterial action. The suggested mechanism of action is its interference; delmopinol hydrochloride is considered a surface active agent with low antimicrobial potency.[46] Claydon et al[47] reported some adverse signs and symptoms like numbness of the tongue, tooth and tongue staining, disrupted taste sensation and mucosal soreness, and erosion in some cases. In various clinical trials, delmopinol has been shown to have moderate antiplaque and antigingivitis efficacy. In these studies, delmopinol fared better than placebo but could score over CHX.[47-49]

Povidone Iodine

Povidone iodine has an affinity for the cell membrane, thereby delivering free iodine directly to the bacterial cell surface. It has a broad spectrum of activity against bacteria, fungi, protozoa, and viruses. The mouthwash has been shown to be effective in reducing plaque and gingivitis and may be a useful adjunct to routine oral hygiene.[50] Absorption of significant levels of iodine through the oral mucosa may make this compound unsatisfactory for prolonged use in the oral cavity.[51]

Dextranase

Dextran is a complex, high-molecular-weight polysaccharide synthesized by *Streptococcus mutans*.[52] Dextran

promotes microbial community development and proliferation, hence improving dental plaque's structural integrity.[53] Degradation of dextran by dextranase has been found to be one of the approaches to remove dental plaque and prevent further caries.[54,55] The dextranases added in commercially available dextranase-containing mouthwash are largely from fungi.[55,56] However, fungal dextranases are reported to show higher optimal temperature in the range 50 to 60°C; hence, they might not be effective in oral use.[57,58] Recently, bacterial dextranases are suggested to be more useful. These bacterial dextranase, especially those from marine origin that are high salt tolerant and stable in a wide range of temperature with the optimal temperature of 35.5°C, could be more suitable for oral use.[55,58]

Propolis

Propolis is a natural resinous material produced by honey bees and used to seal openings in their hives. It is a sticky mass, grayish brown in color with slight aromatic odor, and contains 50% resin and vegetative balsam, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% other substances. The chemical composition of this atoxic natural substance is complex. More than 300 components have been found in propolis, mainly composed of phenolic compounds (e.g., flavonoids, aromatic compounds), terpenes, and essential oil. Flavonoids and cinnamic acid derivatives have been considered as the main primary biologically active components. Even though it has antimicrobial properties, the use of it as a mouthwash is questionable.[59]

Lippia Sidoides

Lippia sidoides extract mouthwash is obtained from the shrub commonly found in the northeast of Brazil. Its camphoric foliage is indicated as a topical antiseptic agent for skin and mucosa surface and also for throat infections. The essential oil obtained from this phytotherapic compound is constituted mainly by thymol and carvacrol and other substances, such as felandreno, cariofileno, p-cimeno, and mirceno.[60] Studies indicated that these major components had shown potent antimicrobial activity against fungi and bacteria and reduced the severity of gingivitis and bacterial plaque.[61,62]

Aloe Vera Extract

Medicinal plants are being tried as antiplaque agents as some of them contain natural phytochemicals that have antimicrobial potential.[63] Aloe vera gel consists of 98 to 99% water and the remaining 1 to 2% of active compounds. The main active ingredients in aloe vera gel are aloin, aloeemodin, aloemannan, acemannan, aloeride, naftoquinones, methylchromones, flavonoids, saponin, sterols, amino acids, and vitamins. A randomized controlled study using 100% aloe vera extract showed significant reduction in plaque formation with no reported side effects.[64] Similar observations were found in other studies.[65] The antimicrobial effect of aloe vera has been demonstrated earlier in an *in vitro* study.[66] It is reported that aloe vera extract inhibits the growth of diverse oral microorganisms such as *S. mutans, Streptococcus sanguis, Actinomyces viscosus*, and *Candida albicans.*

CLINICAL APPLICATION

The ecologic plaque hypothesis states that any disease is caused due to imbalances in the proportions of this resident microflora driven by deleterious changes in local environmental conditions. The presence of biofilms in the mouth is like a double-edged sword. It is essential to get rid of the harmful microorganisms and maintain the beneficial microorganisms.[7] Improper maintenance of oral hygiene along with a substantial environmental change in the oral cavity leads to increase in harmful bacteria, which compete with the beneficial bacteria, thereby leading to disease. For example, caries develops due to increase in sugar intake along with the increased acid production by the cariogenic microorganisms leading to the balance tipping in favor of the mutans streptococci and other caries-causing microbes at the expense of health-associated bacteria.[67,68] In gingivitis, plaque accumulation leads to increased flow of gingival crevicular fluid, which delivers the essential nutrients for many periodontopathic microorganisms. The metabolism of the subgingival microflora makes the site more anaerobic and the local pH increases due to proteolysis with increased colonization of disease-causing bacteria.[11,67] Hence, for prevention of oral diseases, a three-pronged strategy should be devised by the clinician: (a) Improvement of oral hygiene, (b) targeting the pathogenic microbes directly, and (c) maintenance of the oral environment by avoidance of risk behaviors.[11,67]

Antimicrobial agents in oral care products can play an important role in all of these stages, e.g., by killing some of the key bacteria and by reducing (at sublethal concentrations) the deleterious consequences to the host associated with acid production[69-71] and proteolysis[69,72] that create the selection pressures for the overgrowth of putative pathogens in oral biofilms.[73] Hence, the prescription of chemical plaque control agents is not as same as medicine. Antibiotics are given for a fixed period and are directed against some specific microbes, but in dental care, antimicrobial agents are delivered in low doses, unsupervised, and over-the-counter to work effectively over long periods of time to suppress pathogenic microflora and to maintain the ecologic

homeostasis of the oral cavity.[11] Hence, the prescription for chemical plaque control agents requires the clinician to pay close attention to each individual patient's oral environment and his or her risk factors.

FUTURE CHALLENGES IN CHEMICAL PLAQUE CONTROL

The emergence of antimicrobial resistance is currently posing a major global challenge, with an increasing number of microorganisms becoming resistant to commonly used antibiotics.[74] Hence, new approaches for the control of plaque-associated oral diseases are the need of the hour. Probiotics aims to achieve biological plaque control by eliminating pathogenic bacteria. Probiotics not only possess antimicrobial properties but can also modulate the immune system toward antiinflammatory actions.[75,76] Vaccination against oral biofilm-associated diseases is also currently an upcoming area of research. Further studies to evaluate the possible use of these agents is of utmost importance.[77]

Natural products offer structurally diverse substances with a wide range of biological activities, which could be useful for the development of alternative or adjunctive antiplaque therapy. Natural substances potentially active against the cariogenic microflora have been identified. However, understanding the chemistry and derivation of the active components from these natural products is a daunting and challenging task. Thus, the true value of natural products in plaque control and their exact mechanism of action remain largely unknown.[77] Hence, chemical plaque control, though just an adjunct to mechanical plaque control, offers promises, challenges, and unexplored arenas.

CONCLUSION

Mechanical plaque control is the mainstay for prevention of oral diseases, but it requires immense patient cooperation and motivation; therefore, chemical plaque control agents act as useful adjuvants for achieving the desired results. Antimicrobial and antiplaque agents in dentifrices and oral rinses act in several ways to reduce or remove dental biofilms and inhibit bacterial growth. Hence, it is imperative for the clinician to know the effect of these agents so that they can provide the patients with tailor-made prescription and prevent plaque-induced dental diseases.

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