Frontiers in Dentistry

Streptococcus Mutans-Specific Antimicrobial Peptide C16G2-Mediated Caries Prevention: A Review

Janaki Ramya Namburu[1], Arvind Babu Rajendra Santosh[2*], Chandra Shekar Poosarla[3], Suvarna Manthapuri[4], Mythri Pinnaka[1], Venkat Ramana Reddy Baddam[3]

1. SIBAR Institute of Dental Sciences Guntur, Andhra Pradesh, India
2. School of Dentistry, Faculty of Medical Sciences, The University of the West Indies, Jamaica, West Indies
3. Department of Oral and Maxillofacial Pathology, SIBAR Institute of Dental Sciences, Guntur, Andhra Pradesh, India
4. Department of Dentistry, Government Medical College, Nalgonda, Telangana, India

Article Info

Article type:
Review Article

Article History:
Received: 8 Dec 2021
Accepted: 14 May 2022
Published: 28 Jun 2022

Corresponding author:

School of Dentistry, Faculty of Medical Sciences, The University of the West Indies, Jamaica, West Indies

Email: arvindbabu2001@gmail.com

A B S T R A C T

Oral biofilms are a group of healthy synergistic organisms, that on interplay with the immune system undergo transition and colonize the pathogenic bacteria, leading to various diseases like dental caries, gingivitis, periodontitis and a few systemic conditions. Dental caries being the most common disease of the oral cavity, comprise a heterogeneous group of bacteria that can cause imbalance in the biofilm. Caries prevention has been in research for decades, where antibiotics, chemical biocides and fluoride-antimicrobial approaches have not been adequate for this multifactorial disease. In recent years, the major focus of caries prevention has been shifted to plaque-biofilm modification as an ecological approach that would prevent bacterial colonization. Saliva produces various natural antimicrobial peptides that can regulate biofilm modification. Synthetic production of antimicrobial peptides concentrates on selective elimination and a targeted approach towards cariogenic pathogens, precisely *Streptococcus mutans (S. mutans)*. A search in Medline/PubMed, EBSCO and ScienceDirect databases on C16G2, antimicrobial peptides (AMPs) and *S. mutans*, using MeSH (Medical Subject Heading) terms was performed and papers published until 2020 were included for further evaluation. A total of eight articles written in English with available full texts were selected based on the search strategy. They included four publications on AMPs against *S. mutans* and another four articles on AMPs in caries prevention. This review focuses on C16G2 antimicrobial peptide and its potential to modify biofilm and inhibit the targeted bacteria causing dental caries.

Key words: Antimicrobial Peptides; *Streptococcus Mutans;* Mouthwashes; Dental Caries; Anti-Bacterial Agents

➢ **Cite this article as:** Namburu JR, Babu Rajendra Santosh A, Shekar Poosarla Ch, Manthapuri S, Pinnaka M, Ramana Reddy Baddam V. *Streptococcus Mutans*-Specific Antimicrobial Peptide C16G2-Mediated Caries Prevention: A Review. *Front Dent.* 2022;19:17.

INTRODUCTION

Antibiotics, the epitome of "wonder drugs", have a major role in the control and prevention of microbial infections, predominantly bacterial pathogens [1]. However, drug resistance, overuse and misuse are growing concerns in the management of microbial diseases pushing the world on to the cusp of a post-antibiotic era, where formerly efficient treatment procedures have become inapplicable.

Antibiotics, despite having a significant role in modern medicine, have mostly failed to control

and/or prevent many infections due to drug resistance, accentuating the need for developing newer antimicrobial medication management [2]. Recently, antimicrobial peptides (AMPs) have been recognized as potential antibiotic substitutes because of their broad-spectrum killing activity, including the drug-resistant strains [3]. AMPs are genetically common molecules of innate immunity observed mainly within neutrophil granules and in epithelial cell secretions of skin and mucosal surfaces of mammals [4,5]. AMPs are small, amphipathic molecules that possess both hydrophilic and hydrophobic areas with variable amino-acid structure/length and an overall cationic charge [6].

Based on their secondary structures, they can be categorized into four different types: beta-sheet, alpha-helix, extended and loop [7]. These are versatile, highly specific antimicrobial compounds that have a broad range of antibacterial, antiviral and antifungal activity [8]. A healthy cluster of synergistic microbial organisms amalgamate to form an oral biofilm. Microbes in the oral biofilm interact with the host immune system and can colonize, which may lead to dental caries, gingivitis, periodontitis or spread to distant organs causing systemic conditions [9,10]. Dental caries, the most prevalent disease of dental structures, are considered to be a multifactorial disease with predominant pathogenic events lead by *Streptococcus mutans* (*S. mutans*) [11]. Cariogenic bacterial pathogens rapidly metabolize carbohydrates and subsequently produce organic acids and reduce plaque pH, which leads to demineralization of inorganic components of dental hard tissues and irreversible loss of tooth structure [12,13]. This substantiates the concept of endogenous, biofilm mediated disease where acidogenic/ aciduric elements inhabiting the oral flora gain an ecological advantage over other species and interrupt the homeostatic balance in the plaque biofilm, ultimately leading to commencement of the disease process [12].

DISCUSSION

Antimicrobial Peptides

Research studies on prevention of caries are ongoing for decades with multiple modalities such as various types of sodium fluoride and dental sealants. The motive of current research studies shifted to modification of oral ecology-plaque biofilm with a specific aim to prevent bacterial colonization. AMPs are an adverse group of molecules with exceptional antimicrobial features and a great capacity for controlling bacterial infections and altering biofilm environment [8]. AMPs demonstrate a net positive charge and a high ratio of hydrophobic amino acids allowing them to selectively bind to negatively charged bacterial membranes. The ability of AMPs to kill bacteria usually depends on their capability to interact with the bacterial membrane or cell wall [11]. They display a direct and rapid antimicrobial property that can be categorized into two basic groups: The disruptive mechanisms, which cause disruption of physiological integrity of microbial membrane and the membrane undisruptive mechanisms, which act on targets within the cell [5,13].

Independent of the proposed group, the initial interaction between the cationic AMPs and the negatively charged bacterial surface is electrostatic [14].

In most AMPs, the interaction between cationic residues of peptides and the negatively charged moieties of a bacterial membrane can form pores that obliterate the membrane integrity, facilitating targeted microbe lysis [11].

There are four classical models of disruptive mechanisms: (1) Toroidal; (2) Carpet; (3) Aggregate; and (4) Barrel. Lately, novel disruptive models or models indirectly related to membrane disruption have been defined. These models are as follows: (1) Disordered toroidal; (2) Membrane thinning/thickening; (3) Charged lipid clustering; (4) Non-bilayer intermediate; (5) Oxidized lipid targeting; (6) Anion carrier; (7) Non-lytic membrane depolarization; and (8) the Electroporation model [14].

In the case of undisruptive mechanism, they traverse the lipid bilayer without any destruction but destroy bacteria through prevention of intracellular functions [11]. The undisruptive mechanisms rely on AMP passage through the membrane as a result of a combination of characteristics including AMP sequence and composition of the membrane. A number of

cellular metabolism reactions are prevented, which ultimately leads to cell death. Two mechanisms of AMP cell entry have been described including a spontaneous membrane translocation or crossing as a result of a secondary AMP structure that drives permeabilization of the membrane [13,14]. After crossing the membrane, multiple intracellular sites like gene promoters and coding sequences, mRNA-binding sites, enzyme regulatory sites, and protein pre-folding sites can be targeted by AMPs. Inhibition occurs through impeding DNA transcription and/or RNA translation, or causing breakdown of metabolic pathways and cell death by poor protein folding [15].

The main distinctions between microbial and mammalian cells such as membrane composition, polarization, transmembrane potential and structural features protect mammalian cells against AMPs [6].

In contrast to the bacterial membrane, the cytoplasmic membrane of the mammalian cell is loaded with zwitterionic phospholipids, producing a membrane with neutral net charge [16,17]. Thus, hydrophobic interactions are the major promoter of mammalian cell membrane and AMP interplay. In comparison, the electrostatic interactions between AMPs and bacterial membranes are stronger [5]. Furthermore, mammalian cell membranes, differ from microbial membranes in that they possess a large amount of cholesterol [16-18] and are suggested to decrease AMP activity by stabilizing the phospholipid bilayer [19]. Mammalian cells have a lower negative transmembrane potential between (-90 to -110 mV) in contrast to bacterial cells (-130 and -150 mV) [16,17,20]. Strong negative membrane potential in bacteria may likewise assist in selectivity of AMPs between bacterial and mammalian cells [16]. Apart from limited number of pathogens, most indigenous oral microorganisms are beneficial. Broad spectrum killing activity exhibited by the currently available AMPs disrupts the ecological balance of the indigenous microbiota leading to unidentified clinical implications [21,22]. Therefore, establishment of new narrow-spectrum treatments that can preserve the protective advantages of the normal microflora during therapy is essential [23]. Promising studies on AMPs against *S. mutans* are listed in Table 1.

Table 1: Antimicrobial peptide (AMP) studies against *Streptococcus mutans (S. mutans)*

Study outline and conclusion	Author(s)/year
Potent 1 antibiotic component Mutacin B-Ny266 is efficient against *S. mutans* identified in the oral cavity. Antibiotics targeted against microbes in dental plaque is a promising strategy for controlling pathogenic oral microbial flora.	Dufour et al. 2020 [24]
Inhibitory action against adhesion, virulence associated genes and enzymes of *S. mutans* was observed in pomegranate-derived AMPs; Pug-1, Pug-2, Pug-3 and Pug-4. Antimicrobial pathway of Pomegranate against carious pathogens occurs due to anti-adherence properties. Pomegranate AMPs are non-toxic to human keratinocytes.	Kokilakanit et al. 2020 [25]
Biochemical contents produced from *Hylarana guentheri* such as Temporin-GHc and temporin-GHd renders antimicrobial action against bacteria and fungi. The antimicrobial action is achieved by downregulating glucosyltransferases enzyme in *S. mutans.* Selective and targeted antimicrobial action against *S. mutans* occurs in the presence of human erythrocyte.	Zhong et al. 2019 [26]
STAMP molecules are Specifically Targeted AMP synthetic molecules prepared to render antimicrobial property with a specific target against a pathogen. C16G2 is a STAMP molecule prepared by the combination of the killing domain from the antimicrobial agent Novispirin G10 with a targeting domain from *S. mutans* pheromone. C16G2 is prepared to selectively act against *S. mutans* to render anti-carious action in oral cavity without disturbing non-pathogenic resident bacteria in oral flora.	Baker et al. 2019 [27]

Recently, an initiation of a targeted approach to manage oral microbial pathogenesis using a newer version of AMPs called specifically targeted antimicrobial peptides (STAMPs) was developed [22,28].

A typical STAMP molecule requires two functionally independent peptide domains, a killing moiety comprised of a non-specific AMP that can rapidly destroy bacteria, and a targeting moiety comprised of a species specific, high affinity binding peptide [28,29]. The two moieties are subsequently integrated through a small linker, producing a fusion AMP without detrimental changes in the independent functions of two domains [13]. The AMP dimers (fusion peptides) compounded as single linear molecules, frequently possess higher killing dynamics in comparison to their parental peptides [4]. Randomized clinical trial studies against cariogenic microbes and caries management are shown in Table 2.

Table 2: Randomized clinical trials on antimicrobial peptides and caries management/prevention

No.	Study hypothesis	Study findings, inference, & clinical relevance	Author(s)/year
1	Gaseous ozone effect on deep carious pathogens identified from incompletely excavated carious lesions was evaluated. In addition, Vascular endothelial growth factor (VEGF) from pulpal tissue, neuronal nitric oxide synthase and superoxide dismutase (SOD) was also investigated in this study	Gaseous ozone reduced microbial count of bacteria that includes lactobacillus. The levels of VEGF were higher in pulp tissue and SOD activity was lower in the study group than controls. The findings of the study confirmed that gaseous ozone has a biocompatible effect on pulpal tissue by rendering antimicrobial action	Krunić et al. 2019 [30]
2	Salivary human neutrophil peptide 1-3 (HNP 1-3) levels were compared in the study group with probiotic supplements and in the control group. The results of the study showed higher levels of salivary HNP 1-3 among caries resistant children than caries susceptible	*Lactobacillus paracasei* probiotics enhance HNP 1-3 temporarily with significant statistical correlation elevated *Lactobacillus* spp. counts. The study also showed reduced *S. mutans* but did not show statistical correlation	Wattanarat et al. 2015 [31]
3	Importance of salivary proteins adsorbed on enamel surface and its demineralization effect was evaluated	Surfaces of enamel coated with whole saliva, parotid saliva, dialyzed whole and dialyzed protein saliva showed significantly higher levels of protection than uncoated enamel. The parotid and whole saliva rendered better protective action than dialyzed saliva. The findings of the study denoted that ionic contents of saliva provide protection against acid related enamel demineralization	Martins et al. 2013 [32]
4	*S. mutans* adhesion to cellular surface inhibition was studied by plasmon resonance method using synthetic peptide (p1025) to residues of 1025-1044 adhesions	In-vivo study model on streptococcal adhesion investigation revealed prevention of recolonization of *S. mutans* but not *Actinomyces* spp. The results of the study confirmed that peptide molecules inhibited microbial adhesins and prevented colonization	Kelly et al. 1999 [33]

Specifically Targeted Antimicrobial Peptides Targeting *S. mutans*

As discussed earlier, *S. mutans* is considered the primary etiological agent of dental caries. It is well known that, absence of *S. mutans* has been associated with areas containing healthy dentition, while progressively increasing levels of *S. mutans* are found in regions of caries development [34]. A study had mentioned that patients with dental plaque consisting of small amounts of *S. mutans* are resistant to exogenous colonization from cariogenic organism which have shown reduction on dental caries [35]. Thus STAMPs aimed at *S. mutans* can serve as an alternative therapy in preventing dental caries. Development of resistance to AMPs may occur due to contributions from both bacterial cell changes and host tissue alterations which eventually lead to inability of the host to act against bacterial infections. The resistance of the oral bacteria in prolonged AMPs may occur due to changes occurring in the organism such as surface remodelling, biofilm pathogen alterations and host tissue changes like efflux pump mechanism of organisms and proteolytic degradation. Understanding these mechanisms will assist researchers in developing new therapeutic strategies while formulating AMP mouth rinses [1]. Thus, the number of STAMPs targeting *S. mutans* were researched for selecting inhibition of pioneer caries bacteria [36]. C16G2 is a STAMP designed with antimicrobial specificity for *S. mutans* [37]. C16G2 utilizes *S. mutans* produced pheromone (competence stimulating peptide) which acts as the STAMP targeting domain against the cell surface of *S. mutans* [28]. The term C16G2, denotes the 16 amino-acid (C16) sequence of TFFRLFNRSFTQALGK molecule [38]. Whereas, the killing domain is designated as G2, which is derived from a broad spectrum antimicrobial peptide. These 2 peptide sequences are conjoined by a sequence of 3 glycine residues [37]. As per sequence analysis, C16G2 is an amphipathic and cationic alpha-helical peptide which is comparable with the conventional AMPs [39]. The hydrophobic property of C16G2 is substantially greater than that of individual moieties because of the stacking of hydrophobic residues [40]. CSPC16-*S. mutans* is a species-specific AMP but is separate from the ComD surface receptor [28]. A natural *S. mutans*-specific targeting sequence in this pheromone may become attached to a different receptor (lipids, exopoly-saccharides, teichoic acid) on the bacterial surface before interaction with ComD. According to recent studies, C16G2 exerts bactericidal action by a mechanism involving interference with the cytoplasmic membrane. C16G2 build-up on *S. mutans* cell surface results in loss of membrane potential followed by efflux of intracellular contents and disruption of membrane integrity finally causing cell death. The mutual amphipathic characteristic of C16G2 and AMPs gives rise to the STAMP acting as a membrane damaging peptide but with higher target specificity [40]. It has been proposed that C16G2 specifically eradicates *S. mutans* from multispecies biofilms without impacting closely associated non-cariogenic oral streptococci in saliva-derived and planktonic biofilm systems [28,41].

Studies on C16G2 and oral biofilm:

An in-vitro study on human saliva-derived polymicrobial biofilms treatment with C16G2 showed reduction of *S. mutans* counts and revealed a benign oral microbial community with enhanced health-related bacteria populations and less detrimental gram-negative bacteria [42]. C16G2 is considered to be fast-acting against bacteria in under one minute of exposure. The advantage of rapid action in a shorter duration is adequate to us as oral hygiene rinses. C16G2 is soluble in aqueous solutions indicating that STAMP is easily amenable for use in the oral cavity through a mouth rinse medium [28,36,40,43]. Another in-vivo study evaluated efficacy of mouth rinse with C16G2 formulation showed reduction of both plaque and salivary *S. mutans* counts. The study findings also showed prevention of *S. mutans* regrowth despite frequent exposure to sugar.

This is because of reduction in lactic acid

production resulting in the elevation of pH which favors growth of healthy bacteria, thus rendering an unsuitable environment for growth of cariogenic bacteria. Thus, it might be feasible to develop a healthy non-cariogenic microbial ecosystem in the mouth through C16G2-mediated STAMP intervention in clinical practice [41]. An unimpaired dental biofilm without *S. mutans* resists later growth of exogenous *S. mutans* due to reduced sucrose intake of other microbes in the biofilm which delay cariogenesis. Thus the oral microbial community maintained by C16G2 treatment exhibit a healthy microbial population with non-cariogenic species such as *S. mitis*, *S sanguinis* as well as reduced periodontitis associated gram-negative species *Fusobacteria* [42]. C16G2 was recognized by the US food and drug administration as an investigational drug for prevention of dental caries and has efficiently concluded phase 2 clinical trials [8].

CONCLUSION

C16G2 is an effective STAMP against dental caries that can be prepared in an aqueous formulation for use as an oral hygiene rinse. Its selective activity against *S. mutans* is helpful in caries preventive management. Development of C16G2 is a very significant advancement in oral biofilm management and caries prevention. Randomized clinical trials are required to evaluate the clinical utility of C16G2 and its effectiveness as a routine self-care practice.

CONFLICT OF INTEREST STATEMENT

None declared.

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