

Fluorides and Beyond

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Abstract: There is no doubt that the introduction of fluorides, has played a significant role in the decline of prevalence of dental caries. Despite its success, dental caries and cavities remain a global health problem. While fluoride is highly effective, economical agent for caries prevention, Even with regular fluoride use, carious lesions can still develop when there are more dietary sugar exposures therefore it must be recognized that in many situations. **Fluorides Alone May Not Be Sufficient.** Dental caries is multifactorial and all non-fluoride measures should be evaluated properly so that they can be introduced at the community level for its prevention. Though fluoride will continue to be the mainstay of any caries prevention protocol, they alone may not offer complete protection against the disease, and it is generally recognized that the effectiveness of fluoride could be enhanced when combined with additional cariostatic agents. Based on the current understanding of caries process, several preventive strategies have been developed or are under investigation, suggesting a future where caries prevention will not be narrowly focussed on fluoride therapies. This review will state the current status of some non fluoride agents for caries prevention.

Keywords: dental caries, fluorides, xylitol, novamin, caries, prevention, non fluoride agents.

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I. Introduction

Dental caries is one of the most common preventable childhood disease; people are susceptible to this ailment throughout the lifetime. The paradigms of dental caries aetiology focus on the ecology of the dental plaque biofilm and how local environmental factors can modulate this to cause disease. There is no doubt that the introduction of fluoride products, such as dentifrice and mouth rinses, has played a significant role in the dramatic decline in the prevalence and severity of dental caries in many geographies. Despite the success of fluorides, dental caries remains a prevalent oral disease, and cavities remain a global public health problem.¹

Fluoride Alone May Not Be Sufficient

While fluoride is a highly effective and economical agent for dental caries prevention, Even with regular fluoride use, carious lesions can still develop when there are more dietary sugar exposures per day [Duggal et al., 2001; Ccahuana-Vasquez et al Fluoride in various chemical forms, doses, and exposures has physicochemical and biologic effects on cells and tissues^{1,2}. Fluorides mediate their actions through MAPK signaling pathways, leading to changes in gene expression, cell stress, and even cell death. Fluorides can lead to a diverse collection of responses affecting biomineralization. Since 1970's researches started to search for non-fluoride agents for the prevention of dental caries Based on the current understanding of the dental caries process, this review will focus on recent advances of various non-fluoridated caries preventing agents and explore the rationale supporting the need for alternate methods of dental caries control, and will discuss the current status of some ecological approaches to caries prevention.³

Recent Alternatives to Flourides...!!

Arginine:

Arginine, a common amino acid found in saliva is broken down by oral plaque bacteria to acid neutralizing alkali. Urea and arginine can be rapidly metabolized by oral bacteria to elicit a rise in environmental pH. A strong correlation between elevated levels of free arginine in saliva and caries resistance has also been revealed. Arginine has recently been introduced as an additive to toothpaste and other fluoride-containing dental care products. Initially marketed for the treatment of sensitivity of exposed necks of teeth, arginine is now being promoted as a caries-preventive agent.^{1,4} Arginine is an amino acid that occurs naturally in a range of food products and in the saliva. It is metabolized by arginolytic bacteria which produce ammonia-like substances [Wijeyewera and Kleinberg, 1989], which leads to an increase in the pH in the oral biofilm [Huang et al., 2012]. This thereby counteracts the acidic environment conducive to the growth of acid-resistant bacteria.⁵

Antimicrobial peptides

Antimicrobial peptides (AMPs) are a heterogeneous group of molecules with unique antimicrobial characteristics that have great potential for controlling bacterial infections and modifying biofilms. AMPs have a broad range of antibacterial, antiviral, and antifungal activity mediated by selectively interacting electrostatically with negatively charged components of cell membrane phospholipids, resulting in membrane permeabilization and disruption, leading to cell death [Koczulla and Bals, 2003]. Besides naturally secreted salivary AMPs (lactoferrin, cathelicidins, histatins, defensins), a number of AMPs have been synthesized in the laboratory, and these include specific anticaries peptides that have shown the potential to inhibit dental caries.⁷ Another promising anticaries AMP is a synthetic α -helical antimicrobial decapeptide designated KSL-W, which can selectively destabilize the cell membranes of cariogenic bacteria including *S. mutans*, *S. sobrinus*, and *L. acidophilus* [Na et al., 2007; Leung et al., 2009]. Limitations of AMPs include their potential toxicity, susceptibility to proteases, high cost of peptide production, and the reduced cationic activity of most AMPs in physiological fluids like saliva.

Probiotics:

The term probiotics refers to “live micro-organisms, which, when administered in adequate amounts, confer a health benefit on the host” [Teughels et al., 2008]. The local anticaries effects may include competitive inhibition with cariogenic bacteria for nutrition or adhesive surfaces [Terai et al., 2015], selective co-aggregation of MS without disturbing other oral flora [Twetman et al., 2009; Lang et al., 2010], and bacteriocin-producing probiotics targeting MS [Burton et al., 2013].⁸ The most commonly used and studied probiotics belong to the *Lactobacillus* and *Bifidobacterium* bacterial genera, although not all their strains have the same efficacy in the inhibition of *S. mutans* growth or biofilm formation [Schwendicke et al., 2017]. Evidence supporting the application of probiotics for preventing dental caries is controversial,

Prebiotics

The prebiotic approach involves feeding resident microbiota with specific nutrients to create conditions that favour the growth and dominance of healthy bacteria in the biofilm. Oral prebiotic substrates that are especially valuable to prevent caries include arginine, arginine-rich peptides, and urea, as these foods when metabolized create alkalizing effects that counteract the acidogenic environment created by cariogenic bacteria. However, the preponderance of evidence does seem to suggest that the arginolysis is an effective approach to improve oral health and balance the microbial ecology.⁸

Quorum-sensing targets

Another approach that may maintain and support a healthy oral plaque ecology is to interfere with the fundamental cell-cell communications system between biofilm bacteria. This process of quorum sensing (QS) is mediated through small diffusible hormone-like molecules (pheromones) and their specific receptors. For MS, the stress-dependent QS system is primarily comprised of the CSP and its ComD/ComE 2-component signal transduction system for communication between biofilm cells of the same species, while interspecies signalling is mediated via the autoinducer-2 molecule produced by LuxS [Senadheera and Cvitkovitch, 2008]. The CSP-mediated QS system in *S. mutans* affects biofilm formation, acidogenicity, aciduricity, genetic transformation, bacteriocin production, stress response, and the ability to produce persister phenotypes [Leung et al., 2015].⁷ Targeting QS signaling pathways could provide a promising avenue in the development of novel therapeutics to alter cariogenic biofilms.

Another novel QS-modifying compound, 3-Oxo-N, was seen to significantly minimize lactic acid accumulation without affecting biofilm growth even in the presence of fermentable sugars, representing a promising agent for maintaining a healthy, non-cariogenic microbial ecology in dental plaque [Janus et al., 2016].

Natural Products

Natural products include secondary metabolites or phytochemicals derived from plants, fruits, herbs, or spices.⁵ They offer a rich source of structurally diverse molecules with a wide range of biological activities and could prove useful as alternative or adjunctive anticaries agents [Jeon et al., 2011].

Plant extracts

There is a global need for alternative prevention and treatment options and products for oral diseases that are safe, effective and economical.⁸ One such strategy would be to verify the enormous use of medicinal plants. A number of phytochemicals, including antibacterial agents have been derived from edible plants and demonstrate antibacterial properties against *Streptococcus mutans*.

Neem, *Azadirachta indica*:

Wolinsky et al. [24] investigated the inhibitory effects of aqueous extracts from Neem upon bacterial aggregation, growth and adhesion to hydroxyapatite and production of insoluble glucan, which may effect *in vitro* plaque formation.⁹

***Prunus mume*:**

Prunus mume is a common fruit in Asia, which has been used in traditional Chinese medicine. It is considered to be the potential candidate for developing an oral antimicrobial agent to control or prevent dental diseases associated with oral pathogenic bacteria like *Streptococcus mutans*, *S. sobrinus*, *S. mitis*, *S. Sanguinis*, *Lactobacillus acidophilus*, *P. gingivalis*, *Aggregatibacter actinomycetem comitans*.⁸

Green and black tea (*Camellia sinensis*):

Various component in green and black tea (leaves of *Camellia sinensis*, [Theaceae]) notably simple catechins, have anticariogenic activity. These include: a direct bactericidal effect against *S mutans* and *S sobrinus*; prevention of bacterial adherence to teeth; inhibition of glucosyl transferase, thus limiting the biosynthesis of sticky glucan; inhibition of human and bacterial amylases.⁸

Hop plant (*Humulus lupulus*):

Tagashira et al. reported the inhibition of *S. Mutans* and other oral streptococci, by the antimicrobially active ingredients of hop plant. They found that all tested hop constituents inhibited the streptococci with minimum inhibitory concentration at pH 7.5 ranged from 2 to 50 µg/ml.⁹

Oleic acid, Linoleic acid, epicatechin polymer (*Cacao bean husk*):

These shows antimicrobial activity against planktonic cells of mutans Streptococci. It has an inhibitory effect on water-insoluble substances, polymer glucan synthesis, adherence, acid production by mutans streptococci.⁹

Proanthocyanidins, phenolic acids, flavonols (*Cranberry*):

These shows antimicrobial activity against biofilm cells of mutans streptococci. It causes disruption of acidogenic/aciduric properties of planktonic and biofilm cells of *S. mutans*. It has inhibitory effects on Gtf activity and adherence by mutans Streptococci and causes reduction of formation of *S. mutans* biofilms and EPS content⁸

Apigenin and tt Farnesol:

Apigenin and tt Farnesol are two naturally occurring agents that affect the development of cariogenic biofilms. Apigenin inhibits the activity of glucosyltransferases in solution and on the surface of saliva-coated hydroxyapatite ,tt-Farnesol showed modest antibacterial activity against biofilms and its effects on glucosyltransferases were minimal . It also enhances the cariostatic effectiveness of fluoride.⁷

Meswak chewing sticks (*Twigs of Salvadora persica*):

These sticks embedded in agar or suspended above the agar plate had strong antibacterial effects against all tested bacteria. The antibacterial effect of suspended meswak sticks suggested the presence of volatile active antibacterial compound.⁸

Propolis:

Propolis is a natural beehive product, and cacao bean husk extracts have also shown significant antibacterial activity against *S. mutans* and/or *S. sobrinus in vitro* [29,38,39] Propolis extract when used as a mouthwash exhibits an *in vivo* antimicrobial activity against *S. mutans* and might be used as an alternative measure to prevent dental caries. Topical applications of chemically characterized Propolis extracts have also been shown to be highly effective in reducing the incidence and severity of smooth surface and sulcal caries in rats⁹

Chinese Licorice Root:

A new cavity fighting herbal lollipop that contains a special herbal formula extracted from the Chinese licorice root can help to immobilize major organisms responsible for tooth decay. These should be consumed twice a day- one in the morning after breakfast and another after professional teeth cleaning between two and four times a year.⁸

Xylitol: Xylitol reduces the accumulation of plaque on the surface of the tooth. It accumulates intracellularly in MS and inhibits the bacterial growth. Xylitol reduces MS by altering their metabolic pathways. It has long been known to have antibacterial properties, in particular to depress the proportion of *Streptococcus mutans* in plaque, and also to reduce its acidogenicity.¹⁰

Replacement Therapy with “Designer” Bacteria

The rationale for bacterial replacement therapy against dental caries is that relatively avirulent strains of MS are most likely to occupy the same ecological niche in plaque as their more cariogenic counterparts thereby reducing the overall cariogenicity of the plaque biofilm [Sun et al., 2009]. A number of “designer” bacteria have been studied for bacteriotherapy against cariogenic biofilms including a glucan synthesis-defective mutant of *S. mutans*, variants of *S. salivarius* (TOVE-R), and a recombinant alkali-generating ureolytic *S. mutans* strain [Tanzer et al., 1974, 1985; Clancy et al., 2000]. Modulation of oral plaque biofilms with genetically engineered “designer” bacteria has great potential through fostering a healthy oral environment, which prevents the dominance of cariogenic bacteria. A single treatment regimen could lead to persistent colonization by the effector strain affording lifelong protection, with minimal need for patient compliance. Whilst there have been encouraging results with genetically modified strains, the concept of replacement therapy needs to be tested for effectiveness in highly cariogenic environments. Even if successful, the widespread acceptance of genetically engineered “designer” bacteria may prove to be difficult for emotional, ethical, and legal reasons.¹¹

Novamin:

Novamin falls into a newer category of bioactive glass-ceramic material that has been available since the 1960’s as materials to help in bone repair. The active ingredient is a calcium sodium phosphosilicate that reacts when exposed to aqueous media, thus providing calcium and phosphate ions to the applied surface. Examples of Novamin powered technology include Oravive, a product from Natural Health Organics, which is a non-fluoridated, and non-prescription dentifrice containing 5% Novamin. Bioactive glasses have been tested under different clinical situations, such as having an antibacterial effect [63]. Novamin-containing dentifrice is statistically more effective than a placebo dentifrice [64]. One of these studies was done by and compared a dentifrice containing 5% Novamin and Fluoride (MFP) to a commercially available dentifrice in remineralization of subsurface carious lesions in human tooth enamel. It used confocal laser scanning microscopy (CLSM), which is able to distinguish between sound enamel and demineralized enamel using a fluorescent dye.¹¹

Dentifrices:

Tooth-pastes are the valuable adjuncts to oral hygiene as they make brushing more pleasant and more effective. Many attempts have been made at various times to add-therapeutical agents with the object of interfering with oral flora, limiting plaque formation and making teeth more resistant to caries.¹²

Chlorophyll:

Chlorophyll was one of the earliest agents added to the paste and is still present in some tooth-pastes. Although *in vitro* tests showed that chlorophyll- containing tooth pastes limit bacterial growth, but clinical trials have not shown any anti- caries effects¹³.

Ammoniated tooth-paste:

This usually contains urea, and developed in an attempt to control the acid production in plaque. Ammoniated pastes have been superseded by more effective agents, Anti-biotic toothpastes containing penicillin, triclosan or topical anti-biotic such as tyrothricin have also been tried. It was based on the assumption that if acidogenic bacteria are destroyed, caries will be controlled.¹⁴

Anti-enzyme paste:

These toothpastes were introduced on the basis that they interfere with enzyme systems of the bacteria and thus with their growth and function. Various other dentrifices containing herbal products like neem, tulsi, clove oil, propolis are available which show beneficiary effect in preventing dental caries.¹⁴

Chlorhexidine:

Chlorhexidine is a broad spectrum antibiotic that kills Gram-positive and Gram-negative bacteria as well as yeasts at high concentrations. At lethal concentrations chlorhexidine causes irreparable damage to the cell membrane of target microbes, and at sub-lethal concentrations chlorhexidine can interfere with the sugar transport and acid production of the cariogenic streptococci strains, providing a bacteriostatic effect.

Chlorhexidine is typically utilized because of its great retention within the plaque coated enamel surface, and studies report that 30% of the delivered chlorhexidine is retained in the mouth after use.¹⁵

Essential oils:

Essential oils have also been extensively studied for antimicrobial activity against caries-related bacteria. Essential oils derived from plants are typically a complex mixture of approximately 20-60 compounds that are in solution at various concentrations. Overall, the main chemical group is primarily composed of terpenoids, followed by aromatic and aliphatic constituents. Thymol and eugenol inhibit the growth of a wide range of oral microorganisms including mutans streptococci.¹⁶

Trace elements:

Different trace elements has been investigated were zinc, tin, aluminium, copper, iron, strontium, barium, manganese and molybdenum, gold, lead etc. Aluminum, copper, and iron have the most commonly used as cariostatic agent, although each would probably have organo-leptic problems if used in oral care products as simple salts. Moreover, the toxicity of many metals like aluminum, copper, barium molybdenum, would restrict the concentration at which they could be safely used.¹⁶

CPP-ACP:

Recent developments in the area of remineralization include casein phosphopeptide-amorphous calcium phosphate (CPPACP) Dairy products such as milk, milk concentrates and cheese are recognized as non-cariogenic or cariostatic in several laboratory studies due to the presence of milk phosphoprotein, casein. The milk protein, CPP, stabilizes high concentrations of calcium phosphate ions in ACP solutions. The CPP-ACP is taken up by dental biofilms and localizes to the enamel surface as nanoparticles. Calcium, phosphate and fluoride from CPP-ACP, which are released during Acidogenic challenge, help to maintain the supersaturated state of these ions in the biofilm and so promote remineralization over demineralization. Several randomized clinical trials (RCT) have shown that CPP-ACP added to sugar-free chewing gums, tooth paste or dental cream increased enamel subsurface remineralization. These RCT results suggested both a short-term remineralization effect of CPP-ACP and a caries-preventing effect for long-term clinical CPP-ACP use .It works safely; strengthen teeth by delivering calcium and phosphate in a unique soluble form to remineralize enamel. Recaldent will not affect people with lactose intolerance.^{17,18}

II. Conclusion

We have a variety of new agents which can be used to prevent dental caries .Moreover dental caries is a multifactorial and all non-fluoride measures should be evaluated properly in human trials so that they can be introduced at the community level for the prevention of dental caries. There is no doubt that fluoride will continue to be the mainstay of any caries prevention protocol as it still remains the most effective and economical protective agent against dental caries. ¹However, fluoride alone may not offer complete protection against the disease, and it is

generally recognized that the effectiveness of fluoride could be enhanced when combined with additional cariostatic agents [NIH, 2001]. Moreover, current paradigms emphasize the importance of maintaining a healthy and stable oral plaque biofilm for long-term disease control. One way to do this is to limit or exclude refined sugars from the diet; however, within the constraints of present day consumer culture, behavioural dietary changes are difficult to achieve and sustain. Adopting ecological preventive measures can help in correcting the disturbed plaque ecology and drive the advent and persistence of a symbiotic oral microbiome¹⁴. Furthermore, rather than surrogate end points like lower MS levels or reduced acid production, the critically important outcome for all new caries-preventive measures will be whether they can ensure a significant reduction in individual caries experience¹⁷.

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