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Caries Research in the Modern Era… Where Are We Now? A Review.

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Abstract: *Dental caries is an age old disease that has plagued humans ever since existence. The multifactorial etiology of dental caries and the preventive therapies in modulating cariogenic bacteria have witnessed paradigm shifts in the contemporary dental practice. The concept of drill and fill for decayed teeth management is slowly being replaced by novel techniques of eradicating the oral biofilms by combination of concepts of molecular biology and remineralization techniques. In this context, the crucial role of selective inhibition of highly cariogenic bacteria and retention of healthy oral microflora and maintenance of ecological equilibrium has garnered wide spread attention. Several studies by eminent researchers have showed promising potential of novel therapies for caries management. In this golden era of caries research, studies are being conducted on smart anti microbial peptides, probiotics and their influence on the cariogenic bacteria, quorum sensing inhibitors and disruption of cell to cell communication, phytochemicals and their role in modulation of biofilms, dietary modifications as well as the non cariogenic sugar substitutes. This review gives an insight on the current trends in caries research that go beyond the conventional methods of caries management. The above data is obtained by search engines such as pubmed, science direct, google scholar using key words such as caries research, oral biofilms, novel techniques in caries prevention, remineralizing techniques, sugar free substitutes, quorum sensing and inhibition.*

Key words- *Biofilm, quorum sensing, probiotics, phytochemicals, remineralization.*

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I. Introduction

Oral health and its importance in the overall longevity of an individual has gained a wide spread attention in this modern era. In this context, caries research have showed an paradigm shift from the traditional methods of reduction of exposures to sugars, fluoride applications, sugar free substitutes to arginine containing dentrifices, antimicrobial peptides, biofilm mediation via quorum quenching and to using probiotic approaches for reduction of caries. This novel approaches in caries research methodology clearly have a promising potential to lower the economic burden on the health care system. This review discusses the recent advances in caries research and latest concepts in managing dental caries. This review also highlights the collaborative efforts and conclusions drawn by several researchers pertaining to current trends in caries research methods.

II. Discussion

Restriction of sugar consumption to reduce caries

It is common finding that frequent exposures of sugar challenge the overall integrity of teeth. Two strategies that achieve caries control are reduction of sugar consumption as well as reduction of frequent exposures to sugar containing products.[1]The risk factors in the diet are modulated by several factors such as type of food, consumer related facts like sticky nature of food, frequency of sugar exposure, form of the food whether chewable or easily swallowable in addition to the concentration of sugars in the diet. Latest caries research review by Corvan Loveren etal highlights that reducing the amount of sugar intake without reducing frequency seems to be an ineffective caries preventive approach[1]. The importance of quality tooth brushing and regular usage of fluoridated tooth paste should not be underestimated.[1] Similarly, a review by Brian A. Burt, Satish chandra Pai, in 2000 also revealed that restriction of sugar consumption prevents caries but its pivotal role is not so significant in this fluoride era. [2]

Caries reduction by smart antimicrobial peptides

The indigenous bacteria in the oral cavity are a complex community of healthy and cariogenic bacteria. In order to disrupt the pathological biofilm antimicrobial peptides are being proposed. The oral antimicrobial peptides delivery methods in the form of dentrifices, mouth rinses and biological control of caries in this perspective has been under continuous research. In the oral cavity three main families of AMP(antimicrobial peptides) exist which are α-helical peptides without cysteine (the cathelicidin, LL37),peptides with three

disulphide bonds (the α and β- defensins) and peptides with an unusually high proportion of specific amino acids such as the histatins.[3,4,] Their main mode of action involves binding to microbial surface there by leading to cell membrane disruption, disruption of cell wall and nucleic acid synthesis and killing by intracellular mechanisms. [5,6]

However, their high expenses of manufacturing and limited stability, poorly understood pharmacokinetics and proteolytic degradation paved a way for research on antimicrobial peptide mimetics as well. [7] The peptide mimetic based on structure of magainin based on a compound called meta-phenylene ethynylene (Mpe) was found to convincingly prevent the S.*mutans* biofilm formation[8]. In this context ,a study conducted by Beverly A Dale, Renchuan Tao, etal in 2005 highlights that the low salivary levels of alphadefensin may represent a biological factor that contributes to caries susceptibility.[9]

Going forward the caries research done by Randal Eckert etal in 2006 explored the possibility of specifically targeted antimicrobial peptide (STAMP) based on the fusion of a species-specific targeting peptide domain with a wide-spectrum of antimicrobial peptide domain. The main idea was to target streptococcus mutans using a pheromone called competence stimulating peptide (CSP) produced by S *mutans*. Hence selective elimination of cariogenic bacteria sparing the normal healthy oral bacteria is achieved with this research.[10] Echoing the positive results of the above study, the collaborative efforts by Sullivan R., Santarpia P, Lavender S., Gittins E. etal showed that the clinical efficacy of STAMP mouth rinse against streptococcus mutans was indeed effective. The novel antimicrobial peptide rinse usage was associated with reductions in plaque and salivary S. *mutans* lactic acid production and enamel demineralization.[11] Currently this novel peptide C16G2 has been under clinical trials as new caries drug.

Oral microbial control by phytosphingosine

Anti adhesive and anti biofilm properties of cariogenic bacteria was extensively researched and documented in this era. In a similar vein, the invitro studies conducted by Bikker F.J. Hoogenkamp M.A.etal on biofilm models suggested that phytosphingosine (phospholipid) prevented the formation of biofilms.[12] The anti-biofilm activity of sphingosine, phytosphingosine (PHS), and sphinganine evaluated by cukkemane.N and Bikker etal also suggested that sphingolipids may be used to control oral biofilms, especially those loaded with S. mutans.[13]

Caries control by phytochemicals

Phytochemicals are proposed as cheap alternatives to classical antibiotics now-a -days. The phytochemicals demonstrate direct bactericidal or bacteriostatic effects, such as (i) prevention of bacterial adherence to mucosal surfaces of the pharynx, skin, and teeth surface; (ii) inhibition of glycolytic enzymes and pH drop; (iii) reduction of biofilm and plaque formation; and (iv) cell surface hydrophobicity**.** (Ferrazzano et al., 2011; Jeon etal., 2011)[14] **.**

The emerging caries research has yielded positive results with natural plant products in this century. Caries research done by Smullen J, Koutsou G, Foster etal on antimicrobial activity by plant extracts on S. *mutans* revealed that the minimal inhibitory concentration of red grape seed, green tea, unfermented cocoa is high. Wide variety of commercial as well as freshly prepared polyphenolic extracts of green and black tea, lemon, cinnamon, hibiscus, peppermint, grape seed, sloe berry skin, cocoa, blackberry, pomegranate skin, blackcurrant, hawthorn berry skin, red and white wine were tested for their anti-streptococcal activity against oral streptococci in this study[15.]

The plant extracts from Xanthorrhizol (Curcuma xanthorrihiza Roxb) rhizome, Bakuchiol (Psoralea corylifolia L.)seeds**,** Malvin.(Alcea longipedicellata I. Riedl) flowers, Macelignan (Myristica fragrans) seeds, Guaijaverin Psidium guaiava L. leaves, and Magnolol , (Magnolia officinalis) bark have shown promising potential in eradicating S. *mutans* biofilms.[16]

Caries reduction by interference with bacterial quorum sensing

Cell to cell communication among the bacterial biofilms have been the basis of quorum sensing. This bacterial talk among the diversified species of oral microflora helps in virulence of pathogenic bacteria, acquiring genetic competence among biofilms, in addition to providing resistance to adverse environmental conditions. These cell to cell interactions are possible because of small diffusible signal molecules called as autoinducers which help the bacteria in producing, detecting and conveying to each other.[17]. In this context, the most potent pathogen of dental caries S. *mutans* has CSP signaling peptide produced by stress induced conditions like a alarmone to initiate an adaptive response in times of adverse environmental conditions.[18]The mechanism by which quorum sensing can be inhibited is called quorum quenching. Inhibition of quorum sensing can be accomplished in several ways, including enzymatic degradation of signaling molecules, blocking signal generation and blocking signal reception.[19]

Quorum sensing inhibitors are produced naturally by Australian red alga called as halogenated furanones. Research has indicated that furanones are capable of interfering with quorum sensing behavior of several bacterial strains. Another compound called L- canavine found in legumes is an analog of arginine. An elaborate research by Gonzalez etal in 2006 showed that that arginine analog is a QSI (Quorum sensing inhibitor) compound that affects the quorum sensing of diversified bacterial strains. Human hormones like epinephrine and norepinephrine cross communicated with QS system according to a study done on enterohaemarrhagic E. coli. Other QSI compounds like Medicago truncatula, chlamydomonas reinhardtii, pencillium compounds also showed promising potential as quorum quenchers**.**[20]

Similarly a recent study by Shailee jee, Tarun showed that quorum quenching obtained by punica granatum, (pomegranate) eucalyptus, Magnifera indica (mango) and Acacia nilotica(gum Arabic tree) has an effective anti bacterial spectrum**.**[21]

Role of probiotics in caries reduction

Probiotics as defined by the World Health Organization are live micro-organisms, which, when administered in adequate amounts, confer a health benefit on the host.[22] Lot of research on probiotics has been evident in the post genomic era. The probiotic bacteria like S. salivarius, (Maseda L, Kulik etal 2012) L.reuteri,(Jorgensen. Mr, Kragelund etal 2017), L. Acidophilus, L. Casei, (Schwendicke.f, Korte.F etal 2017) Bifido bacterium (Gruner . D, Paris, Fong F. L. Shah etal 2016) have shown to decrease antagonism, coaggregation, modulate biofilm cariogenicity and improve resistance to caries attack respectively.[23]

Probiotics have also shown to exhibit antagonism with other oral microbial flora in addition to modulating the biofilm forming properties. More so, the research on probiotics also unraveled their role in enhancing host immune response and interactions with oral epithelium.[23] Similarly a study done by E. Caglar etal in 2006 showed that the probiotic Lactobacillus reuteri significantly reduced the levels of salivary mutans in young adults when delivered by prepared straws and lozenges.[24] The same authors when conducted a study on yogurt containing Bifidobacterium showed statistically significant lowered counts of streptococcus mutans in salivary biofilms of young adults with the usage of this probiotic yogurt.[25]

However a systematic review by Maria Grazia Cagetti, Stefano Mastroberardino etal in 2013 concludes that randomized clinical trials on probiotic research are inconclusive and lack scientific evidence.[26] However, bioengineered probiotics using various concepts of genomic sequencing and genetic engineering are under continuous research to tailor bacteria with higher degree of specificity and ecological shift.[27] Recently the beneficial action of S. dentisani as a probiotic has been proposed by Arantxa Lopez- Lopez etal in 2017.The authors claimed that these bacteria are active colonizers and are efficient in increasing healthy oral microflora.[28]

Remineralization therapy for caries reduction

Though fluoride mediated regeneration has become the cornerstone of current caries management , fluoride systems only have shown surface remineralization in sub surface lesions. (Cochrane etal 2010). In addition to this, emerging research has classified fluoride as chemical neurotoxicant and this raised safety concerns regarding high concentration fluoride products. (Grand jean & L Andrigan 2014). [29,]Modern caries management relies on biomimetic approach that synergizes fluoride efficacy. Of these regenerative therapies such as Dentine Phosphoprotein 8DSS derived peptides have shown promising avenues as they have dual capacity of binding to calcium and phosphate ions as well as hydroxyl apatite surface. (George etal1996, Yarbrough etal 2010)[29]. A recent study by yang etal in 2016 showed that 8DSS dentine peptides can inhibit demineralization and synergistically act with fluoride for anti caries action.[30]

Recently, recombinant porcine amelogenin (rP172) was found to stabilize calcium phosphate clusters and promote the growth of enamel crystals on acid etched surfaces**.** [Fanet al., 2009; Ruan et al., 2013, 2016].[29] Similar studies by Connelly etal showed the phosphorylated amelogenin regulates enamel crystal formation[31] . On the other hand, Electrically Accelerated and Enhanced Remineralization uses iontophoresis for remineralization of sub surface lesions.([Pitts and Wright, 2018][29]. Well documented research on Casein Phosphopeptide-Amorphous Calcium Phosphate a biomimetic remineralizing agent is also found to be encouraging. It stabilizes Ca2+ and PO4 3– ions [Reynolds,1987] and has shown the ability to inhibit cariogenic streptococci inducing the formation of non cariogenic plaque.[29,32] Tricalcium phosphate coupled with carboxylic acids and surfactants was also under trails to boost remineralization activity of carious lesions.[29]

Sugar substitutes in caries reduction

Several studies have quoted the anti cariogenic potential of sugar substitutes. Xylitol, a naturally occuring 5-carbon sugar poyol has shown to inhibit MS growth by disruption of energy production processes leading to cell death .[Marttinen et al., 2012]. Similarly a review by Peter de Cock etal in 2016 highlighted that Erythritol a non caloric polyol sweetner is more effective for plaque control, caries control, inhibition of growth

and activity of S. mutans when compared to sorbitol and xylitol.[33] Erythritol effect persisted up to 3 years after the end of the intervention.(Falony G etal 2016.)

III. Conclusion

This review highlights that the conclusions drawn by eminent researchers in caries prevention. Well documented evidence reveals that the amount of sugar consumption and frequency of sugar exposures in diet are directly proportional to rise of carious lesions. The role of antimicrobial peptides and their selective inhibition of cariogenic microflora shows promising trends in caries research. Quorum quenching compounds and quorum sensing inhibitors along with phytochemicals are capable of revolutionizing the caries treatment protocol. Probiotics research can reduce the pathogenic oral flora selectively. Sugar substitutes are non- cariogenic and can be deemed as best alternatives to sugar containing food products.

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