PROBIOTICS IN DENTAL CARIES PREVENTION

ABSTRACT:

Background: Changing lifestyle has resulted in deterioration of oral health in people of all age groups. The increasing global problems with the traditional disease management strategies have prompted the investigators to be in constant search of alternatives for managing these health issues.

Highlight: Probiotics is one such promising alternative to traditional disease management that has gained a lot of importance in improving oral health. The effect of probiotics on dental caries and its related risk factors is gaining momentum in the current era.

Conclusion: This narrative review summarised the available literature on probiotics in caries prevention.

Keywords: Bifidobacterium, Dental Caries, Oral health, Probiotics, Lactobacillus, Streptococcus

INTRODUCTION:

Dental caries still remains one of the most common diseases worldwide, although a decline of the prevalence has been recorded in western countries (1). The disease is triggered by the interaction over time among cariogenic microorganisms (mainly mutans streptococci and lactobacilli), a diet rich in fermentable carbohydrates and host factors, like as saliva secretion rate and buffering capacity (2). When sugared food/drinks are supplied frequently, acidogenic and aciduric strains increase selectively in the oral environment. These changes, over time, shift the demineralization/remineralization balance toward net mineral loss, leading to the caries lesion development (3). The microbial community of caries is diverse

and contains many facultatively and obligately-anaerobic bacteria (4).Mutans streptococci (MS) have been considered for a long time the major pathogens involved in caries development (5). The main characteristics of virulence of the Streptococcus mutans are their acidogenicity, ability to survival in acidic environments, the ability of biofilm formation and adherence to the tooth. In recent years, it was described that the microflora on the tooth surface changes with caries lesion development, from a predominance of non-mutans streptococci and Actinomycesspp.to dominance of MS and other non-mutans bacteria, including lactobacilli and Bifidobacteriumspp (6).

Comment [U1]: consistency of writing the name of the species, is Mutans streptococci the same as Streptococcus mutans?

CARIES PREVENTION:

Prevention of dental caries is based on the reduction in the number of cariogenic bacteria which leads to the environment that facilitates remineralization. There are several conventional methods agents to prevent occurrence of dental caries. Many agents have been shown to have an anticariogenic effect or to have the potential for such an effect. They can be categorised by their modes of action into three groups: those which affect plaque and plaque bacteria, those which affect tooth enamel chemistry and those which buffers oral pH (7). According to literature the most commonly used agents are chemoprophylactic agents, antimicrobial peptides, sugar substitutes like xylitol, fluoride therapy and casein phosphopeptides (8-13)

Preventive strategies are needed and recommended to control caries risk factors mainly based on dietary changes i.e., sweeteners intake reduction andenhancing host resistance (14). Sometimes, antibacterial agents are administered in order to reduce cariogenic micro-flora, however, a complete eradication of caries-associated microorganisms has proved to be difficult and almost impossible to obtain (15). Rather it might eradicate the entire oral flora that leads to undesirable effects. In order to overcome this drawback of

conventional methods, selective inhibition methods of pathogens responsible of dental caries are being studied at recent times (16). One such approach is use of probiotics against dental caries.

DEFINING THE TERM PROBIOTICS:

According to WHO the term probiotics is defined as,"Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (17). These microorganisms belong to the natural human flora in order to survive inthe acid environment during transit to the intestines.One of the main probiotic health claims is the positive change in microbiota composition traditionally investigated in regard to intestinal health (18). Probiotics are recognized to perform several actions in the digestive system as to prevent cellular adhesion and invasion of pathogenic bacteria, modify the intestinal environment and modulating the local and systemic inflammatory immune response (19). In the last decade, the use of probiotics has generated interest within the dental community with the development of studies focused on reducing caries incidence (20).

The effect of probiotics on dental caries and its related risk factors has been evaluatedin several experimental studies, using different strains; Lactobacillus rhamnosus GG, L. casei, L. reuteri, L. plantarum,L. brevis CD2, Bifidobacteriumspp, etc. were proposed and used to obtain caries incidence reduction, mutans streptococci and lactobacilli count change, plaque pH control and root caries lesions reversal (21-24). Several appropriate vehicles of administration of probiotic strains have been proposed. However,specifically formulated deviceswith slow release of the microbial strain might be neededin order to oral diseases prevention and control.

MECHANISM OF ACTION OF PROBIOTICS:

Probiotic bacteria include a broad spectrum of harmless and physiologically distinct strains, primarily belonging to the genera Lactobacillus and Bifidobacterium. Research into the health-promoting effects of probiotics has mainly focused on alleviating medical conditions, such as infections of the gastrointestinal tract (25). Several mechanisms have been proposed for the potential beneficial effect of probiotics. These can be classified into four broad lines:

1.The production of antimicrobials (bacteriocins) or acids that can inhibit the proliferation of pathogens. 2. Competition for cell adhesion sites (competitive inhibition or replacement therapy) with pathogens and/or co-aggregation to biofilm. 3. Modulation of local and systemic immune functions. 4. Degradation of toxins (26).

All available data show that the effects of probiotics are species- and strain-specific (27-29). There are studies which shown the effects of probiotics on reducing the incidence of cavities, in which the reduction took *Streptococcus mutans* in the oral cavity mainly with the probiotic *L. reuteri* ATCC 55730. The strains of *L. salivarius* BGHO1, *L. fermentum* BGHO36 and BGHO 64, *L. gasseri* and *L. delbrueckii* BGHO89 subsplactis BGHO99 who had antagonistic action on *Ataphylococcus aureus, Enterococcus faecalis, Micrococcus flavus, Salmonella enteritidis, Streptococcus pneumoniae* and *Streptococcus mutans,* except on the growth of *Candida albicans* are identified from samples in the tooth surface and healthy oral mucosa. They also found that strains of *L. gasseri* and *L. salivarius* BGHO89 BGHO1 were tolerant to low pH and high concentration of bile salts (30-33).

Streptococcus salivarius strain JH is a potential probiotic candidate which produces multiple proteinaceous antimicrobials (bacteriocins), the inhibitory spectrum that includes Streptococcus mutans, one of the principle causative agents for the development of dental caries. The genome of strain JH has previously studied and it was found to show to contain

the biosynthetic loci for the bacteriocins salivaricin A3, streptin and streptococcin SA-FF22. Thus, strain JH also produces salivaricin E, a 32 aa lantibiotic with a mass of 3565.9 Da, which is responsible for the inhibition of S. mutans growth (34).

According to literature, there are different mechanism of action for different strains of probiotic in the oral cavity. So, with these actions of probiotic strains, the metabolic activity of biofilm in the oral cavity and composition can be altered which leads to the prevention of dental caries. However, there are between 75 and 100 bacterial species in the oral cavity of each patient, with different combinations of species. So, if that's the case, we might require a mixture of beneficial strains rather than a single strain as oral bacteriotherapy (35).

Comment [U2]: Please explained the statement.... that different mechanism of action for different strains of probiotic in oral cavity

PROBIOTIC STRAINS:

Based on the literature search, there are wide range of strains which include Streptococcus salivarius, L. paracasei, L. caseii, L. rhamnosus, L. acidophilus, L. reuteri, L. plantarum, L. brevis and Bifidobacterium lactis. In vitro studies on monocultures of different probiotic lactobacilli strains have shown a varying acid production, while clinical trials have not revealed an impact on plaque acidogenicity (46,47).

A randomised open label clinical trial has been done to evaluate the effects of the lactic acid bacterium *Lactobacillus salivarius* on caries risk factors and it was concluded that oral consumption of *L. salivarius* WB21 and TI 2711 provided better resistance to caries risk factors compared to the xylitol tablet with no side effects related to advance of caries in the oral cavity (36). A double-blinded, randomized, placebo-controlled study evaluated the efficacy of the probiotic L. paracaseiGMNL-33 for reducing caries-associated salivary microbial counts in healthy adults. And concluded that 2-weekperiod of medication was needed for L. paracaseiGMNL-33 via oral administration route to become effective in the probiotic action. And short-term probiotic intervention seemed to enhance its inhibitory effect

against S. mutans after the intervention (37). And another double-blinded, randomized, placebo-controlled trial has done to provide a preliminary evaluation of S. salivariusM18 for its probiotic application to the prevention, or a reduction in the risk, of dental caries and found that S. salivariusM18 has oral health benefits when it is administered regularly (38). L. salivarius can secrete intermediates that is capable of inhibiting the formation of cariogenic S. mutans and C. albicans biofilm; and also inhibits fungal morphological transformation thus reducing the pathogenicity of C. albicans; ultimately weakens its pathogenic potential (39). A short-term daily ingestion of lactobacilli-derived probiotics which was a prepared prepared straws or lozenges has been delivered and it reduced the levels of salivary mutans streptococci in young adults (40). yoghurt containing LGG has an inhibitory effect on oral pathogenic bacteria and is beneficial in caries prevention on its daily consumption (41). An invitro study investigated the effect of L. lactis HY 449 on cariogenic biofilm and concluded that it possessed inhibitory mechanisms and useful probiotic for the prevention of dental caries (43). A randomized double blinded clinical trial demonstrated that S. salivariusK12 over a 28-day period does not adversely affect the human host on daily ingestion and supports the safety of its oral delivery in a food-based carrier (44). It has been proved that levels of microorganisms in saliva which is responsible of development of dental caries has been reduced with probiotic Bifidobacteria in yogurt (42). *L. rhamnosus*has been concluded as a candidate for prevention of dental caries since it inhibits oral biofilm formation by decreasing glucan production of *S. mutans* and has antibacterial activity and did not integrate into oral biofilm (45).

Comment [U3]: Explain abbreviation of LGG ?

AVAILABLE FORMS OF PROBIOTICS:

There are various forms of probiotics available that can be used on daily basis. Common probiotic bacteria used in clinical studies targeting oral health are Lactobacillus spp. and Bifidobacterium spp., in vehicles such as milk, yogurt, cheese, drops, gum, ice

cream, lozenges and tablets (48). The number of *S. mutans* have been reduced by using the milk formLactobacillus rhamnosus GG strain, Cheese form of Lactobacilli mix and Yoghurt form of Lactobacillus reuteri ATCC 55730, Bifidobacteriumanimalis DN-173010 (49-52). In addition to these results, Chewing gum, tablet and Lozenge forms of Lactobacillus reuteri ATCC 55730 and ice cream form of Bifidobacteriumlactics Bb-12 have shown to decrease the count of *S. mutans* on wide range of age groups (53-55).

Milk, Cereals, Drops forms of Lactobacillus rhamnosus LB21, Lactobacillus paracasei F19, Lactobacillus reuteri DSM 55730 are present and they found to decrease the outcome of dental caries (56-58). Streptococcus uberis KJ, Streptococcus oralis KJ, Streptococcus rattus JH14 are available as Tablet form and has inhibitory effect of dental caries (59). Ideally, the delivery should be suitable for all ages especially young children, since, it has been recommended that early exposure in life would bring in a permanent colonization of health promoting strains (60-62). However, still research goes on the identification of ideal administration vehicle (63).

FUTURE FOR PROBIOTICS IN CARIES PREVENTION:

The main goal of probiotics use in prevention of caries is to destroy or reduce the bacteria which is cariogenic, mainly mutans streptococci and replace it with noncariogenic bacteria (64). In order to prevent the occurrence of dental caries, probiotic bacteria shouldadhere to the oral mucosa and dental tissues as part of the biofilm and compete with the growth of dental pathogens (65). Probiotics had showed quite a few promising results in caries prevention, but there are only few clear clinical outcomes pertaining to prevention of caries. So, the proper scientific evidence are still in search. A regular continuous daily intake

of probiotic is probably required through vehicles like toothpastes or mouthrinses. For all anticaries product to be effective in its action, almost daily usage is needed, therefore probiotics should be incorporated in our daily preventive products like toothpaste. In spite of this, probiotics can also be administered in daily dietary supplements, and it is considered effective to some extent in prevention of caries (66).

FURTHER RESEARCH AND EMERGING PROBIOTC STRAIN:

Caries management strategies have travelled through various paths and are now witnessing a paradigm shift toward preventive approach. Bacteriotherapy is one of the most potential concepts to prevent dental caries (67). There are previous studies on reduction of mutans streptococci count with the help of available probiotcstarin such as *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri*, and *Bifidobacterium.* However, these strains possess certain limitations in their mechanism of action against biofilm and their evidence is still insufficient. In order to overcome those drawbacks of previously available strains, new probiotic strains are under search. One such emerging starin is *Streptococcus thermophilus* and it was found to be an effective probiotic for oral health (68,69) *Streptococcus salivarius*, a Gram-positive bacterium, is now currently being used as an oral probiotic (70). The most commonly used probiotic *S. salivarius* strains are K12 and M18. In addition to the above strains, *S. salivarius* strain JH has also been found to possess a potent anti-MS activity (71). And future research on probiotics for caries prevention should be based on new strains, vehicle of administration and prescription methods of probiotics for patients (66).

Comment [U4]: Please add a conclusion or resume from the author based on a review of the literature citation in this manuscript...

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Comment [U5]: ancient references are replaced with references that are updated at least the last 5-10 years

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