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A critical appraisal of the effects of probiotics on oral health

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ABSTRACT

Intense research in the field of probiotics persistently reveals novel benefits derived from these microorganisms. Probiotics have been consumed directly or indirectly through various food forms ascertaining to their wide gamut of healthy effects on humans. For the initial semi centennial, the primary role of probiotics was considered for maintaining gut health by preventing or treating infections, modulating host immune response and enhancing vitamin secretion etc. The potential benefits anticipated, arising out of the application of probiotics in the field of oral health has lately attracted the attention of researchers across the globe. Recent studies including clinical trials strongly suggest the active role of probiotics in prevention and treatment of oral infections, including dental caries and other periodontal disease. Probiotics have a unique ability to create a biofilm, which acts as protective lining and helps in replacing any biofilm-growing pathogen. This article summarizes the currently available data on the potential benefits of probiotics in maintaining oral health.

1. Introduction

Literature suggests that more than 700 species of microorganisms inhabit the oral cavity (Palmer, 2014). These include mostly prokaryotes which are further divided into two groups namely Gram positive (*Streptococcus, Enterococcus, Micrococcus, Peptococcus, Peptosteptococcus, Lactobacillus, Corynebacterium, Actinomyces, Arachnia, Rothia, Eubacterium, Propioni bacterium, Bifidobacterium, Bacillus and Clostridium*) and Gram negative (*Nisseria, Veillonela, Campylobacter, Eikenella, Actinobacillus, Capnocytophaga, Heamophilus, Simonsiella, Bactertoides, Fusobacterium, Porphyromonas, Provotella, Laptotrichia* and *Wolinella*) and some eukaryotes (protozoa, yeasts, mycoplasma, candida, spirochetes). The total collection of microorganisms residing in the oral cavity has been often referred to as the oral microbiota, oral microflora or the oral microbiome (Dewhirst et al., 2010). These microorganisms nourish from saliva and the gingival crevicular fluid enabling the maintenance of oral ecosystems. The overall general health and dietary habits of the host greatly influence the microbiome in the oral cavity. The wide range of pH, nutrient availability, shedding and non-shedding surfaces, salivary and crevicular fluids are the influencing elements of the oral microenvironment. While most of these resident microorganisms appear to be harmless there are some capable of oral infections, including caries (tooth decay), gingivitis and periodontitis (gum infections), and endodontic (root canal) infections. Deranging the oral bacterial homeostasis by any process of weakened immunity or any external factor such as steroid therapy can cause opportunistic infections like candidiasis, actinomycosis, mucositis, etc (Julkunen et al., 2017). Adverse diets can also change the composition of the oral microbiome leading to the onset of caries, erosion of the enamel and periodontal disease. Once infected the treatment options are very painful, expensive and time taking. Given the extent of the problem, oral diseases are a serious public health issue. They cause considerable loss of productivity on account of the pain, impairment of function and reduced quality of life apart from financial burden to the host. Oral diseases are the fourth most expensive disease to treat in developed countries (Listl, Galloway, Mossey, & Marcenes, 2015). According to NIH, National institute on aging, the oral cavity needs regular care and maintenance in the form of brushing, mouthwash and floss to keep it disease free. Various oral probiotic strains for preventing and treating oral diseases ranging from caries to halitosis have been summarized in Table 1.

Probiotics are emerging as a powerful prophylactic in oral care. Bacteriotherapy in the form of probiotic bacteria with an inhibitory effect on oral pathogens is a promising and cost-effective concept developed lately (Çaglar, Kargul, and Tanboga, 2005). Health promoting bacteria have been consumed for thousands of years in many civilizations but it was Elie Metchnikoff who introduced the concept of probiotics, which means, “for life” (“The prolongation of life: Optimistic studies,” 2004) By WHO definition, probiotics are ‘live microorganisms

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Table 1
List of probiotics studied for limiting the progress of various oral diseases and their causative pathogens.

Disease	Causative agent	Therapeutic probiotics	Type of study	Results	References
CARIES	*Streptococci mutans, Streptococcus sobrinus Bifidobacteria nonmutans Streptococci, Actinomyces* spp., *Propionibacterium* spp., *Veillonella* spp. and *Atopobiumspp*	*L. acidophilus*	In-vivo	Short-term consumption of probiotic curds showed marked salivary pH elevation and reduction of salivary *S. mutans*.	Srivastava et al., 2016
		***L.** reuteri*	*In-vivo*	Forty-two healthy adults with gingival inflammation took chewing gums containing two strains of *L. reuteri* over the course of 2 weeks. As a result BOP (Bleeding on probing) improved and GCF (gingival crevicular fluid) volume decreased in all groups during the chewing period. The pro-inflammatory cytokines levels also decreased.	Twetman et al., 2009
		L. acidophilus and Bifidobacterium lactis	*In-vivo*	Allergic responses in an ovalbumin (OVA)-induced allergy mice decreased when administered with *L. acidophilus AD031, Bifidobacterium lactis AD011, and L. acidophilus AD031* plus *B. lactis AD011,* 2 weeks before the sensitization. The groups treated with probiotics had decreased levels of degranulated mast cells, eosinophil granules, and tail scabs.	Kim et al., 2008
		L. paracasei	*In-vivo*	78 human subjects participated in a study wherein they took *L. paracasei* GMNL-33 and a placebo oral tablet three times per day. A significant count reduction in the salivary *S. mutans* was detected.	Chuang et al., 2011
		L. salivarius strains WB21 and T1271	*In-vivo*	A short-term administration trial using *L. salivarius WB21*-containing tablets was performed in eight healthy volunteers. Trial showed that the *L. salivarius WB21*-containing tablets significantly decreased the number of mutans streptococci.	Nishihara, Suzuki, Yoneda, & Hirofuji, 2014
		L. paracasei SD1	*In-vivo*	The use of a probiotic strain, *Lactobacillus paracasei SD1*, has shown to reduce mutans Streptococci numbers in Sixty school children volunteers.	Wattanarat et al., 2015
		Streptococcus thermophiles and L. bulgaricus	*In-vitro*	In vitro, yoghurt containing *Streptococcus thermophilus* and *Lactobacillus bulgaris* showed selective anti-mutans activity, suggesting that the overall decrease in mutans streptococci in vivo could be due to a bactericidal effect on *S. mutans* but not on *S. sobrinus*.	Petti, Tarsitani, & D'Arca, 2008
PLAQUE	*Porphyromonas gingivalis,* carcinogenic*: Streptococcus sobrinus* and *S. mutans*	*Lactobacillus paracasei* ssp.*paracasei* and *Lactobacillus rhamnosus*	In-vitro	*L. paracasei* ssp.*paracasei* and *L. rhamnosus* had a high capacity to antagonize important oral pathogens, including *S. mutans* and *Porphyromonas gingivalis*	Sookkhee et al., 2001
		L. salivarius strains WB21 and T12711	*In-vivo*	The short-term administration trial showed that the *L. salivarius WB21*-containing tablets significantly decreased the number of mutans *Streptococci*.	Nishihara et al., 2014
		Lactococcus lactis	*In-vivo*	Short-term consumption of probiotic curds containing *Lactococcus lactis* showed marked salivary pH elevation and reduction of salivary *S. mutans* counts	Srivastava et al., 2016
		L. plantarum strain 299v	*In-vitro*	*L. plantarum* 299v hampers *S. mutans* growth and biofilm formation in vitro and results suggest that the antimicrobial activity of Lactobacilli seems to be strain-specific and pH-dependent.	Vuotto et al., 2014

(*continued on next page*)

Table 1 (*continued*)

Disease	Causative agent	Therapeutic probiotics	Type of study	Results	References
GINGIVALIS	*P. gingivalis* and *P. intermedia*	*L. rhamnosus*	*In-vitro*	The immunomodulatory probiotic strain *L. rhamnosus* ATCC 9595 is proposed to be essential for maintaining healthy tissue, with multiple roles including co-aggregation, adhesion, and priming immune responses to ensure rapid and efficient defense against *P. gingivalis* ATCC 33277.	Mendi et al., 2016
		L. brevis, L. reuteri strains (DSM17938 and *ATCCPTA5289)*	In-vitro	Plaque inhibitory, anti-inflammatory and antimicrobial effects of *L. reuteri* and *L. brevis* may also be antagonistic, leading to a reduction in the quantity of plaque and therefore an improvement in the gingival index	Gupta, 2011
		L. casei Shirota	In-vivo	Twenty-eight adults consumed a probiotic milk drink containing *L. casei* Shirota reducing the effects of plaque-induced gingival inflammation associated with a higher plaque score due to the high-carbohydrate content of the probiotic milk.	Slawik et al., 2011
		L. casei Shirota and *L. reuteri* ATCC 55,730	In-vitro	The biofilms formed by *S. mutans* ATCC 25,175 and *P. gingivalis* ATCC 33,277 were treated with *L. casei* strain Shirota and *L. reuteri* ATCC 55,730 and appropriate controls in a time-dependent experiment from 15 min to 24 h showing potential anti-biofilm activity .	Vuotto et al., 2014
		L. plantarum 44,048 and NC8	*In-vitro*	Growth inhibition of *P. gingivalis* was obtained by viable Lactobacillus and culture media from *L. plantarum* NC8 and 44,048 The two-peptide bacteriocin from *L. plantarum* NC8 (PLNC8 αβ) was found to be efficient against *P. gingivalis*.	Khalaf et al., 2016
		L. ruteri	*In-vitro*	A reduced *S. mutans* level was shown after a two-week use of *L. reuteri* enriched yoghurt; effects were observed during use and for a few days after discontinuation.	Gupta, 2011
PERIODONTITIS	*Porphyromonasgingivalis, Treponema denticola, Tannerella forsythia, Aggregatibacter actinomycetemcomitans, Bacteroides* sp., *Actinomyces* sp. *Staphylococcus intermedius and C. albicans*	*L. helveticus*	*In-vivo*	Analysis of 12 random control trials revealed that oral administration of probiotics improved the recognized clinical signs of chronic and aggressive periodontitis. Continuous probiotic administration, laced mainly with Lactobacillus species, was necessary to maintain these benefits	Matsubara et al., 2016
		L. salivarius WB21 and *L. fermentum*	*In-vitro*	Both strains showed antagonistic activity on the growth of *S. mutans* and *Streptococcus pneumonia*.	Strahinic et al., 2007
		Bacillus subtilis and *L. salivarius*	*In-vivo*	The use of a mouth rinse containing *Bacillus subtilis* or the oral administration of tablets containing *Lactobacillus salivarius* reduced the number of periodontal pathogens.	Vuotto et al., 2014
		E. faecium WB2000	*In-vitro*	*E. faecium* WB2000 may reduce oral malodor by inhibiting the growth of P. gingivalis and neutralizing CH3SH.	Suzuki et al., 2016
HALITOSIS	*P. gingivalis*	*S. thermophiles*	*In-vitro*	*S. thermophilus* inhibited growth of *P. gingivalis,* and its spent culture medium was shown to reduc emission of VSCs gas.	Lee & Baek, 2014
		S. salivarius K12	*In-vitro*	*S. salivarius* K12 suppressed the growth of all Gram-positive bacteria tested in the study.	Masdea et al., 2012

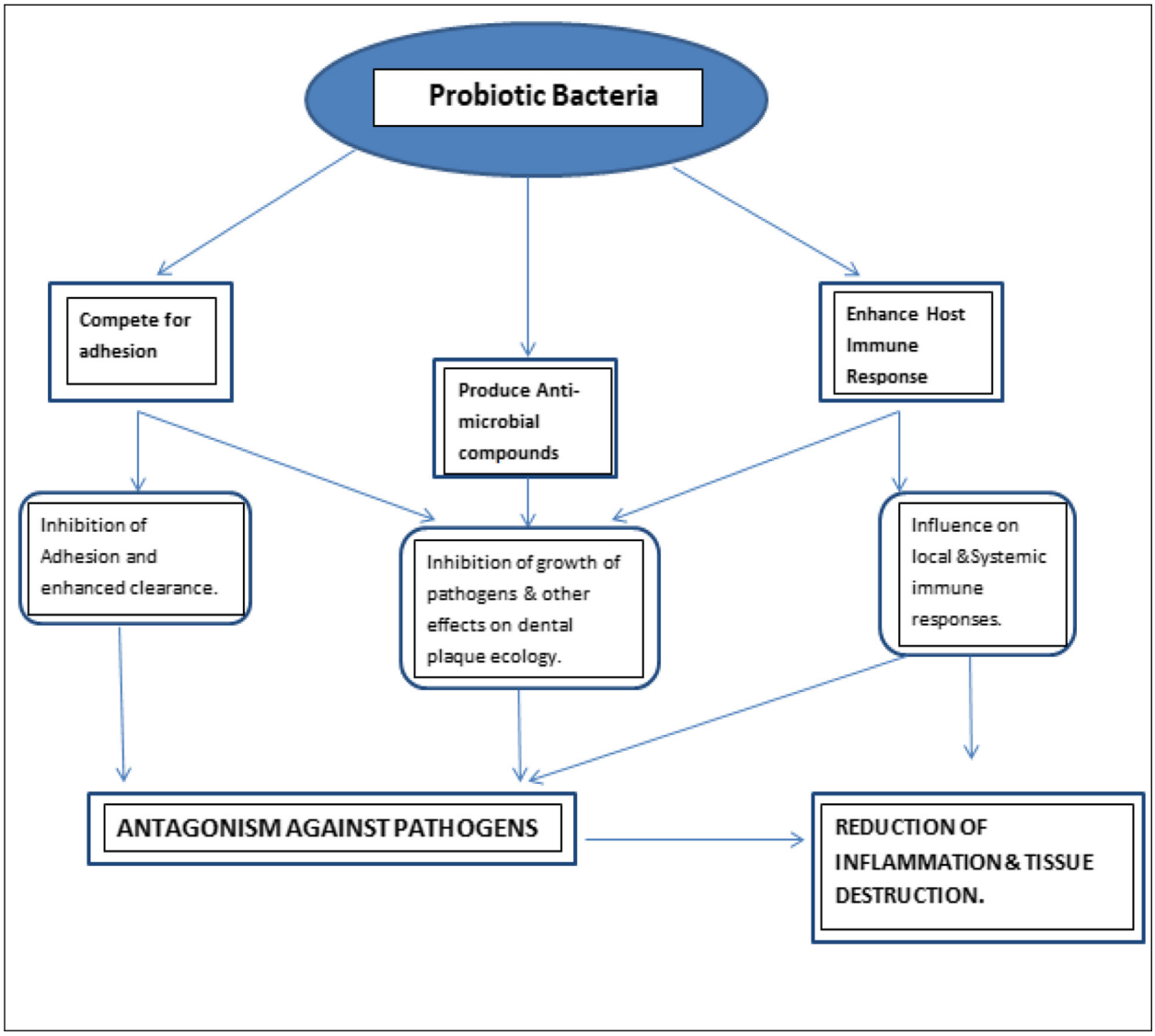

Fig. 1. Mechanism of action of probiotics in the oral cavity ().
Adapted from: Haukioja, 2010

which when administered in adequate amounts confers a health benefit on the host' (Food and Agriculture Organization and World Health Organization Expert Consultation, 2001). Since the last decade of twentieth century, probiotics have gained considerable and significant advances in functional- and health-food domain. Traditionally, probiotics have been associated with gut health, and most clinical interest has been focused on the prevention or treatment of gastrointestinal infection and diseases. However, during the last couple of decades, an increasing number of health benefits of probiotic bacteria have been reported, including enhancement of the adaptive immune response, treatment or prevention of urogenital and respiratory tract infections, and prevention or alleviation of allergies and atopic diseases in infants (Ettinger, MacDonald, Reid, & Burton, 2014).

Probiotics have been suggested to play a vital role in the prevention and treatment of oral diseases such as dental caries, periodontitis, halitosis, candida infections and gingivitis; when consumed regularly (Fig. 1). In recent years the role of probiotics in maintaining the ecological equilibrium and its effectiveness in normalization of oral microbiota has been a subject of intense investigation. These studies have been systematically summarized by many reviews in the past (Zaura & Twetman, 2019; Longo, Souza Ramos, Nunes, Santamaria, & Jardini, 2018; Frencken et al., 2017; Gruner, Paris, & Schwendicke, 2016; Matsubara, Bandara, Ishikawa, Mayer, & Samaranayake, 2016). Regulation of microflora composition offers the possibility to influence the development of mucosal and systemic immunity. Probiotics reduce the harmful properties of pathogenic microorganisms by naturally colonizing the oral cavity. Changing the actual composition of infected area from an inflammatory cytokine-rich environment to a more benign environment by inhabiting beneficial organisms contributes to systemic health as a whole. The most commonly used species in oral probiotic preparations are *Lactobacillus bulgaricus, L. acidophilus, L. casei, L. helveticus, L. lactis, L. salivarius, L. plantarum, Streptococcus thermophilus, Enterococcus faecium, E. faecalis, Bifidobacteriu*m and *Saccharomyces boulardii.* There has been a shift in the use of probiotics solely as adjunctive dental care towards a more robust routine therapy strategy in the last few years (Martin-Cabezas, Davideau, & Tenenbaum, 2016). Probiotics have been shown to increase the lifespan of voice prosthesis devices by inhibiting the adhesion of undesirable microorganisms (Schwandt, van Weissenbruch, van der Mei, Busscher, & Albers, 2005). The role of probiotics in prevention of oral diseases needs to be explored further with special emphasis on long term studies. The aim of this review is to highlight the use of probiotics in oral care and explore the clinical evidence to support the efficacy of probiotic therapy on oral health.

2. Diseases and probiotics

Any adverse change in the resident microflora, their metabolic activity and their local distribution leads to various diseased conditions of the oral cavity. The use of probiotics reverses the imbalance in the oral-ecological equilibrium, modulate pathogenic potential of biofilm, and effectively normalize the microbiota. The ability of probiotics to adhere to mucus and epithelial cells, as well as to co-aggregate, is one of the most important selection criteria for potential probiotic strains (Vuotto, Longo, & Donelli, 2014). Azad, Sarker, and Wan (2018) revealed that the immunomodulatory activity is the most important mechanism-of-action of probiotics not only on pathogenic bacteria but also on viruses. This may be due to the increased salivary levels of matrix metalloproteinase (MMP-9) and tissue inhibitor of metalloproteinases (TIMP-1) following consumption of probiotics (Jäsberg, Tervahartiala, Sorsa, Söderling, & Haukioja, 2018). Several studies have confirmed the antiviral activity of probiotics due to their immunomodulatory effect (Kassaa, 2017)). A study by Khani et al. (2012) suggests that *L.rhamnosus* enhances macrophage activation and viability for HSV-1 (Herpes Simplex Virus-1) elimination, when compared with non-probiotic *Escherichia coli*. A study by Cutler and Jotwani (2006) suggests that probiotics modulate host immunity both systemically and locally. Their study revealed the presence of "Oral lymphoid foci" in interdental papillae, the active site for local immune modulation. Probiotics are administered to maintain or restore the natural saprophytic micro-flora against a pathogen invasion, which is central to the development of the major oral diseases (caries and periodontal disease).

(1) CARIES

Dental caries, commonly known as cavities or tooth decay, can be defined as a localized chemical dissolution of tooth surface resulting from metabolic events in a biofilm (dental plaque) covering the affected area. The damage is associated with the dental hard tissue which progresses to inflammation and death of the vital pulp tissue leading to symptoms like toothache, tooth sensitivity, staining on the tooth etc. As per the Global Oral Health Data Bank, prevalence of caries ranges from 49% to 83% across the globe (Frencken et al., 2017). *Streptococcus mutans* is the main causative organism in caries development due to its ability to produce highly branched, water-insoluble glucan, mutan (Krzyściak, Jurczak, Kościelniak, Bystrowska, & Skalniak, 2014). This mutan, from which the bacteria derive its name, facilitates bacterial establishment in the oral biofilm. These biofilms are very stable bacterial communities that can tolerate low pH on account of the rapid metabolism of sucrose, fructose and glucose. The low pH conditions lead to an increase in acidogenic species, such as *Actinomyces* spp., *Atopobium* spp., *Bifidobacteria, nonmutans Streptococci, Propionibacterium* spp. and *Veillonella* spp. The *Streptococci* survive well on the buccal epithelial cells of the dorsum of the tongue and are reservoirs for supragingival and subgingival plaque. The low pH conditions can further lead to demineralization of tooth enamel leading to its erosion (Neel, Aljabo, Strange, Ibrahim, Coathup, Young, Bozec, & Mudera, 2016).

Jeong, Kim, Song, and Seo (2018) reported a novel isolate, *L. kefiranofaciens* DD2, from kefir which effectively inhibits *S. mutans* and *S. sobrinus* in an in-vitro oral environment. Furthermore, it influenced the biofilm formation by these two pathogens by inhibiting the expression of several genes including those encoding for carbohydrate metabolism, adhesion, and other regulatory mechanisms. A recent study by Piqué, Berlanga, and Miñana-Galbis (2019) revealed that *L. rhamnosus GG* has the highest value of adhesion and inhibits Streptococcus by producing different antimicrobial components such as organic acid, hydrogen peroxide, carbon peroxide and diacetyl bacteriocins. (López-López et al., 2017) report a novel probiotic Streptococcal species, *Streptococcus dentisani,* isolated from dental plaque of caries-free individuals. The strain was shown to inhibit the growth of major oral pathogens like *S. mutans, Fusobacterium nucleatum,* and *Prevotella intermedia* through the production of bacteriocins, and also buffers acidic pH of the oral cavity. *Lactococcus lactis* was observed to incorporate itself as biofilm similar to that of dental plaque and diminishes the colonization of *Streptococcus oralis, Veillonella dispar, Actinomyces naeslundii* and *Streptococcus sobrinus* (Huang, Li, & Gregory, 2011). In a study by Lin, Chen, Tu, Wang, and Chen (2017) four probiotic strains of *Lactobacilli* displayed strong inhibitory effects on *Streptococcus mutans*, isolated from children with active caries, with the inhibition rate reaching 70–90%. These probiotic strains (*L. casei* Shirota*, L. casei* LC01*, L. plantarum* ST-III and *L. paracasei* LPC37) also significantly reduced the numbers of *Streptococcus mutans, S. sanguinis* and other bacteria in mixed biofilms compared with the control group.

A double blinded study on 31 children by Yadav, Poornima, and Roshan (2014) revealed reduction of dental caries progression by *L. casei Shirota*. This may be attributed to its adhesive ability to dental surface that inhibits biofilm formation by pathogenic bacteria. Tehrani, Akhlaghi, Talebian, Emami, and Keyhani (2016) reported that consumption of *L. acidophilus* containing probiotic curd (10^{10} to 10^{11} cfu/ml) for 7 days resulted in marked reduction in salivary *S. mutans* count due to significant increase in oral pH. Combination of *L. rhamnosus* LB21 with fluoride was shown to be very effective in reducing caries occurrence in school children and also remineralization of dental enamel, in older adults (Petersson, Magnusson, Hakestam, Baigi, & Twetman, 2011). A study by Näse et al. (2001) reports that consumption of milk containing *L. rhamnosus GG* by children presented lower caries incidences, compared with consumption of milk without probiotics. Cagetti et al. (2013) observed regular consumption of probiotic milk containing *L. rhamnosous GG* and *L. reuteri* reduced *S. mutans* associated caries risk and initial caries development. Contrarily, a clinical study on 363 preschoolers, who were given 200 mL of milk with *L. rhamnosus* 5×10^6 and *Bifidobacteruim longum* 3×10^6 for 9 months, did not show any significant reduction in tooth caries compared to the control. This may due to the usage of milk as the carrier for probiotics which was also given to the control group as milk is known for its anticariogenic properties (Vakil, Shetty, & Hegde, 2016).

Çaglar et al. (2008) reported significant reduction in *S. mutans* count in young adults who consumed ice-cream containing *Bifidobacterium animalis* subsp. *lactis* (BB12) strain. *L. reuteri* DSM 17938 and ATCC PTA 5289 were reported to delay the regrowth of mutans streptococci (MS) in a randomized, double-blind; placebo-controlled study on 62 healthy subjects (Romani Vestman et al., 2013). Rodriguez et al. (2016) observed that after consuming *L. rhamnosus* SP1 (10^7 CFU/mL) supplemented probiotic milk for ten months the caries prevalence in preschool children dropped from 65.8% to 54.4%. Furthermore, the incidence of cavitated lesion was also much lower (9.7%) in probiotic group than in the placebo group (24.3%).

(2) PLAQUE

Dental plaque has been recognized as the single most important factor contributing to the etiology of dental caries. It is a cohort of micro-organisms involved in a wide range of physical, metabolic and molecular interactions. The plaque provides the pathogenic micro-organisms with a favorable niche for growth and simultaneous protection from antimicrobial agents and host defenses. If not cleaned regularly, plaque can cause damage by buildup of tartar leading to gum problems, tooth decay and even tooth loss.

Probiotics reduce plaque induction by neutralizing free electrons, modulating systemic immune system and also by regulating mucosal permeability. Strains of *Streptococcus thermophilus* and *Lactococcus lactis* strains were shown to adhere to saliva coated hydroxyapatite beads in an in-vitro study by Comelli, Guggenheim, Stingele, and Neeser (2002). *L. lactis* NCC2211 successfully incorporates itself into a biofilm, thus mimicking the dental plaque, and modulates the growth of the cariogenic *Streptococcus sobrinus* OMZ176. A randomized, double-blind, placebo-controlled study by Shimauchi et al. (2008) revealed a

significant decrease in the plaque index and probing pocket depth in smokers who took *L. salivarius* WB21 (6.7×10^8 CFU) and Xylitol (280 mg/tab) three times a day for 8 weeks. Salivary lactoferrin also showed decrease in the smokers compared to baseline. Lactoferrin is an antimicrobial glycoprotein whose levels in the gingival crevicular fluid are directly correlated with clinical parameters of periodontitis (Wei et al., 2004).

A dietary study conducted on 942 adults by Shimazaki et al. (2008) revealed a direct relationship between periodontal health and the consumption of lactic acid foods such as yoghurt. A 42 day randomized clinical trial on 30 volunteers by Vivekananda, Vandana, and Bhat (2010) revealed plaque inhibition, anti-inflammatory, and antimicrobial effects of *L. reuteri*. In a study by Teanpaisan, Piwat, and Dahlén (2011) lactobacilli were isolated from oral cavity of 165 young children for their inhibitory effect against common oral pathogens. Six of these strains namely, *L paracasei SD1, L. casei LD2, L. salivarius SD3, L. plantarum SD4, L. ramhnosus SD5* and *L. fermentum SD6* showed strong inhibitory effect against *S. mutans* and *S. sobrinus*, as well as, gram-negative gingivitis causing periodontal pathogens *P. gingivalis* and *A. actinomycetemcomitans*.

(3) GINGIVITIS

Gingivitis is caused by the accumulation of bacterial plaque and tartar leading to the inflammation of the gingiva or gums. The most common causative organism is *Porphyromonas gingivalis*, which colonize sub gingival sites and cause tissue damage by invading gingival epithelial cells leading to progression of chronic inflammatory diseases. GI (Gingival Index) and BOP (Bleeding on probing) is the markers of inflammation and represents parameters of gingivitis. Gingipain proteases produced by the pathogenic bacteria contribute to the virulence of the organism by disrupting the host complement system (Slaney, Gallagher, Aduse-Opoku, Pell, & Curtis, 2006).

Probiotic strains help in managing gingivitis by stabilizing the flora of the oral cavity. Acidogenic probiotic bacteria such as *Lactobacilli*, *Streptococci* and *Bifidobacterium* release antimicrobial substances that have inhibitory effect against pathogens through co-aggregation, production of toxic byproducts and competing for substrates. Nisin, a commercially available antimicrobial agent found effective in the reduction of plaque buildup and gingivitis in beagle dogs as compared to treatment with chlorhexidine and a placebo (Howell et al., 1993).

L. salivarius TI 2711 was reported to reduce *P. gingivalis* counts (Matsuoka, 2004). *S. salivarius* have adherent pili that contribute to their adherence to mucin, a major component of saliva. *L. brevis* (CD2) containing lozenge were shown to reduce gingival inflammation, calculus levels and temperature sensitivity in a clinical study (Della Riccia et al., 2007). At the completion of the trial all patients showed no signs of gingivitis, which may be attributed to the anti-inflammatory properties of *L. brevis* (CD2). *L. plantarum* 44048 and NC8 strains inhibit *P. gingivalis* by releasing bacteriocin PLNC8 αβ. These peptides are attracted to negatively charged lipid A and phosphate group of the lipopolysaccharide (LPS) molecule, which initiate the process of pore formation. It increases permeability of liposomes causing structural changes and disruption in membrane integrity leading to cell lysis (Khalaf et al., 2016). The regular consumption of *L. reuteri*-containing lozenges proved to be a beneficial in the control of pregnancy-associated gingivitis and plaque coverage in healthy pregnant women (Schlagenhauf et al., 2016). Twetman, Derawi, Keller, Ekstrand, Yucel-Lindberg, Stecksén-Blicks (2009) also reported the reduction of pro-inflammatory cytokines in gingival crevicular fluid upon consumption of *L. reuteri*-containing chewing gums.

(4) PERIODONTITIS

Periodontal diseases are the most common inflammatory destructive conditions involving both the soft and hard tissue. The disease is initiated by components of the plaque which develops on the hard root surface adjoining the soft tissues that supports periodontium. The disease might extend to the gingiva (gingivitis) or to deeper supporting structures leading to the destruction of the periodontal ligament and the alveolar bone. According to WHO, 15–20% of middle-aged (35–44 years) adults encounter tooth loss due to severe periodontal (gum) diseases. As reported by Llambés, Arias-Herrera, and Caffesse (2015) severe periodontitis causes tooth mobility which may lead to loss of the affected tooth. Periodontal pathogens may also invade systemic circulation and cause end toxemia, complicating pregnancy outcomes, and causing diabetes and nosocomial pneumonias. *Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, A. actinomycetemcomitans, Bacteroides* sp., *Actinomyces* sp., *Staphylococcus intermedius,* and *Candida albicans* are the common pathogens associated with chronic periodontitis. A recent study by Arjunan et al. (2018) reports the role of *P. gingivalis* in activation of anti-apoptotic pathway thereby promoting immune suppression as well as oncogenic cell proliferation. *A. actinomycetemcomitans* causes juvenile localized periodontitis and require various virulence factor namely leukotoxin, cytolethal distending toxin (Cdt), lipopolysaccharide (LPS), bone resorption inducing toxins, and epitheliotoxin to survive the environment of oral cavity. Its biofilm has tenacious attachments on surfaces due to an existence of fimbriae, is tolerant to antimicrobial agents and impossible to be phagocytized by immune cells because of the restricted penetration of immunity factors by extracellular polysaccharides.

Probiotics help in periodontitis by stabilizing the flora of the oral cavity. Most strains of *Lactobacillus* suppress growth of periodontal pathogens. Many latest studies showed application of beneficial bacteria, as an adjunct to scaling and root planing, can inhibit the recolonization of periodontopathogen and in overall pocket depth reduction and clinical attachment gain. Probiotics adhere to dental tissues as a part of the biofilm (or plaque) and compete with the growth of cariogenic bacteria or periodontal pathogens (Penala et al., 2016). A study by Allaker and Stephen (2017) suggests that probiotics could be useful in the improvement of oral health, mostly in subjects at a high risk of periodontal disease. *L. ruteri, L. brevis, L. rhamnosus and L. salivarius* WB2I inhibit periodontitis causing pathogens. *L. brevis* is effective in curing chronic periodontitis, gingival index and plaque index. They also inhibit the release of nitric oxide consequently reducing the release of salivary prostaglandins (PGE_2) thus diminishing activation of salivary matrix metalloproteases (MMPs) (Kuka, Gursoy, Alturfan, Ustundag, & Kuru, 2019). These metaloproteases have the ability to suppress T-cell receptor, compromising immunity. They show anti-inflammatory effect in patients with chronic periodontitis. There is significant improvement in the plaque index, gingival index and bleeding on probing in the patients suffering from chronic periodontitis. *Lactobacillus helveticus* produces short peptides that act on osteoblast and contributes to bone formation. They reduce the bone resorption associated with periodontitis (Matsubara et al., 2016). They showed that probiotic bacteria can be used as an adjuvant to conventional treatment of periodontitis with no side effects on the host. They may augment the antimicrobial effect of mechanical plaque removal, reducing the necessity for surgical intervention, and replace antibiotics in the management of human periodontal infections in future. In an in-vivo study by Maekawa and Hajishengallis (2014), *Lactobacillus brevis CD2* displayed significantly decreased bone loss and lower expression of inflammatory cytokines in the gingiva when compared to placebo-treated mice. *Lactobacillus SD1–SD6 and L. brevis CD2*, exhibit a strong inhibitory effect against Gram negative periodontal pathogens, *P. gingivalis, A. actinomycetemcomitans* and *Prevotella melaninogenica*.

2.1. Probiotics and Candida albicans

Candida spp. is present on the surface of different body parts including oral cavity of humans. About 75% of adults have candida present in their oral cavity. Usually it is a harmless fungus but under

specific conditions, it can become pathogenic and lead to infections. Among all the candida species, *C. albicans* is majorly responsible for causing fungal infection known as "Oral Candidiasis" in the oral cavity. Oral Candidiasis cases are growing rapidly over the last few decades, because of the increase in some immune-correlated chronic illnesses and the intensive use of some drugs, such as antibiotics, chemotherapy, and immunosuppressants (Farah, Lynch, & McCullough, 2010).

Lactobacillus rhamnosus, L. casei, and L. acidophilus inhibit *C. albicans* yeast-to-hyphae differentiation, biofilm formation, cell adhesion and filamentation. This candicidal effect was attributed to either the interference of interfacial interactions or the production of exometabolites that destabilize the biofilm organization and architecture; however none was confirmed (Matsubara et al., 2016). Sharma and Srivastava (2014) reported the fungicidal activity present in spent culture filtrate of *L. plantarum* LR14 on *C. albicans*. A proteinaceous metabolite was shown to exhibit membrane damaging effect leading to significant reduction of cell viability and biofilm formation. Probiotic potential of *Lactobacillus plantarum* LR14 has also been reported (Ghosh, 2008). The artificially synthesized plantaricin peptides PlnE, F and J displayed fungicidal activity against *Candida albicans* (Sharma & Srivastava, 2014). Rossonia et al. (2018) also suggested that Lactobacillus strains can produce acids or exometabolites capable of inhibiting *C. albicans* biofilms suggesting potential probiotics to prevent oral candidiasis.

Another study suggested that co-incubation with probiotic cells and supernatants of *L. plantarum* SD5870, *Lactobacillus helveticus* CBS N116411 and *Streptococcus salivarius* DSM 14685 under hyphae-inducing conditions led to reduction in *C. albicans* biofilm formation and modulation of gene expression (James, MacDonald, Chanyi, Cadieux, & Burton, 2016). Among different species of lactic acid bacteria isolated from the oral cavity *L. paracasei* and *L. rhamnosus* strains were two species that had the greatest number of clinical isolates able to inhibit *C. albicans* (Sookkhee, Chulasiri, & Prachyabrued, 2001). In another study, colonization of *C. albicans* on oral mucosa was significantly decreased by probiotic bacterial *L. acidophilus and L. rhamnosus* (Matsubara, Silva, Paula, Ishikawa, & Nakamae, 2012). In an in vivo study, Jørgensen, Kragelund, Jensen, Keller, and Twetman (2017) showed *L. reuteri* strains (DSM17938 and ATCCPTA5289) to be able to reduce Candida load by production of lactic acid and other organic acids that cause co-aggregation and modification of oral pH.

(5) HALITOSIS

Under anaerobic conditions, Gram-negative bacteria (*Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia, and Treponema denticola*) degrade food proteins and produce Volatile Sulfur Compounds (VSCs: hydrogen sulfide, methyl mercaptan, and dimethyl sulfide), contributing to the progression of periodontal disease as well as halitosis (Persson, Edlund, Claesson, and Carlsson, 1990). These volatile compounds, which originate from the oropharynx or from expired alveolar air, include sulphur containing gases like hydrogen sulphide, methanethiol and dimethyl sulfide. They may also include traces of other gases, such as indole, skatole, putrescine, cadaverine and acetone. These are the dominant cause of halitosis while the disturbed commensal microflora equilibrium in halitosis is responsible for malodor (Porter and Scully, 2006). The bad odor apart from being a health issue is also a social deterrent for the host.

Reduction in halitosis was observed after gargling with rinse containing *Weissella cibaria*. It showed marked reduction in the levels of hydrogen sulfide (H_2S) and Methanethiol ($2CH_3SH$) by approximately 48.2% and 59.4% respectively. *W. cibaria* secretes hydrogen peroxide and bacteriocins that acts against Gram positive bacteria and works in coaggregation with *Fusobacterium nucleatem* (Bonifait, Chandad, & Grenier, 2009). It adheres to host epithelial cell wiping away the pathogenic bacteria. A 28 day clinical study on 25 healthy young adults with self-reported malodourous morning breath showed promising results after using probiotic chewing gum containing *L. reuteri* (DSM 17938 and ATCC PTA 5289). The volunteers reported beneficial effects on oral malodour assessed by organoleptic scores. A 90 day double-blinded, placebo-controlled, randomized clinical trial by Soares, Carvalho, and Tinoco (2019), revealed significant reduction in periodontal parameters and halitosis following oral administration of *Lactobacillus reuteri, L. salivarius* and *L. acidophilus.*

The replacement of bacteria implicated in halitosis by colonization with probiotic bacterial strains may have potential application as adjuncts for the prevention and treatment of halitosis.

E. faecium WB2000 may reduce oral malodor by inhibiting the growth of *P. gingivalis* and neutralizing methyl mercaptan (Suzuki, Higuchi, & Nakajima, 2016). Lee and Baek (2014) reported the inhibition of growth of H_2S, CH_3SH, and CH_3SCH_3 producing *P. gingivalis* by *Streptococcus thermophiles*. *S. salivarius* K12 is reported to suppress the growth of H_2S producing *Solobacterium moorei* (Masdea et al., 2012). In a double blind crossover, randomized, placebo-controlled clinical trial, twenty-three patients were given a probiotic tablet containing *L. salivarius* WB21 (6.7×108 CFU) and xylitol (280 mg) thrice daily. In the first crossover phase, the test group group took the probiotic for 14 days, whereas the placebo group took the placebo. Following a washout period of 2 weeks, the groups were reversed for next phase of 14 days. Organoleptic test scores were significantly lower ($P < 0.001$ and $P = 0.002$) in both phases compared with the respective baseline scores. The concentration of volatile sulfur compounds (VSCs) also decreased significantly in the probiotic phase compared with the placebo (Suzuki et al., 2014).

Iwamoto (2010) studied the oral health of patients suffering from halitosis by oral administration of probiotic *lactobacilli* showed improvement in physiologic halitosis and bleeding. Masdea et al. (2012) demonstrated the antimicrobial effect of *Streptococcus salivarius* K12 against halitosis causing bacteria and also recommended it as a valuable candidate for the development of an antimicrobial therapy for halitosis. Zupancic, Kriksic, and Kovacevic (2017) also investigated the potential of oral probiotic *S. salivarius* K12 in reducing halitosis, attributing its low pathogenicity and strong bacteriocin-like inhibitory substances (BLIS)-producing capability but data are still deficient. Yoo et al. (2019) also documented the previous findings and summarize the evidence based on the meta-analysis of three double-blinded placebo-controlled randomized clinical trials (RCT). The preliminary data suggested the recommendation of probiotics for the management of halitosis; however, the available evidence is quantitatively and qualitatively insufficient for further recommendations in terms of administration strategies and pretreatment.

3. Conclusion

Oral health has a direct impact on an individual's wellbeing and quality of life. Oral diseases can limit the individual's capacity of eating, speaking and smiling thereby greatly damaging personal and social life. Latest research, both in vitro and in vivo, has unveiled significant role of probiotic strains in prevention of a vast gamut of oral health problems ranging from caries to halitosis and periodontal diseases. Studies have shown the direct role of probiotics in inhibiting oral pathogens as well as changing the oral microenvironment which acts as a deterrent for further colonization by the pathogens. Indigenous probiotic preparations have also been shown to significantly prevent or reduce oral diseases when administered continuously for a few weeks. Most of the studies included in this review indicate towards daily consumption of probiotics to produce the intended effects, such as inhibiting pathogens, growth of indigenous species and maintaining the pH balance. It was also revealed that the action of probiotics is not universal instead specific oral diseases require specific probiotic interventions/combinations to impart the intended effects. Therefore, probiotics can be adopted as a novel approach to prevent the demineralization of enamel, improve periodontal health, eliminate halitosis and reduce the prevalence of *C. albicans* in adults. Moreover, the selection of the best-suited probiotic

for oral health is an issue that certainly calls for further study. Research to unravel the mechanisms of possible probiotic action and long-term clinical trials are further needed before including them into daily oral-health regimen.

4. Future aspects

Novel probiotic solutions, targeting oral health, constitute a new class of products that are a great leap beyond the conventional over the counter solutions. With the changing lifestyle and feeding habits, globally, it is anticipated that rise in oral diseases will be proportional to other lifestyle diseases. Identification of strains from indigenous fermented products such as kefir, curd, etc. followed by rigorous pre-clinical and clinical trials can help generate novel probiotic with desired effects. These natural strains can reduce our dependency on chemical based interventions for daily upkeep of oral health and prevention of diseases. Similarly, for serious oral diseases genetically modified microbes may open up a whole new dimension to the concept of probiotics in the near future. The strain can be modified to encompass biofilm formation, bacteriocin production etc. and simultaneously endure the feeding habits of the host. Alternatively, the said strains could be used to enhance the properties of a natural oral microbiota. Host oral microbiota characterization can also be a possibility in the near future to understand the underlying conditions. This can help deciding the treatment options or therapy to shift the balance towards the beneficial microbiota. However, all the products effective in oral health care are required to be administered daily, so a possible way of administration could be to incorporate probiotics in toothpaste, mouthwash, chewing gums, sugar-less candy for kids etc. Some of these products are already available over-the-counter in western countries and are fast gaining popularity in others. Tapping the commercial potential of the emerging oral-probiotic market by the industry can turn out to be a win–win situation for all.

Ethical statement

Our research work did not include any human subjects and animal experiments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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