INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES

(p-ISSN: 2348-5213: e-ISSN: 2348-5221)

www.ijcrcps.com

DOI: 10.22192/ijcrcps Coden: IJCROO(USA) Volume 8, Issue 10 - 2021

Review Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2021.08.10.004

A review on Role of Probiotics Microorganisms in Oral health.

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Introduction

Probiotics can be defined as living microbes, or as food ingredients containing living microbes, that beneficially influence the health of the host when used in adequate numbers (Ashwell, 2004). Both definitions have in common the idea that probiotic microorganisms are living. Furthermore, the efficacy and safety of probiotics should be scientifically proven. Probiotic effects are strain specific; thus each individual bacterial strain must be tested separately for the health benefit in question, and the effects described for one strain cannot be directly applied to others (Vrese and Schrezenmeir, 2008)

Species used as probiotics

They can be yeast, bacteria or moulds. But most commonly, bacterial species are predominant which mainly includes –

1. **Lactic acid producing bacteria** – *Lactobacillus sacidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus fermentum, Lactobacillus lactis* etc
2. **Nonlactic acid producing bacteria** – *Enterococcus faecalis, Enterococcus faecium, Escherichia coli Nissle, Streptococcus thermophiles, Propinobacterium* etc
3. **Bifidobacterium** species – *Bifidobacterium adolescentis, bifidobacterium bifidum, bifidobacterium breve, bifidobacterium lactis, bifidobacterium longum* etc
4. **Nonpathogenic yeast** – *Sacchromyces boulardii*
5. **Non spore forming** – *Coccobacillus*

The *Lactobacillus* species help in the production of enzymes to digest and metabolize proteins and carbohydrates. They aid in the synthesis of vitamin B and vitamin K and facilitates breakdown of bile salts. They enhance innate and acquired immunity as well as help in the

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inhibition of pro-inflammatory mediators. More recently, a study demonstrated that long term consumption of milk caused a significant reduction in caries risk. *Bifidobacterium* species are strictly anaerobic and predominate the large intestines.

Over 30 species had been identified. The benefits from these include metabolization of lactose, generate lactic ions from lactic acid and synthesize vitamins. They also ferment indigestible carbohydrates and produce beneficial short chain fatty acids. They are believed to be beneficial in reducing antibiotic associated Diarrhoea and traveler's Diarrhoea. They relieve constipation, alleviate inflammatory bowel disease and prevent DNA damage. Finally, they may prevent or delay the onset of cancers (Narwal, 2011; Nagaraj et al., 2012; Munjal and Munjal, 2014).

During the last few years, several authors have suggested that probiotic bacteria originally planned for gut health could also be beneficial to oral health. The aim of this review is to examine potential mechanisms of probiotic bacteria in the oral cavity and to summarize observed effects of probiotics with respect to oral health. Finally, some future aspects are briefly discussed. This review focuses on probiotic lactobacilli and bifidobacteria, genera that are most used in various probiotic products.

Oral health

The mouth has a varied and heterogeneous microbial community. Oral health can be a state of being free from chronic mouth and tooth pain, such as oral and throat cancer, tooth loss, periodontal disease, and the other diseases that affect this tissue. The etiology of periodontal diseases and caries shows the prevalence of these both having microbial components. Host microbiota has important role in the individual's health. The theory from Nobel laureate Ilya Metchnikoff says "we fight microbe with microbe" and has attracted numerous followers [Dore et al. 2015].

Mechanisms of probiotic influences in the oral cavity

The mechanisms by which probiotics exert their effects are largely unknown, but may involve modifying gut pH, antagonizing pathogens through the production of antimicrobial compounds, competing for pathogen binding and receptor sites as well as for available nutrients and growth factors, stimulating immunomodulatory cells, and producing lactase. Probiotic bacteria have been shown to influence the immune system through several molecular mechanisms (Bhushan and Chachra, 2010)

1. Adherence and colonization of the gut (Bonifait et al. 2009)
2. Suppression of growth or epithelial binding/invasion by pathogenic bacteria and production of antimicrobial substances (Sharma et al. 2012)
3. Improvement of intestinal barrier function (Chopra and Mathur, 2013)
4. Controlled transfer of dietary antigens
5. Stimulation of mucosal and systemic host immunity (Stamatova and Meurman, 2009).

Probiotics can help prevent and treat oral diseases through several mechanisms that includes

1. Direct interaction – causing enmeshing in securing of oral microorganism to proteins, inhibition of pathogen adhesion, colonization and biofilm formation, induction of cyto-protective proteins expression on host cell surfaces, inhibition of collagenases.
2. Competitive exclusion – agility on plaque evolution and on its complex ecosystem by competing and intervening with bacterial attachments and engaging in metabolism of substrate and yielding of chemicals like organic acids, hydrogen peroxide and bacteriocins that inhibit oral bacteria.
3. Indirect actions – modulating systemic immune function, effect on local immunity, eventuality on non-immunologic defense mechanisms, modulation of cell proliferation and cytokine induced apoptosis, regulation of mucosal permeability, as antioxidants and hamper plaque

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induction by neutralizing the free electrons (Pandya, 2016)

Probiotics and dental 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.

Streptococcus mutans is the main causative organism in caries development due to its ability to produce highly branched, water-insoluble glucan, mutan (Krzysciak et al. 2014). This mutan producing 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.

To have a beneficial effect in limiting or preventing dental caries, a probiotic must be able to adhere to dental surfaces and integrate into the bacterial communities making up the dental biofilm. It must also compete with and antagonize the cariogenic bacteria and thus prevent their proliferation. Finally, metabolism of food-grade sugars by the probiotic should result in low acid production. The advantage of incorporating probiotics into dairy products lies in their capacity to neutralize acidic conditions.

Jeong et al. 2018 reported a novel isolate, *L. kefiranofaciens* DD2, from kefir which effectively inhibits *S. mutans* and *S. sobrinusin* an *invitro* 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 Pique et al. 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.

In a study by Lin et al. 2017 reported that four probiotic strains of *Lactobacilli* (*L. casei* Shirota, *L. casei* LC01, *L. plantarum* ST-III and *L. paracasei* LPC37) displayed strong inhibitory effects on *Streptococcus mutans*, isolated from children with active caries, with the inhibition rate reaching 70–90%. These probiotic strains also significantly reduced the numbers of *Streptococcus mutans*, *S. sanguinis* and other bacteria in mixed biofilms compared with the control group. Tehrani et al. 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. 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. Caglar et al. 2008 reported significant reduction in S. mutans count in young adults who consumed ice-cream containing *Bifidobacterium animalis* subsp.lactis (BB12) strain.

Probiotics and periodontal disease

Periodontal diseases include gingivitis and periodontitis. They are manifested by bleeding on probing, swelling, color alterations, pain, and tooth mobility in advanced stages. Scaling and root planning and deep pocket debridement are usual treatments (Dore et al. 2015). Periodontal pathogens could be regulated by means of antagonistic interactions. The main pathogenic agents associated with periodontitis are *P. gingivalis, Treponema denticola, Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans*. These bacteria have a variety of virulent characteristics allowing them to colonize the sub-gingival sites, escape the host's defence system and cause tissue damage.

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The persistence of the host's immune response also constitutes a determining factor in progression of the disease.

Studies have proved that the prevalence of lactobacilli, particularly *Lactobacillus gasseri* and *L. fermentum*, in the oral cavity was greater among healthy participants than among patients with chronic periodontitis. Various studies have reported the capacity of lactobacilli to inhibit the growth of periodontopathogens, including *P. gingivalis, Prevotella intermedia* and *A. actinomycetemcomitans*. Together, these observations suggest that lactobacilli residing in the oral cavity could play a role in the oral ecological balance (Bonifait et al. 2012; Gupta, 2011)

The first studies of the use of probiotics for enhancing oral health were for the treatment of periodontal inflammation (Kragen, 1954). Patients with various periodontal diseases, gingivitis, periodontitis, and pregnancy gingivitis, were locally treated with a culture supernatant of a L. ACIDOPHILUS strain. Significant recovery was reported for almost every patient. There has been significant interest in using probiotics in treatment of periodontal disease recently, too. The probiotic strains used in these studies include *L. Reuteri* strains, *L. brevis* (cd2), *L. casei* shirota, *L. salivarius* wb21, and *Bacillus subtilis*. *L. reuteri* and *L. brevis* have improved gingival health, as measured by decreased gum bleedin (Krasse et al. 2006; Della Riccia et al. 2007; Twetman et al. 2009)

The use of probiotic chewing gum containing L. reuteri ATCC 55730 and ATCC PTA 5289 also decreased levels of pro-inflammatory cytokines in GCF (Twetman et al. 2009) and the use of *L. brevis* decreased MMP (collagenase) activity and other inflammatory markers in saliva (Della Riccia et al. 2007). *B. subtilis* seemed to reduce the number of periodontal pathogens (Tsubura et al. 2009). Use of tablets containing *L. salivarius* WB21 has been shown to decrease gingival pocket depth, particularly in high-risk groups such as smokers, and also affect the number of periodontopathogens in plaque (Shimauchi et al. 2008; Mayanagi et al. 2009).

Probiotics and oral candida infections

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 et al. 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*. 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.

In another study, colonization of *C. albicans* on oral mucosa was significantly decreased by probiotic bacterial L. acidophilus and *L. rhamnosus* (Matsubara et al. 2012). In an in vivo study, Jorgensen et al. (2017) showed L. reuteri

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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.

Probiotics and 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 et al. 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 (H2S) and Methanethiol (2CH3SH) 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 et al. 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 et al. 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.

Conclusion

The interest in oral probiotics has been growing during the last decades. Most of the studies have been conducted with probiotic strains originally suggested for gut health; however, it is important to realize that each of the suggested health benefits should be studied for each bacterial strain individually. 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. 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.

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Subject: Microbiology

Quick Response Code

DOI: 10.22192/ijcrcps.2021.08.10.004

How to cite this article:

S. Savitha, N. Yogananth and T. Sivakumar. (2021). A review on Role of Probiotics Microorganisms in Oral health. Int. J. Curr. Res. Chem. Pharm. Sci. 8(10): 37-43.

DOI: http://dx.doi.org/10.22192/ijcrcps.2021.08.10.004

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