Probiotics: Contributions to Oral and Dental Health

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Abstract

Probiotics have been extensively researched for their beneficial health promoting effects. Previously, the mainstream of research was limited to the gastrointestinal flora, but in the past few years it has been more focused towards the oral and dental health perspectives. Few randomized controlled trials have been conducted in this area, though the investigations on probiotics versus oral and dental health are still in their cradle. The aim of this review is to assess the potential mechanisms of probiotic bacteria in the oral cavity and summarize observed effects of probiotics with respect to oral and dental health. The review focuses on probiotic *lactobacilli* and *bifidobacteria*, genera that are most widely used in various probiotic supplements. It also discusses the potential of probiotic strains in oral cavity colonization, interspecies interactions, and possible effects on host immunomodulation.

Key Words: Probiotics, Oral health, Lactobacillus, Bifidobacterium, Candida

Introduction

According to the generally accepted definition, a probiotic' is a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance' [1]. WHO [2] describes probiotics as "live microorganisms which, when administered in adequate amounts in food or as dietary supplement confer a health benefit on the host". This term has been derived from the Greek language which means "for life". The term Probiotic, as an antonym to the term antibiotic, was first used by Lilly and Stillwell [3] in 1965 to describe substances secreted by one microorganism which stimulates the growth of another. The concept of probiotics was brought forward in the first decade of 1900 by a Ukrainian bacteriologist and Nobel Laureate Elie Metchnikoff [4] who observed that bacteria in the fermented milk competed with the microorganisms that are injurious to health. While studying the flora of the human intestine, he developed a concept that senility is caused by poisoning of the body by the products of some of the harmful bacterias of the gut. He proposed a diet containing fermented milk products rich in live lactic acid bacteria to neutralize deleterious effects of these gut organisms. He credited these fermented products for extending the longevity of some populations of Bulgaria, Turkey and Armenia. He discovered *Lactobacillus bulgaricus* and claimed that cholera could be controlled by the presence of antagonistic organisms in the intestine.

Fuller [5] described probiotics as a live microbial food supplement, which beneficially affects the host animal by improving its microbial balance. Tanboga and colleagues [6] credited Hull and colleagues and Holcombh and colleagues for introducing *Lactobacillus* acidophilus and *Bifidobacterium bifidum* respectively, into research work as the first probiotic species.

Probiotic Strains in the Oral Cavity

Probiotics can be bacteria, molds, or yeast. But the majority of probiotics are bacteria. The most common probiotic strains belong to the genera *Lactobacillus* and *Bifidobacterium*, the former one being more popular [7]. *Lactobacillus* species from which probiotic strains have been isolated include *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus lactis*, *Lactobacillus helviticus*, *Lactobacillus salivarius*, *Lactobacillus plantrum*, *Lactobacillus bulgaricus*, *Lactobacillus rhamnosus*, *Lactobacillus johnsonii*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, *Lactobacillus del-brueckii*. *Bifidobacterium* strains include *Bifidobacterium bifidum*, *Bifidobacterium longum*, and *Bifidobacterium infantis*. Other strains include *Streptococcus thermophilus*, *Enterococcus faecium*, *Enterococcus faecalis*, and *Saccharomyces boulardii*. A probiotic may be made out of a single bacterial strain or it may be a consortium as well. Probiotics can be in powder form, liquid form, gel, paste, granules or available in the form of capsules, sachets, etc [8].

An essential property of a microorganism to be 'an oral probiotic' is its ability to adhere and to and colonize surfaces in the mouth. Probiotic microorganisms may not have oral cavity as their inherent habitat, hence their role to confer benefit on oral health remains questionable. Paster et al. [9] used culture-independent molecular methods to determine bacterial diversity in human subgingival plaque and estimated around 500-600 total species diversity in the oral cavity. Kazor et al. [10] detected 200 additional unknown species on the tongue dorsa of patients with halitosis and healthy patients. This made the number of species in the mouth to reach 700. Marsh and Martin [11] reported that *Lactobacilli* genera constitute approximately 1% of the cultivable oral microflora. Teanpaisan and Dahlen [12] implemented polymerase chain reaction techniques to differentiate oral *Lactobacillus* species from saliva and recovered the most common species like *L. fermentum*, *L. rhamnosus*, *L. salivarius*, *L. casei*, *L. acidophilus*, and *L. plantarum*. Similar observation was reported by Colloca et al. [13] regarding diversity in the oral *lactobacilli* flora in healthy human mouth. Ko˜ ll-Klais et al. [14] detected no differences in salivary counts between chronic periodontitis and healthy mouths. They also found *L. gasseri* and *L. fermentum* being the predominant lactobacilli species among other isolates. After one year, the same workers [15] observed a higher prevalence of homofermentative *lactobacilli* in healthy mouths compared to mouths affected with chronic periodontitis. These research work suggests that *lactobacilli* as members of resident oral microflora could play a vital role in the microecological balance in the mouth. The probiotic *lactobacilli* strains found were due to frequent consumption of dairy products or if mouth is their permanent habitat is questionable. Long-term

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follow-up studies to support this evidence are not available. The different bacterial strains considered probiotics in the oral cavity are demonstrated in *Table 1*.

Table 1. Bacterial test strains considered probiotics in the oral cavity. (HA-hydroxyapatite, VSC- volatile sulphur compounds, GCF- gingival crevicular fluid).

Workers	Bacterial strain	Result
Meurman et al. [21]	*Lactobacillus* GG (ATCC 53103)	Inhibited growth of *S. mutans* and *S. sobrinus*
Busscher et al. [24]	*Lactobacillus rhamnosus* GG *Lactobacillus casei*	Inhibited growth of *S. mutans*
Nase et al. [22]	*Lactobacillus rhamnosus* GG	Reduced salivary counts of *S. mutans*
Comelli et al. [34]	*Streptococcus thermophiles,* *Lactobacillus lactis*	Integrated into biofilm present on HA surface and interfered with growth of *S. sobrinus*
Ahola et al. [23]	*Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* LC 705	Reduction in the number of *S. mutans* in the saliva and a reduction in dental plaque
Nikawa et al. [36]	*Lactobacillus reuteri*	Reduced salivary counts of *S. mutans* up to 80%
Caglar et al. [26]	*Bifidobacterium* DN- 173 010	Inhibited growth of *S. mutans*
Elahi et al. [57]	*Lactobacillus acidophilus*	Rapid decline in *C. albicans* in mice
Caglar et al. [25]	*Lactobacillus reuteri* ATCC 55739	Reduced salivary levels of *S. mutans*
Burton et al. [81]	*Streptococcus salivarius* K12	Reduced levels of VSC
Kang et al. [75]	*Weissella cibaria*	Inhibited biofilm formation by *S. mutans* and prevented their proliferation
Caglar et al. [33]	*Bifidobacterium lactis* Bb-12	Reduced salivary levels of *S. mutans*
Petty et al. [31]	*Streptococcus thermophiles*, *Lactobacillus bulgaricus*	Selective bactericidal action on *S. mutans*
Stamatova and Meurman [32]	*Lactobacillus casei* ATCC 11578	Inhibited S. mutans adhesion to saliva coated HA
Twetman et al. [43]	*Lactobacillus reuteri* ATCC55730 *Lactobacillus reuteri* ATCCPTA5289	Reduced levels of pro-inflammatory cytokines TNF-α and IL-8 in GCF
Cildir et al. [42]	*Bifidobacterium animalis* N 173010	Reduced salivary counts of *S. mutans*
Haukiojo [44]	*Lactobacillus salivarius* WB21	Reduced levels of *P. gingivalis* and Prevotella intermedia in subgingival plaque
Rebolledo et al. [41]	*Lactobacillus rhamnosus*, *Lactobacillus johnsonii*	Reduced colonization of *S. mutans*
Messora et al. [47]	*Bacillus subtilis*	Reduction in attachment loss and alveolar bone loss
Teughels et al. [48]	*Lactobacillus reuteri*	Reduced levels of *P. gingivalis* and reduction in pocket depth
Ritthagol et al. [39]	*Lactobacillus paracasei* SD1	Reduced salivary counts of *S. mutans*

Probiotics: Mechanism of Action

One of the proposed mechanisms of probiotics is that these strains act by inhibiting the pathogenic microorganisms by competing for the limited substrates required for fermentation or the receptors. Some researchers [16,17] have shown that the probiotic strains prevent the adherence of the pathogenic bacteria to the host cell by strengthening the barrier effect of the intestinal mucosa. Also, there is release of certain gut-protective metabolites such as arginine, glutamine, short-chain fatty acids and conjugated linoleic acids. Probitics work like an antimicrobial agent by secreting the certain products like bacteriocins, hydrogen peroxide (H_2O_2) and organic acids such as lactic, acetic and butyric acid [18]. Probiotics containing *L. rhamnosus* GG also lower the intestinal pH [18]. Authors [19-21] have observed the other possible mechanism of probiotic strains, where *L. rhamnosus* GG have been found to agglutinates pathogenic bacterias, binds and metabolize toxic metabolites. Adjoined with this, these strains have shown their capacity to regulate the intestinal motility and mucus secretion [22-24].

Considerable evidence has obtained from the various animal studies regarding modulation of mucosal and systemic immune systems of the host by probiotic strains [25,26]. Kaila and colleagues [25] have shown an increased IgA specific antibody cell response to rotavirus in 39 children with acute rotavirus diarrhea, after administering milk product containing *L. casei* GG. Link-Amster and colleagues [26] have reported a significant rise in specific serum IgA titre in patients supplemented with *L. acidophilus*, *B. bifidum* Bb12 and *S.*

thermophilus during when they injected attenuated *Salmonella typhi* Ty21a vaccine.

Probiotics act on dental plaque formation, its complex ecosystem and are involved in binding of oral microorganisms to proteins. They stimulate macrophages, produce cytokines, escalate natural killer cell and raise the levels of immunoglobulins [27]. The increase in the number of Immunoglobulin A producing cells is the most remarkable property induced by probiotic organisms and also by fermented milk yogurt [28]. Other mechanism may include mucin production, down regulation of inflammatory responses [29], defensin production, inhibit pathogen induced production of pro-inflammatory cytokines, inhibiting collagenases, decreasing Matrix Metalloproteinase (MMP) production, induction of expression of cytoprotective proteins on host cell surfaces, etc. Since mouth represents the first part of the gastrointestinal tract, at least some probiotic mechanisms may also play a role in this part of the system and also they can be introduced here at much higher concentration with minimum loss in number [2,28,30]. Probiotics inhibit pathogens but do not inhibit friendly bacteria. Studies have shown that once the pathogenic organisms are replaced the reintroduction of the pathogen does not occurs easily [31].

Probiotics for Oral and Dental Health

Probiotics and dental caries

Dental caries is a multifactorial disease of bacterial origin that is characterized by acid demineralization of the tooth enamel [32]. The role of oral administration of probiotics on dental caries has been studied in several research experiments using different test strains of probiotic bacteria. Several researchers [31,33-36] have proved the potential of these probiotic strains (*L. rhamnosus* GG and *L. casei*) to hamper growth of oral streptococci. Ahola and colleagues [35] evaluated the effect of a short-term consumption of probiotic-containing cheese on dental caries and found reduction in the incidence of caries in children. Inclusion of *L. rhamnosus* GG and *L. rhamnosus* LC 705 in milk or processed cheese lowered the salivary counts of *S. mutans*. Caglar and colleagues [37] observed a definite *S. mutans* count reduction after a 2-week consumption of yogurt containing the probiotic bacterium *L. reuteri*. This indicated the necessity of continual administration of the probiotic in order to achieve its effect. Similarly, the relationship between probiotic *bifidobacterium* and counts of *S. mutans* was tested by Caglar and colleagues [3,38]. They observed a statistically significant reduction in salivary mutans. However, further investigations are needed for concluding the relation between *S. mutans* and *bifidobacterium* strains.

Anderson and Shi [39] suggested that the operative approach in caries management might be challenged by probiotic implementation with subsequent less invasive intervention in clinical dentistry. Future studies are required before this goal could be achieved. Majority of studies describing the correlation between probiotic strains and *streptococci* pathogens do not fulfil the criteria of investigations for evidence-based medicine.

Bonifait and colleagues [40] discussed the role of probiotics in prevention of dental caries. They believed that a probiotic must adhere to dental surfaces and integrate into bacteria that make up the dental biofilm, compete with and antagonize cariogenic bacteria to prevent their proliferation, and produce little acid in the metabolism of food-grade sugars. Two bacteriocins (reuterin and reutericyclin) secreted by *L. reuteri* found inhibiting the growth of a wide variety of pathogenic bacterias. This *lactobacilli* strain has strong capacity to adhere to host tissues and has inflammatory effects.

Probiotic *L. reuteri* in various forms like chewing gum [41], tablets [37], lozenge [42], or as administered in yogurt [43] has been observed to decrease *S. mutans* level in saliva. Some workers [38,44] have shown a significant growth inhibition of *S. mutans* when yogurt with *Bifidobacterium* DN-173 010 was administered in young adults. Stamatova and Meurman [44] have shown that *L. casei* ATCC 11578 affect the adherence of the *streptococci* to saliva coated hydroxyapatite (HA), by slightly inhibiting the adherence of S. mutans and it could even release the already bound *streptococci* from the HA. Caglar and colleagues [45] demonstrated a significant reduction of *S. mutans* when ice-cream containing *Bifidobacterium lactis* Bb-12 was administered. Comelli and colleagues [46] evaluated the effects of 23 lactic strains used as probiotics in oral cavity and showed that *S. thermophilus* and *L. lactis* were the only species which integrated into a biofilm present on a HA surface and interfered with the development of the cariogenic species *S. sobrinus*. However; Kang and colleagues [47] demonstrated that isolates of *W. cibaria* possessed the capacity to inhibit, both in vitro and in vivo, biofilm formation by *S. mutans* and to prevent proliferation of this bacterial strain. Petti and colleagues [43] noticed that yogourt containing *S. thermophilus* and *L. bulgaricus* had selective bactericidal effects on *S. mutans* bacterial strain. Nase and colleagues [34] conducted a long-term (7 months) study in 594 children of 1 to 6 years of age who were given a regular supplement of milk containing *L. rhamnosus* GG. They evaluated the effects of this regular consumption on dental caries and caries risk in children and concluded that children those 3-4 years of age had significantly fewer dental caries and lower salivary counts of *S. mutans*. Nikawa and colleagues [48] showed that a regular consumption of yogourt supplemented with *L. reuteri* over a period of 2 weeks decreased the concentration of *S. mutans* in the saliva by up to 80%.

Bhushan and Chachra [49] showed that *Lactobacillus* strains like *L. paracasei* and *L. plantarum* also interfere with *S. mutans*. These strains hydrolyze urea to ammonia with the help of their urease enzymes. This activity influences plaque biochemistry and metabolism which reduces cariogenicity, thus indicating the usefulness of ureolytic bacteria in promoting dental health [49]. These species reside in dental plaque and the ammonia released from salivary and dietary substrates prevent the colonization of cariogenic pathogens. This action also ensures internal pH homeostasis. Reddy and colleagues [2] believed that the presence of this effector strain in indigenous flora would keep the host protected. The first toothpaste (Plidenta Pro-t-action) in the world which contained *L. paracasei* probiotic was found to co-aggregates *S. mutans* and reduces caries activity in the oral cavity [50]. Jose and colleagues [31] evaluated the effect of systemic consumption of probiotic curd and use of probiotic toothpaste

on the count of *S. mutans* in plaque around orthodontic brackets. They agreed that *lactobacillus*, *streptococci* and *bifidobacterium* species are genetically designed to have greater adhesion and hence competitively inhibit *S. mutans*.

Ritthagol and coworkers [51] carried a double-blinded, randomized, placebo-controlled study to evaluate the effect of probiotic milk powder containing *L. paracasei* SD1 on the count of *S. mutans* in the mouth of the orthodontically treated cleft lip and palate patients. They found that this probiotic strain reduces *S. mutans* count and also able to colonize the oral cavity in those patients. They reported that it could be detected up to 4 weeks following cessation of dosing. Some workers [2,52] discussed the role of genetically modified probiotics which possessed enhanced properties. *S. mutans* BCS3-L1 was such modified strain which was designed to prevent dental caries. Recombinant DNA technology deleted the gene encoding lactate dehydrogenase in BCS3-L1 which made it unable to produce lactic acid. This strain was designed to produce elevated amounts of a novel peptide antibiotic (mutacin 1140) that offers it a strong selective benefit over other *S. mutans* strains. A designer probiotic *Lactobacillus* strain expressed antibodies targeting one of the major adhesions of *S. mutans* and was able to decrease both the viable counts of *S. mutans* and the caries score in a rat model [49]. A probiotic mouthwash (ProBiora3) containing low acid-producing *S. rattus* JH145, *S. oralis* KJ3, and *S. uberis* KJ2 was found to inhibit the growth of pathogenic *streptococci* strains. Rebolledo and colleagues [53] evaluated the effect of *L. rhamnosus* and *L. johnsonii* containing probiotics on the growth of *S. mutans* and found that it decreased the colonization of *S. mutans*. They suggested that these probiotics could be used in the prevention and prophylaxis in high risk cariogenic patients.

Fixed orthodontic appliances in the mouth can permit microorganisms to accumulate, grow and proliferate, leading enamel demineralization. Short-term intake of fruit yogurt containing *bifidobacteria* has shown to alter the levels of *S. mutans* and *lactobacilli* in patients with orthodontic fixed appliances. Cildir and colleagues [54] showed in experimental studies that 200 g once daily fruit yogurt containing *B. animalis* N 173010 significantly reduced *S. mutans* counts in two weeks. *Lactobacilli* count was not altered. Jose and colleagues [31] showed that the consumption of probiotic curd (Active plus) and the topical application of probiotic toothpaste (GD) caused significant decrease in the *S. mutans* levels in the plaque around orthodontic brackets.

Probiotics and periodontal disease

Periodontal disease is classified into 2 types: gingivitis and periodontitis. Gingivitis is characterized by inflammation limited to the unattached gingival, whereas periodontitis is a progressive, destructive disease that affects all supporting tissues of the teeth, including the alveolar bone [55]. The main pathogenic bacterias causing periodontitis includes P. gingivalis, Treponema denticola, Tannerella forsythia and Aggregatibacter actinomycetemcomitans [55]. These pathogens possess a variety of virulent characteristics allowing them to colonize the subgingival areas, escape the host's defence mechanism system and cause tissue damage [55]. The persistence of the host's immune response also determines the progression of the disease [55].

Koll-Klais and colleagues [14] observed a greater prevalence of *lactobacilli* (*L. gasseri* and *L. fermentum*) in the mouth of healthy individuals than those affected with chronic periodontitis. Krasse and colleagues [56] evaluated the effects of *L. reuteri* supplemented probiotics in individuals affected with moderate to severe form of gingivitis. They observed a reduction in plaque index in those patients after 14 days of ingestion of probiotics incorporated into chewing gum. Riccia and colleagues [57] studied the anti-inflammatory effects of *L. brevis* CD2 in a group of patients with chronic periodontitis. After administration of probiotic containing *L. brevis* in the form of lozenges, a reduction in plaque index, gingival index and bleeding on probing was observed in all those patients. The authors noted a significant reduction in salivary levels of prostaglandin E_2 (PGE_2) and matrix metalloproteinases (MMPs) and suggested that this effect of L. brevis could be attributed to its capacity to prevent the production of nitric oxide. This led to the release of PGE_2 and the activation of MMPs to impart beneficial anti-inflammatory effects [57]. Shimazaki and colleagues [58] conducted an epidemiological study to assess the relationship between the consumption of dairy products and periodontal disease. The researchers observed that individuals, particularly non-smokers, who regularly consumed yogurt or beverages containing lactic acid, showed lower probing depths and less loss of clinical attachment than individuals who consumed few dairy products [58]. However, authors couldn't notice the similar beneficial results when the dairy products like milk or cheese was consumed. Various researches [14,59] have revealed the capacity of lactobacilli to inhibit the growth of pathogenic bacterias causing periodontitis like P. gingivalis, Prevotella intermedia and A. actinomycetemcomitans, thus suggesting their role in maintaining the oral ecological balance. Twetman and colleagues [59] performed a short-term study where they tested an effect of chewing gums containing probiotic *L. reuteri* ATCC55730 and ATCCPTA5289 on the levels of inflammatory mediators in gingival crevicular fluid (GCF). They noted a drastic decrease in the levels of pro-inflammatory cytokines TNF-α and IL-8 in GCF. Reddy and colleagues [2] reported that inclusion of probiotic strains in periodontal dressings at optimal concentration of 108CFU/ml reduced the number of most frequently isolated periodontal pathogens which included *Bacteroides sp.*, *Actinomyces sp.*, and *S. intermedius*, and also *C. albicans*. It was also observed that inhabitant *lactobacilli* inhibit *P. gingivalis* and *Prevotella intermedia*. Haukioja [60] showed that tablets containing *L. salivarius* WB21 reduced pathogens in subgingival plaque and decreased pocket probing depth and plaque index in individuals with high risk of periodontal disease such as smokers. Some workers [61,62] observed a significant suppression of the recolonization of *P. gulae* and *P. intermedia* after a subgingival application of *S. sanguinis*, *S. salivarius*, and *S. mitis* in a beagle dog model, following scaling and root planning. Dave and colleagues [30] claimed that Acilact (a probiotic complex of five live lyophilized lactic acid bacteria) improve both clinical and microbiologic parameters in gingivitis and mild periodontitis patients. *L. brewis* probiotics reflected their anti-inflammatory effects in chronic periodontitis conditions. This species when delivered

through lozenges found to improve plaque index, gingival index, and bleeding on probing. The anti-inflammatory effects of these strains are due to their capacity to prevent production of nitric oxide and consequently the release of Prostaglandin E2 and activation of MMPs induced by nitric oxide. Other *lactobacillus* strains like *L. helveticus* produces short peptides that act on osteoblastic cell and increase their activity in bone formation. This effect reduces bone resorption associated with periodontitis. Bonifait and colleagues [40] reported lower probing depths and less loss of clinical attachment in individuals who consume regular yogurt or beverages containing lactic acid compared to those who consume few of these products. Mallikarjuna and colleagues [50] observed a greater prevalence of *L. gasseri* and *L. fermentum* among healthy patients than those patients with chronic periodontitis. Messora and colleagues [63] evaluate the effects of probiotic *Bacillus subtilis* in rats with ligature induced periodontitis (LIP) and found reduction in attachment loss and alveolar bone loss. It was also identified that it protected the small intestine from reactive changes induced by LIP, thus improving the intestinal morphology. Teughels and colleagues [64] conducted a randomized placebo-controlled study in patients with chronic periodontitis and observed that *L. reuteri* containing probiotic lozenges caused significant pocket depth reduction, attachment gain in moderate and deep pockets and reduction in *P. gingivalis*. Probiotics decrease pH and don't allow plaque bacteria to form dental plaque and calculus which are the causative factors for periodontal disease. It also forms antioxidants which neutralizes the free electrons needed for the mineral formation, thus prevents plaque formation.

Probiotics and halitosis

According to Scully and Greenman [65], halitosis or bad breath results from various causes like consumption of particular foods, metabolic disorders, respiratory tract inspections, etc., but mostly it is associated with an imbalance of the oral microflora. Some gram negative anaerobic bacteria residing in periodontal pockets and on the dorsal surface of tongue degrade salivary and food proteins to produce amino acids, which are further converted into volatile sulphur compounds (VSC) like hydrogen sulphide and methanethiol [44,65]. Probiotics breaks these putrescence odors by fixating on the toxic gases/ VSCs and converts them into gases required for metabolism. In vitro and in vivo studies revealed that the production of VSC by *Fusobacterium nucleatum* was inhibited after the ingestion of *W. cibaria* [66]. A marked reduction in the levels of hydrogen sulfide and methanethiol was detected after gargling with *W. ciberia* containing mouth rinse. It was seen that hydrogen peroxide and bacteriocins produced by *W. ciberia* was responsible for causing inhibition of *F. nucleatum* growth [66].

Kazor and colleagues [10] found the predominance of *Atopobium parvulum*, *Eubacterium sulci* and *Solobacterium moorei* on the dorsal surface of the tongue among individuals with halitosis. The authors also observed *S. salivarius* most frequently among healthy individuals without halitosis and considered these species as a commensal probiotic of the oral cavity [10]. *S. salivarius* produces a bacteriocin known as salivaricin, has been found to reduce the number of microflora producing VSC including hydrogen sulfide, methyl mercaptan and dimethyl sulfide [67]. Chewing gum or lozenges containing *S. salivarius* K12 reduces levels of VSC by inhibiting gram positive bacterias in patients with halitosis [68,69]. *S. salivarius* K12 secrete bacteriocin like inhibitory substances (BLIS) which acts as powerful antimicrobial molecules which boosts immune system of the host [68,69]. It also decreased *S. mutans* count in saliva of orthodontic adolescents and long term ingestion prevented sore throat in childrens. Researchers [70-74] found that *W. confusa* isolates and bacteria forming lactic acid also appear to decrease halitosis.

Probiotics and oral candidiasis

Candida albicans is among the most common infectious organisms in the oral cavity. The elderly individuals are vulnerable to Candida infection, which is frequently provoked by chronic diseases, medication, poor oral hygiene, reduced salivary flow, or the impairment of the immune system [72]. *Candida* colonization may be asymptomatic, but heavy growth usually causes local candidiasis which may display various types of mucosal lesions and symptoms [72]. This makes to control the proliferation of yeast. Probiotic *L. rhamnosus* GG has been observed to modify human gut microbial balance by reducing the proliferation of *C. albicans* [73,74]. Wagner and colleagues [75] tested the biotherapeutic effects of probiotic *L*. GG on candidiasis in immuno-deficient mice and observed a drastic reduction in *Candida* counts in the alimentary tract. Manzoni and colleagues [76] conducted a randomized study in preterm neonates and found that oral supplementation of *L. rhamnosus* GG reduced the enteric colonization of *candida*, as measured by colonies isolated from oro-pharyngeal, gastric aspirate, stool, and fecal specimens. Some species of *lactobacilli* possess the ability to adhere the mucosal epithelium competing for adhesion sites with *candida* [76]. These species produce hydrogen peroxide and antifungal cyclic dipeptides, which inhibit the in vitro growth of *candida* [76,77].

C. albicansL. acidophiluslactobacillicandidalactobacilliL. plantarumL. reuteriC. albicansC. albicans

Administration of probiotics

Several literatures have discussed the appropriate forms of administration of probiotic strains for oral and dental health purposes *(Table 2)*. Dairy products supplemented with probiotics are a natural means of oral administration and easily adopted in dietary regime. However, for the purposes of prevention or treatment of oral diseases, specifically targeted applications, formulas, devices, or carriers with slow release of probiotics might be needed. Montalto and colleagues [81] performed a double-blind, randomized, controlled study in 35 healthy volunteers, in which they administered probiotic mix both in capsules and in liquid form for 45 days and found that this means of administration increases salivary counts of *lactobacilli*. Caglar and colleagues [37] designed a special straw with a reservoir containing probiotics for comparing the effect of two non-dairy delivery methods. They used a Life top straw (BioGaia AB, Stockholm, Sweden) and a lozenge for delivering probiotics and checked the effectiveness of *L. reuteri* to reduce the number of *S. mutans*. Both means of administration showed significant reduction in salivary *S.*

mutans levels in half of the patients when compared with subjects who received placebo. A recent invention for dental caries prophylaxis is a chewing gum containing *L. reuteri Prodentis*. This gum was recommended to consume twice daily and was marketed to regulate *S. mutans* counts in the mouth. However, the most suitable means of delivery and dosages of probiotics for various oral health purposes have not been defined [82].

Table 2. Various mode/vehicle of probiotic administration for oral and dental health (VSC-volatile sulphur compounds, GCF- gingival crevicular fluid).

Workers	Bacterial strain	Mode/Vehicle	Result
Nase and colleagues [23]	*L. rhamnosus* GG	Milk	Reduced salivary counts of *S. mutans*
Nikawa and colleagues [37]	*L. reuteri*	Yogurt	Reduced salivary counts of *S. mutans* by up to 80%
Montalto and colleagues [70]	*L. sporogenes*, *L. bifidum*, *L. bulgaricus*, *L. thermophilus*, *L. acidophilus*, *L. casei*, *L. rhamnosus*	Capsule and Liquid	Increased salivary counts of lactobacilli without significant decrease in *S. mutans* counts
Kang and colleagues [55]	*W. cibaria*	Mouth rinse	Reduction of VSC
Caglar and colleagues [26]	*L. reuteri* ATCC 55739	Straw or Tablet	Reduced salivary counts of *S. mutans*
Krasse and colleagues [45]	*L. reuteri*	Chewing gum	Reduction in plaque index
Hatakka and Ahola [69]	*L. rhamnosus* GG, *Prorionibacterium* JS	Cheese	Reduced risk of high yeast counts and hyposalivation
Caglar and colleagues [30]	*L. reuteri*	Chewing gum	Reduced salivary counts of *S. mutans*
Riccia and colleagues [46]	*L. brevis* CD2	Lozenge	Reduction in plaque index, gingival index and bleeding on probing
Caglar and colleagues [31]	*L. reuteri*	Lozenge	Reduced salivary counts of *S. mutans*
Caglar and colleagues [34]	*B. lactis* Bb-12	Ice-cream	Reduced salivary counts of *S. mutans*
Petty and colleagues [32]	*S. thermophilus* and *L. bulgaricus*	Yogurt	Selective bactericidal effect on *S. mutans*
Twetman and colleagues [48]	*L. reuteri* ATCC55730 and ATCCPTA5289	Chewing gum	Reduced levels of pro-inflammatory cytokines TNF-α and IL-8 in GCF
Cildir and colleagues [43]	*B. animalis* N 173010	Fruit yogurt	Reduced salivary counts of *S. mutans*
Haukioja [49]	*L. salivarius* WB21	Tablet	Reduction in pocket probing depth and plaque index
Ritthagol and coworkers [40]	*L. paracasei* SD1	Milk powder	Reduced salivary counts of *S. mutans*

Probiotics: Safety measures

In the past few years, the tremendous probiotic supplementation of different food products led to discuss an important aspect of safety regarding its consumption. The putative probiotic strains should not be pathogenic, should not possess any growth-stimulating effects on bacteria causing diarrhea. They should not have an ability to transfer antibiotic resistance genes. The probiotics should be able to maintain genetic stability in oral microflora environment [83]. The increased consumption of probiotic containing supplements leads to increased concentrations of these strains in the host. Excessive consumption of probiotics containing *lactobacilli* strains may cause *lactobacillus* bacteremia, which is a rare entity. The data on the clinical significance of this entity are mainly found through case reports published in scientific journals. Boriello and colleagues [84] found the documentation of approximately 180 reported clinical cases in the last 30 years. Clinical features of *Lactobacillus* bacteremia shows great variations ranging from asymptomatic to septic shock-like symptoms. Any viable bacteria are capable enough to cause bacteremia in immuno-compromised patients or those who have severe underlying diseases. Husni and colleagues [85] and Cannon and colleagues [86] reviewed the pathogenic relevance of *Lactobacillus* and found that the affected patients were already registered with other systemic diseases such as diabetes, cardiovascular diseases, gastrointestinal disorders, malignancies, or organ transplant patients. This realized the need of careful monitoring in this issue in the future. Various authors carried research studies in immuno-compromised patients to check the relevance of *lactobacilli* strains. Wolf and colleagues [87] conducted a controlled study, in which 35 HIV-positive patients were exposed to *L. reuteri* strains and found no clinically significant side effects. Salminen and colleagues [88] observed no increase in *Lactobacilli* (*L. rhamnosus* GG) in blood culture samples when screening the Finnish population for the period of 1990-2000. Salminen and colleagues [89] again reported no adverse effects from *L. rhamnosus* GG ingestion in general or HIV-positive patients. In the participated HIV-positive patients, CD4 cell counts were analyzed and were given suitable and highly active antiretroviral therapy. LGG-containing probiotics are not likely to exert any major health associated risks among HIV-positive patients. Animal experiments have also proved an induction of mucosal and systemic immune responses rendering protection against pathogenic bacterias after inoculating *lactobacilli* species as antigens at mucosal sites

[90,91]. Grangette and colleagues [90] have shown that recombinant *L. plantarum* are capable of inducing mucosal immune response against tetanus toxin, delivered by an intranasal route. Similarly, Oliveira and colleagues [91] have demonstrated the induction of systemic and mucosal immune response and decrease in *S. pneumonie* colonization by nasal inoculation of mice with recombinant lactic acid bacteria expressing pneumococcal surface antigen.

The safety criterion which must be given a significant value is related to the absence of acquired antibiotic resistances in potential probiotic individuals. Probiotics may cause transferral of antimicrobial resistance genes in between microorganisms. Lester and colleagues [92] showed an in vivo transfer of the vanA resistance gene from an *Enterococcus faecium* isolate of animal origin to an *E. faecium* isolate of human origin in the intestines of human volunteers. Antibiotic susceptibility tests claimed that the genes in some probiotic strains are responsible for certain antibiotic resistances. Huys and colleagues [93] have searched the genetic basis of tetracycline and minocycline resistance in potentially probiotic *L. plantarum* CCUG 43738. Similar study was carried by Masco and coworkers [94], who agreed antimicrobial susceptibility of *Bifidobacterium* strains from humans, animals, and probiotic products. These experiments suggest the requirement of a minimal safety evaluation while selecting strains for probiotic preparation. Further studies are needed in this area as the resistance developed to most commonly recommended antibiotic drugs is of great global concern. Hence, before recommending any probiotic therapy, transferral of resistance genes needs to be carefully investigated.

Probiotics: Future aspects

The issue of safety is of utmost importance during the past few years due to the increased probiotic supplementation of different food products. Oral lactic acid bacteria and bifidobacteria have been isolated and experimented for various oral and dental health purposes, including dental caries, periodontitis, and halitosis [66,68,95-99]. Some workers [46,99] studied the various dairy strains with the aim of characterizing potential new oral probiotics. However, the new probiotic products targeted for oral health purposes do not necessarily comprise the same strains as products now available in market. Burton and colleagues [68] claimed that the species might not necessarily belong only to genera *Lactobacillus* or *Bifidobacterium* for which they carried a preliminary study of the effect of probiotic *S. salivarius* K12 on oral malodor parameters. Zahradnik and colleagues [100] assessed the safety and effectiveness of a probiotic mouthwash containing three different oral *streptococci* (ProBiora3) for reducing the number of pathogenic bacteria associated with dental caries and periodontal disease.

Genetically designed bacterias might open a new door to the concept of probiotics. The designed strain could be used to replace the original pathogenic strains that naturally colonize the oral cavity. Hillman and colleagues [101] attempted the modification of an effector strain for replacement therapy of dental caries. This resulted the generation of an *S. mutans* strain with a complete deletion of the open reading frame of lactate hydrogenase and thus significantly reduced cariogenicity. Marcotte and colleagues [102] suggested other option that could enhance the properties of a potentially beneficial strain and constructed the *L. paracasei* strain with a functional scVF (single-chain variable fragment) antibody against RgpA protease of *Porphyromonas gingivalis*. Though various strains of probiotic microflora were tested for their viability through culture tests, a significant proportion of bacteria are not yet cultivable. Sliepen and colleagues [103] discussed microbial interactions influence inflammatory host cell responses. They claimed that heat-killed beneficial oral *streptococcus* strains exert effects similar to those of a living bacterium. Lahtinen and colleagues [104] studied the degradation of 16S rRNA and attributes of viability of viable but non-culturable probiotic bacteria. They observed that the viable but non-culturable probiotic bacteria maintain properties of viable bacterias [104].

Conclusion

During last decades, a keen interest has been developed in the field of oral probiotic therapy. Several experiments have been carried on probiotic strains residing in the gastrointestinal microflora, however, it is important to evaluate each of the suggested health benefits should be researched for each individual bacterial strain. A probiotic bacterium in the oral cavity is not necessarily an oral probiotic. Same species of bacteria might not have beneficial effects for oral and dental health issues. Different desirable properties are expected in those strains in respect to oral and dental health purposes. Some of the probiotic strains used in various probiotic supplements may colonize the oral cavity during their consumption period; thereby it necessitates understanding the effects of probiotic strains in the oral cavity. Probiotics seem to affect both microbial flora and immune responses of the host. Additionally, it is difficult to predict the extent to which probiotic supplements can influence relatively stable microbial environment. Moreover, the risk of transferring antibiotic resistance from probiotics to virulent microorganisms cannot be ignored. Thus, experimental research work unraveling the mechanism of possible probiotic effects adjoined with long-term clinical trials is a need of time, so that benefits of probiotic therapy can be rendered to humans. Health-promoting effects of probiotics sare well documented in the literature; however, their recommendation for oral and dental health benefits is not yet justified.

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