A comprehensive review of the application of probiotics and postbiotics in oral health

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Oral diseases are among the most common diseases around the world that people usually suffer from during their lifetime. Tooth decay is a multifactorial disease, and the composition of oral microbiota is a critical factor in its development. Also, *Streptococcus mutans* is considered the most important caries-causing species. It is expected that probiotics, as they adjust the intestinal microbiota and reduce the number of pathogenic bacteria in the human intestine, can exert their health-giving effects, especially the anti-pathogenic effect, in the oral cavity, which is part of the human gastrointestinal tract. Therefore, numerous *in vitro* and *in vivo* studies have been conducted on the role of probiotics in the prevention of tooth decay. In this review, while investigating the effect of different strains of probiotics *Lactobacillus* and *Bifidobacteria* on oral diseases, including dental caries, candida yeast infections, periodontal diseases, and halitosis, we have also discussed postbiotics as novel non-living biological compounds derived from probiotics.

1 Introduction

The World Health Organization estimates that about half of people suffer from oral diseases. About 2.4 billion people have permanent teeth decay and, 532 million children are also affected by primary teeth decay (Collaborators et al., 2020). Oral health care is expensive, and in high-income countries, about 5% of the total health costs are spent on it. In other countries, the required costs are higher than the capacity (Collaborators et al., 2020). Tooth decay is a disease related to several different factors. Factors such as a cariogenic diet, poor oral health, high counts of cariogenic bacteria, dental plaque, inadequate saliva flow, and lack of sufficient fluoride exposure are among the environmental risk factors that cause tooth decay (Petersen, 2003; Selwitz et al., 2007; Laleman et al., 2014; Iheozor-Ejiofor et al., 2015; Laleman and Teughels, 2015). As a general fact confirmed by various studies, the composition of oral microbiota is closely associated

with oral health, and its disruption is an important step in oral disease (Zainab et al., 2016). *S. mutans*, one of the bacteria in the oral microflora, is known as the basic cause of dental decay and one of the biofilm-forming bacteria (Abd and Ali, 2016). Many clinical studies conducted on different people in the community have reported the correlation between *S. mutans* levels and caries (Loesche, 1986; Tanzer et al., 2001). It should be noted that the association between *S. mutans* levels and the occurrence of caries in people is different for various reasons, including genetic factors in the etiopathogenesis of tooth decay, and certain patients may be more vulnerable or resistant to caries (Werneck et al., 2010; Renuka et al., 2013). Although the intervention of various factors is effective in causing tooth decay, microbiological factors are the main factor. Therefore, it is believed that bacteriotherapy can be an effective way to prevent oral disease (Flichy Fernández et al., 2010; Laleman et al., 2014; Laleman and Teughels, 2015; Gruner et al., 2016). Since the oral cavity is the first part of the gastrointestinal system, it is logical that probiotics exert their effects on the oral and affect its microbiota just like the gut (Burton et al., 2013). probiotics are live microorganisms that, if consumed in enough amounts, are advantageous to host health (Walker and Buckley, 2006). *In vitro* studies have shown the advantageous effects of different strains of probiotics against oral pathogens (Dierksen et al., 2007; Haukioja et al., 2008; Hedberg et al., 2008; Twetman et al., 2009a; Lee et al., 2011; Lee and Kim, 2014; Han et al., 2019). *In vivo* studies have also mentioned the effects of probiotics in the prevention or cure of periodontal diseases and tooth decay. However, some trials have reported conflicting results (Gruner et al., 2016; Jayaram et al., 2016). The possible mechanisms of probiotics' action on oral health are the same mechanisms mentioned in gastrointestinal studies (Meurman, 2005) (Figure 1). Evidence suggests that part of the antimicrobial effects of probiotics is associated with the substances they produce, including bacteriocins, organic acids, fatty acids, and hydrogen peroxide (Miles, 2007; Cheng et al., 2021). Considering some of the challenges and limitations that exist for using probiotics in food products, the use of metabolites or their non-living components (postbiotics) can be a new and appropriate solution (Rad et al., 2021b). Among the challenges that are related to the use of probiotics and can be solved by postbiotics is the creation of clinical problems, especially in people with a weakened immune system (Sartor, 2016; Homayouni Rad et al., 2020b), the probability of transmission of resistance genes to pathogenic microorganisms and the emergence of antibiotic resistance (Mathur and Singh, 2005; Homayouni-Rad et al., 2020a), and the need for high costs to provide an ongoing cold chain from production to consumption (Sawada et al., 2016). Accordingly, in this review, while examining the effects of different strains of probiotics on oral and dental health, we will also look at the impact of postbiotics.

2 Microbiome and oral health

Microbes live in different parts of the body, and the ratio of the count of cells in the human body to the count of microbes is about 1:10 (Hillman et al., 2017). Advances in biological technologies have led to many studies to understand better the composition and impact of microbiota on human diseases (Gill et al., 2006). There are four main locales of microbial colonization in the body: the oral, intestines, skin, and vagina (Relman and Falkow, 2001); therefore, the oral cavity is one of the largest microbial sites, and the microbiome is stored on the teeth, tongue, soft and hard palates, gingival sulcus, and tonsils, and is an important factor in health and diseases related to the oral and teeth (Aas et al., 2005; Paster et al., 2006) (Figure 2). Using whole metagenome sequencing methods, it has been determined that bacteria such as *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Bacteroidetes*, and *Firmicutes* constitute about 80-95% of the total oral microbiome (Bik et al., 2010; Ahn et al., 2011). The most prevalent species identified in the oral cavity using different methods including *Actinomyces*, *Prevotella*, *Streptococcus*, *Fusobacterium*, *Leptotrichia*, *Veillonella*, *Rothia*, *Corynebacterium*, *Capnocytophaga*, *Selenomonas*, *Treponema*, *Haemophilus*, and TM7 Genes 1 and 5 (Liu et al., 2012). When oral homeostasis is disrupted, and the dominance of good bacteria is lost, the conditions for dysbiosis and the growth of a diverse population of pathogenic bacteria with parasitic lifestyles are created. Liu et al. (2012) showed that dysbiosis occurs before the clinical symptoms of periodontal disease are evident, so examining the balance of oral microbiota can help as a tool for the initial detection of periodontitis. Also, in disease conditions, oral bacterial diversity decreases, and fewer bacterial genera predominate. For
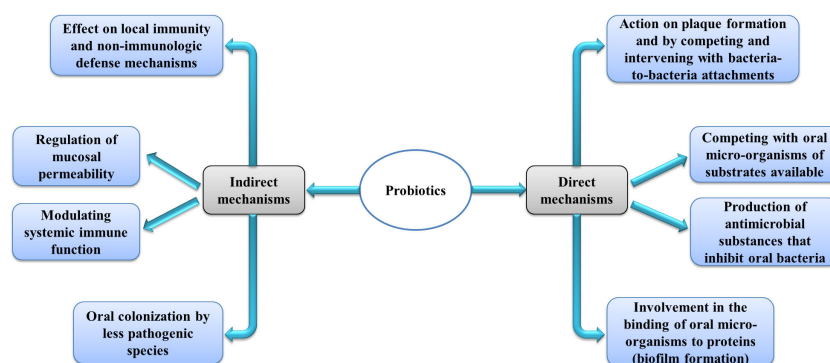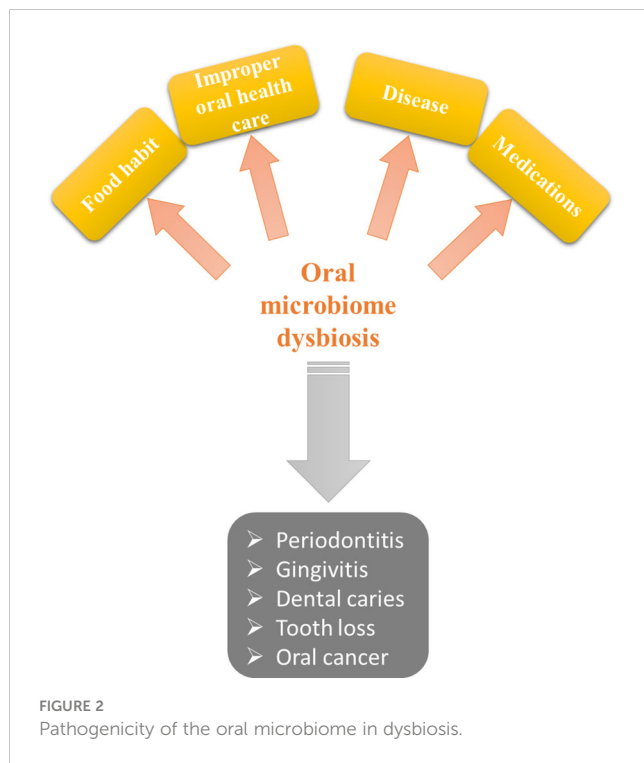

FIGURE 1
Possible mechanisms of probiotic in the oral cavity.

FIGURE 2
Pathogenicity of the oral microbiome in dysbiosis.

example, Gomar-Vercher et al. (2014), after collecting saliva samples from 12-year-old children, found that the two bacteria, *Porphyromonas* and *Provetella*, show an increasing percentage in children with caries compared to healthy people, and as the severity of the disease increases, bacterial diversity decreases. Two factors play a role in tooth decay: the immune system and diet. The oral microbiota creates an acidic environment on the teeth as a result of a frequent carbohydrate diet, and in this situation, acid-tolerant and acidogenic bacteria probably cause demineralization and cause tooth decay (Tanner et al., 2018). The study by Palmer et al. (2010) also showed that caries risk assessment often involves diet and bacteria and showed a correlation between the detection and abundance of *S. mutans* with the existence of caries. A study of 39 healthy and 51 caries people showed that the bacterial profiles of intact enamel in healthy people were significantly different from the bacterial profiles of intact enamel in sick people (Aas et al., 2008). Species like *Staphylococcus intermedius*, *Eubacterium saburreum* clone GT038, *Kingella oralis*, *Streptococcus cristatus*, and *Gemella morbillorum* were found at a high level in healthy people. They were at significantly decreased levels in the healthy enamel of diseased people in permanent teeth. Other health-related species in permanent teeth, like *Streptococcus* sp. group H6, *Streptococcus* sp. clone CH016, *Eubacterium* sp. clone EI074, *Campylobacter showae*, *Capnocytophaga sputigena*, *Leptotrichia* sp. clone DT031, and *Fusobacterium nucleatum* subsp. *polymorphum* were found at decreased levels in plaque from white spot or dentin lesions of diseased people compared to the levels detected in healthy people (Aas et al., 2008). On the other, *S. mutans*, *Streptococcus salivarius*, *Lactobacillus fermentum*, *L. gasseri*, *Prevotella* clone AO036, *Propionibacterium* FMA5, and *Atopobium genomospecies* C1 were found in the teeth of healthy subjects at low levels, while in dentin

cavities and deep-dentin cavities were found at high levels, so caries-associated species were considered (Aas et al., 2008). In The study by Johansson et al. (2016), a clear correlation was observed between the frequency of *S. mutans* and caries. In this study, Romanian teenagers with an average age of 14.4 and a history of minimal dental care were found to have abundant dental plaque and a mean decayed, missing filling surface (DMFS) score of 20.1. In contrast, Swedish teenagers with an average age of 17 and a mean DMFS of 7.5 had regular dental care and also had a minimum observable dental plaque. On top of having more caries experience, Romanian teenagers showed a higher abundance of *S. mutans* diagnoses than Swedish ones (85% compared to 50%). On the other hand, there is evidence of microbiotas associated with non-*mutans* caries and not identifying *S. mutans* in about 10-15% of people with active caries (Hardie et al., 1977; Boyar et al., 1989; Van Houte, 1994; Beighton, 2005; Aas et al., 2008). These data suggest that potential acid-producing species are involved in caries, some of which have not yet been cultivated (Fitzgerald and Keyes, 1960). For example, *Scardovia wiggsiae* was detected in about 40% of children with active caries who did not have *S. mutans* (Tanner et al., 2011). Therefore, this species may be one of the important factors of caries in the absence of *S. mutans*. In a study by Hughes et al. (2012), different parts of the microbiota were cultured in rich blood containing agar and in an acid isolation medium with low pH. The greatest difference between the microbial population of children without tooth decay and ECC (Early childhood caries) children was in the acid isolation medium. The results of this study showed that there was a significant difference between health and caries in the acid-resistant population. Acid-resistant species included were the *S. mutans*, *Actinomyces odontolyticus*, and several having no name *Actinomyces* spp., *Bifidobacterium*, *Scardovia*, and *Lactobacillus* species. Also, two species related to caries, i.e., *S. mutans* and *S. wiggsiae*, had a significant difference between disease and health conditions in both types of bacterial isolation in acid or blood agar conditions (Hughes et al., 2012). In a study, researchers cultivated several new species of *Actinomyces* that were resistant to acidic conditions. Therefore, the potential for acid production at a low pH was considered to Discover the caries potential (Van Houte, 1994). For a long time, *Actinomyces* have been known as part of the caries microbiome and have been a significant group in the induction and development of caries (Takahashi and Nyvad, 2011). Several studies have also associated *Veillonella* spp. with dental decay. Bradshaw and Marsh (1998) reported that *Veillonella* was the most populous organism, especially in low pH after all glucose-pulsing regimens. Noorda et al. (1988) reported that acid production was higher in bacterial plaques mixed with *V. alcalescens* and *S. mutans* than plaques that consist of only one of these two species. Also, Mikx and van der Hoeven (1975) confirmed an active relationship between acid-producing bacteria and *Veillonella* species. On the other hand, *Veillonella* spp. may be consequential for acid-producing bacteria by reducing nitrate (Doel et al., 2005). Silva Mendez et al. (1999) reported that low concentrations of nitrite and pH levels of less than 7 (0.2 mM) killed *S. mutans*. These findings indicate that nitrite in saliva affects the growth and survival of cariogenic bacteria. Nadkarni et al. (2004) and Chhour et al. (2005) found that

Prevotella-like and *Prevotella* bacteria master the varied polymicrobial community in some cases of caries, which suggests that *Prevotella* play a role in the development of dental decay. In addition, co-aggregation between six species of *S. constellatus* ND10-13A, *S. bovis* II/2 ND2-2, *L. acidophilus* ND7-2A, *S. sanguinis* II ND7-3, *C. sputigena* ND2-12A, *P. intermedia* ND8-9A, and *F. nucleatum* NT6-6A, showed that these strains can co-aggregate with many oral bacteria and while forming dental plaque and bringing it to maturity, they will also control the composition of the microbial community (Kolenbrander et al., 1983; Kolenbrander, 2000). Evidence suggests that a wide range of bacterial strains are involved in tooth decay. In the study conducted by Chhour et al. (2005), also it was stated that there were 75 species or phylotypes in 10 caries lesions. Up to 31 species have been reported separately in each sample. Various species of *Lactobacilli* make up about 50% of the species, and about 15% are *Prevotellae*. Other species with high affluence are *F. nucleatum, Pseudoramibacter alactolyticus, Dialister* spp., *Selenomonas* spp., *Eubacterium* spp., *Olsenella* spp., *Bifidobacterium* spp., members of the *Lachnospiraceae* family, and *Propionibacterium* sp. (Chhour et al., 2005). In more studies, it was stated that *Lactobacillus* and *Mutans* spp. are dominant in advanced caries (Munson et al., 2004; Corby et al., 2005). In a study, it was stated that the number of *S. mutans* decreased after the cure compared to before the cure (Hughes et al., 2012). While, in another study, it was indicated that the treatment was associated with a change in the microbial profile, but this change was not significant for *S. mutans* (Tanner et al., 2011). The object of the treatment is to keep the tooth structure and intercept its further decay (Khushbu and Satyam, 2016), but since there is evidence that dental decay at first is a reversible disease that has a multifactorial cause, dentists are no longer seeking to use interventional treatment at a specific starting point of the appearance and severity of the disease. Nowadays, it is quite explicit that the restorative treatment of dental caries alone does not treat caries, and the caries process should be controlled with the patient's participation throughout his life (Pitts, 2004). Also, considering that the treatment of dental diseases is not possible for all members of society due to the need to spend a lot of money and time, prevention is a more economical way. Therefore, personal hygiene and diet modification should be considered (Khushbu and Satyam, 2016). It has been said about children that their oral microbiota originates from the oral microbiota of the child's main caregiver, the mother. Therefore, it is very important to focus preventive and therapeutic measures on child caregivers to prevent tooth decay in children (Tanner et al., 2002).

3 *Lactobacillus* bacteria and oral health

Tooth decay is a local demineralization of the hard tissues of the crown and root surface of the tooth, which happens in a bacterial accumulation that adheres to the tooth surfaces, called dental plaque, which is made of a gelatinous substance (Gupta and Gupta, 2015). *S. mutans* has been introduced as the main species

of caries-causing bacteria due to its strong acid production and high tolerance to acidic conditions (Sales-Campos et al., 2019; Hasslöf and Stecksén-Blicks, 2020). Research has shown that the number of *S. mutans* in the saliva of people without caries is normally between 10^4 and 10^5 CFU/mL (Deepti et al., 2008), But at 10^6 CFU/mL, the risk of caries increases significantly (Klock and Krasse, 1979). In this regard, 10^5 CFU/mL has been considered the threshold of caries in clinical studies (Caglar et al., 2008b; Ghasemi et al., 2017; Bafna et al., 2018).

Probiotic bacteria may cause chemical and physical alterations in the microbial flora of people's oral cavity (Teughels et al., 2007). Theoretically, probiotics have stronger adhesion to oral tissues than pathogens and can compete for adhesive surfaces. This leads to bacterial aggregation and co-aggregation and the formation of a new biofilm (Twetman, 2012; Piwat et al., 2015; Takahashi, 2015; Morales et al., 2016). Probiotics compete with the oral microbial flora and pathogens for adhesion sites, nutrients, and growth factors, thus protecting oral health. These bacteria aggregate after sticking to the oral cavity and prevent the adhesion of pathogenic bacteria through the production of antimicrobial components like acids, bacteriocins, and peroxides. Therefore, probiotic bacteria may prohibit the growth of caries-causing bacteria and periodontal diseases, create an immune response against pathogens, and prevent oral tissue destruction and inflammation in the oral cavity (Sanders, 1969; Yasui et al., 1999; Roberts and Darveau, 2002; Wilson, 2005; Twetman, 2012; Twetman and Keller, 2012; Devine et al., 2015; Laleman et al., 2015; Gruner et al., 2016; Morales et al., 2016). Various researchers have surveyed the effect of the consumption of probiotics on tooth decay. For example, (Jindal et al., 2011); Wattanarat et al. (2015), concluded that the use of probiotics could decrease the count of *S. mutans* and thus have a prohibitory effect on tooth decay. Nadelman et al. (2018) concluded during a meta-analysis that probiotics, including *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, could significantly reduce the count of *S. mutans* compared to control groups and prevent tooth decay. The results of this meta-analysis are consistent with systematic reviews that showed a significant decrease in the count of *S. mutans* after probiotic consumption (Cagetti et al., 2013; Laleman et al., 2014; Gruner et al., 2016).

Strains such as *Bifidobacterium* spp. and *L. rhamnosus*, *L. reuteri*, and *L. casei* have all shown the capability to change the colonization of carious bacteria, which can prevent tooth decay (Meurman and Stamatova, 2007). Kõll-Klais et al. (2005b) examined *Lactobacillus* strains in their research and reported that 69% of the strains could inhibit the growth of *S. mutans*, and 82% of the strains can inhibit the growth of *Porphyromonas gingivalis*. Both *L. salivarius* and *L. fermentum* have been found to have antagonistic activity against the growth of *S. mutans* (Strahinic et al., 2007). Also, *L. salivarius* TI 2711 isolated from a healthy human has shown an inhibitory effect on *P. intermedia*, *P. nigrescens*, and *P. gingivalis* after co-cultivation (Ishikawa et al., 2003). In a study by Sookkhee et al. (2001), the ability to inhibit the growth of various oral pathogens by 3790 lactic acid bacteria (LAB) was investigated, and it was stated that *L. rhamnosus* and *L. paracasei* have a strong antibacterial effect on several oral pathogens. Considering the digestive benefits of *Lactobacilli* and the fact that the *L.*

rhamnosus GG strain is not cariogenic due to its inability to consume sucrose or lactose (Homofermentative *Lactobacilli*), Meurman et al. (1995) became the first researcher to show the inhibitory effect of this bacterium on a cariogenic pathogen. Therefore, it is expected that this bacterium has been conducive to oral health (Stamatova et al., 2009). In this regard, it has been stated that *L. rhamnosus* GG ATCC 53103 produces a growth-prohibitory compound against *Streptococcus sobrinus* and is suggested to decrease the risk of caries (Haukioja et al., 2006). *Lactococcus lactis* has been introduced as another effective strain of *Lactobacilli* in eliminating the colonization of pathogenic oral bacteria and modulating the oral microflora. This bacterium has shown the ability to eliminate the colonization of bacteria such as *Actinomyces*, *V. dispar*, *S. oralis*, and cariogenic *S. sobrinus* (Comelli et al., 2002).

On the other hand, some studies have claimed that *Lactobacillus* themselves are correlated to the initiation and development of caries (Chuang et al., 2011; Sidhu et al., 2015). During their metabolism, *Lactobacilli* produce acids that may increase the risk of caries (Huang et al., 2015). Shimada et al. (2015) found that the number of *Lactobacilli* was significantly higher in children who had tooth decay than in children without decay. Therefore, they concluded that the number of *Lactobacilli* in the oral cavity is associated with the progression of caries. In other studies, evidence suggests that *Lactobacilli* are more correlated with caries development than with initiation of caries and play a momentous impress in the development of tooth decay (Edwardsson, 1974; Maltz et al., 2002; Karpiński and Szkaradkiewicz, 2013; Caufield et al., 2015). Also, it has been reported that the count of *Lactobacilli* after probiotic consumption was not significantly different between the control and experimental groups (Çaglar et al., 2005; Çaglar et al., 2006; Caglar et al., 2007; Caglar et al., 2008b; Petersson et al., 2011; Singh et al., 2011; Cildir et al., 2012; Mortazavi and Akhlaghi, 2012). In a study, it was stated that the count of *Lactobacilli* decreased in one of the two probiotic groups after oral probiotic consumption (Cogulu et al., 2010). In contrast, it was noted in two studies that the count of *Lactobacilli* increased significantly (Aminabadi et al., 2011; Keller and Twetman, 2012). Therefore, according to the reports of most studies, it can be claimed that the consumption of probiotics does not cause the initiation of tooth decay. In this regard, it was reported in an intervention study that the consumption of *Lactobacilli* by children decreased the risk of tooth decay and primary caries in them (Reddy et al., 2011). Until now, the effect of the consumption of different strains of probiotics on tooth decay has been investigated in several studies [Table 1]. Regarding the literature investigation, most studies stated that the consumption of probiotics efficiently prevents tooth decay development, and they advise a controlled consumption of probiotics to reach advantageous effects.

4 *Bifidobacteria* and oral health

Interest in using probiotic *Bifidobacteria* to prevent and treat oral microbial diseases is increasing. Nevertheless, the results reported from clinical studies aimed at investigating the effect of

Bifidobacteria on oral microbiota are conflicting and controversial. Some studies have reported that *Bifidobacteria* have anti-caries effects, and others have published the opposite results. Few studies have surveyed the effect of *Bifidobacteria* on *S. mutans*, and some of these studies have also surveyed the effects of *Bifidobacteria* along with *Lactobacilli*. In the meta-analysis conducted by Gruner et al. (2016), it was shown that *Bifidobacterium* does not effectively reduce the count of *Lactobacilli* in saliva. Still, it has a significant reduction effect on the count of *S. mutans*. Also, studies that used supplements of *Bifidobacterium* and *Lactobacillus* spp., reported a reduction in the count of *S. mutans* in the oral cavity (Mahantesha et al., 2015; Ghasemi et al., 2017). Similar results have been reported in people who did not use fluoride (Ghasemi et al., 2017). While in some studies, the use of *Bifidobacterium animalis* BB-12 and other species of *Bifidobacterium* genus in people who did not use fluoride failed to show its therapeutic effects on tooth decay (Pinto et al., 2014; Nozari et al., 2015). A meta-analysis was conducted to investigate the difference in the count of *S. mutans* in saliva before and after consuming *Bifidobacterium*. The pooled results of four studies did not show significant differences (Pinto et al., 2014; Nagarajappa et al., 2015; SrivaStava et al., 2016; Javid et al., 2020). In a study, it has been stated that *Bifidobacteria* did not have a significant effect on reducing the count of *S. mutans* but significantly reduced the number of *P. gingivalis* in the biofilm (Jäsberg et al., 2016). On the other hand, Valdez et al. (2016) showed that *Bifidobacterium* can make an acidic environment and enhance the formation of biofilm so that *Bifidobacterium* may have a cariogenic effect on teeth. Haukioja et al. (2008) stated that *Bifidobacterium* could cause tooth demineralization because of the production of organic acids. Also, Dual-species biofilms formed by *S. mutans* and *Bifidobacteria* produce more acid than *S. mutans* biofilm alone, and as a result, more pH drops will occur (de Matos et al., 2017). Zhai et al. (2009) investigated the distribution of *Bifidobacterium* in the oral cavity and the association between *Bifidobacterium* and tooth decay in children. In this clinical study, the results indicated that the rate of *Bifidobacterium* was 47.5% in patients with severe ECC and 0% in healthy people without caries. Table 2 shows the results of clinical studies conducted to investigate the effect of *Bifidobacterium* on oral health. The number of studies that have used *Bifidobacteria* alone and separately from *Lactobacilli* is limited. This has made it challenging to decide on the effect of *Bifidobacteria* on the count of *S. mutans* and tooth decay. Therefore, in the future, more studies should be conducted with food products containing only *Bifidobacteria*.

5 Probiotics and *Candida* yeast infections

Candida albicans fungus is one of the prevalent infectious agents in the oral cavity. At older ages and in immunodeficiency conditions, the risk of yeast infections increases (Jiang et al., 2016). *Candida* has different species, and the species that are usually isolated from the oral cavity include *C. krusei*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. albicans*. Increasing antifungal

TABLE 1 Human *in vivo* studies on the effect of *Lactobacilli* on oral health.

The studied community	Number	Probiotic strain	Dose of probiotics (CFU/ml)	Carrier food	Study period	Result	Reference
Children (1-6 years)	571	*L. rhamnosus* GG	$5\text{-}10\times10^5$ (Three times a day, 200 ml each time, 5 days a week)	Milk	7 months	Reduce the risk of decay	(Hatakka et al., 2001)
Children (7-14 years)	150	*L.rhamnosus, B.lonum, Saccharomyces cerevisiae*	$1.25\times10^9/20ml$	Water (20 ml)	14 days	A statistically significant decrease (p<0.001) in the count of *S. mutans* in saliva was recorded after 14 days of probiotic ingestion	(Jindal et al., 2011)
Children (6-12 years)	60	*L.reuteri*	2×10^8	Lozenge	28 days	A significant reduction in the count of *S. mutans* and *Lactobacilli* in saliva and decreasing the risk of tooth decay	(Cannon et al., 2013)
Adults (21-24 years)	120	*L.reuteri* ATCC 55730	–	Group A: water (200 ml) Group C: tablet (once a day)	3 weeks	Unlike *Lactobacilli*, a significant reduction was observed in salivary *S. mutans*	(Çaglar et al., 2006)
Adults (18-35 years)	74	*L. rhamnosus* LC705, *L. rhamnosus* GG	*L. rhamnosus* LC705 (1.2×10^7) and *L. rhamnosus* GG (1.9×10^7)	Cheese (5×15 g per day)	3 weeks	The results indicated that there was no significant difference between the groups in the number of *S. mutans* after the intervention, but a significant decrease was observed in the intervention group compared to the control group during the post-cure period (P=0.05)	(Ahola et al., 2002)
Adults (20-35 years)	28	*L. casei* shirota	10^8	Fermented milk (65 ml daily)	4 weeks	Reduction of biomarkers associated with gingival inflammation and reduction of gingival crevicular fluid volume and bleeding in probing scores	(Slawik et al., 2011)
Adults (20-26 years)	78	*L. paracasei* GMNL-33	3×10^8	Tablet (thrice a day)	2 weeks	Significant reduction in the count of caries *S. mutans*. A 2-week oral administration period for *L. paracasei* GMNL-33 may be required for the probiotic to become effective	(Chuang et al., 2011)
Adults (18-25 years)	40	*L. paracasei* SD1	7.5×10^8	Reconstituted milk powder (10 g in 50 ml water)	4 weeks	The results showed that short-term daily use of *L. paracasei* SD1 reduces the number of oral *S. mutans*	(Teanpaisan and Piwat, 2014)
Adults (average of 25 years)	64	*L. salivarius* WB21, *L. salivarius* TI 2711	*L. salivarius* WB21: 6.7×10^8 CFU/ tablet, *L. salivarius* TI 2711: 2.8×10^8 CFU/tablet	Tablet	2 weeks	In both *L. salivarius* WB21 and TI 2711 groups, the count of *S. mutans* decreased and the count of *Lactobacilli* increased.	(Nishihara et al., 2014)
older adults (58-84 years)	160	*L. rhamnosus* LB21	10^7	Milk (200 ml daily)	15 months	If milk with fluoride and/or probiotics is consumed daily, the lesions of soft and leathery primary root caries may be reversed in older people	(Petersson et al., 2011)
Children (1-5 years)	248	*L. rhamnosus* LB21	10^7	Milk (150 ml with 2.5 mg fluoride per liter)	21 months	The results showed that daily use of probiotics and fluoride by preschool children reduces the incidence of caries	(Stecksén-Blicks et al., 2009)
Children (2-3 years)	261	*L. rhamnosus* SP1	10^7	Milk (150 ml)	40 weeks	Reducing the severity and progression of caries in children compared to the control group	(Kaye, 2017)
Children (7-12 years)	40	*L. reuteri* (ATCC 55730	–	Chewing gum (three a day)	3 weeks	In addition to the decrease in the count of salivary *s. mutans* after the intervention, a significant	(Kaur et al., 2018)

(Continued)

TABLE 1 Continued

The studied community	Number	Probiotic strain	Dose of probiotics (CFU/ml)	Carrier food	Study period	Result	Reference
		and ATCC PTA 5282)				reduction in plaque and gingival scores was also observed	
Children (12-14 years)	122	L. paracasei SD1	10^7	Milk powder (5g/day)	6 months	After completing the study, fewer caries lesions were detected in the probiotic-consuming group. Also, in the group with a high risk of caries, a significant reduction in new caries was detected (4.5 times), while no such decrease was observed in the group with a low risk of caries	(Teanpaisan et al., 2015)
Children (1.5-5 years)	124	L. paracasei SD1	10^7	Milk powder (5g/day)	3 month	The use of milk powder containing L. paracasei SD1 as a safe strain for young children reduced the levels of salivary S. mutans and also delayed the development of new caries.	(Pahumunto et al., 2018)
Children (12-14 years)	40	L. paracasei SD1	–	Milk powder (5g/day)	6 months	L. paracasei SD1 able to control the level of S. mutans and stimulate sIgA	(Pahumunto et al., 2019)
Infants	171	L. paracasei F19	10^8	Cereals	9 months	Early intervention with LF19 did not affect the prevalence of dental caries, S. mutans, or Lactobacilli.	(Hasslöf et al., 2013)
Children (13-14 years)	201	L. rhamnosus SD11	$5×10^{10}$ (Fermented milk) and $7.5×10^7$ (condensed milk powder)	Fermented milk and condensed milk powder	9 months	The consumption of probiotics by children caused the number of S. mutants, the percentage of caries progress, and caries lesions to decrease significantly.	(Piwat et al., 2019)
Children (average of 16 years)		L. reuteri (ATCC PTA 5289 and DSM 17938)	10^9	Lozenge	17 month	No significant change was observed between the treatment and placebo groups in the incidence of white spot lesions, as well as the count of S. mutans and Lactobacilli.	(Gizani et al., 2016)
Children (6-10 years)	25	L. rhamnosus GG ATCC 53103	–	Yogurt	2 weeks	Thirty days after consuming yogurt, a significant increase in the buffer capacity of saliva was observed. Also, the number of S. mutans decreased significantly, but the number of Lactobacillus did not change significantly.	(Glavina et al., 2012)
Children (12-15 years)	40	L. rhamnosus hct 70	$2.34×10^9$ CFU/daily	Milk (150 ml)	3 weeks	Probiotic consumption reduced the count of S. mutans immediately after the end of the intervention and also after 3 weeks.	(Juneja and Kakade, 2012)
Children (6-8 years)	31	L. casei Shirota	–	Milk (60 ml)	10 days	A significant decrease (p=0.003) in the number of S. mutans colonies was observed in the group consuming probiotics.	(Yadav et al., 2014)
Adults (average of 25 years)	13	L. reuteri (PTA 5289 and SD2112) or L. rhamnosus GG	$2×10^6$/tablet L. reuteri, $1.96×10^6$/tablet L. rhamnosus	Tablet	2 weeks	The number of S. mutants remained unchanged, and no change in the acidogenicity of plaque was observed with probiotic consumption. In the L. reuteri group, the number of people with lactobacillus in the plaque increased (p=0.011), unlike the L. rhamnosus group.	(Marttinen et al., 2012)
Adults (average of 26 years)	18	L. reuteri (ATCC PTA 5289 and DSM 17938)	10^8 of each strain	Lozenge	2 weeks	The number of salivary S. mutans, unlike Lactobacilli (p<0.05), in the experimental group did not show any significant changes during the intervention.	(Keller and Twetman, 2012)
Adults (19-35 years)	62	L. reuteri (ATCC PTA 5289 and DSM 17938)	10^8 of each strain	Lozenge	6 weeks	It seems that daily use of L. reuteri cannot delay the regrowth of S. mutans after thorough oral disinfection using chlorhexidine	(Keller et al., 2012a)
Adults (21-24)	80	L. reuteri (ATCC PTA	$1 × 10^8$ CFU/gum ATCC 55730 and	Chewing gum	3 weeks	Unlike salivary Lactobacilli, the count of S. mutans in the probiotic consumption group	(Caglar et al., 2007)

(Continued)

TABLE 1 Continued

The studied community	Number	Probiotic strain	Dose of probiotics (CFU/ml)	Carrier food	Study period	Result	Reference
		5289 and ATCC 55730)	1×10^8 CFU/ gum ATCC PTA 5289			showed a significant decrease compared to the baseline level after the intervention	
Adults (average of 20 years)	20	L. reuteri (ATCC PTA 5289 and ATCC 55730)	1.1×10^8	Lozenge (once daily)	10 days	In the probiotic consumer group, the number of salivary S. mutans was significantly decreased (P < 0.05)	(Caglar et al., 2008a)
Infants	113	L. reuteri ATCC 55730	10^8	Oil derived from breast milk	13 months	Daily consumption of L. reuteri from birth to one year has reduced the prevalence of caries and gingivitis score in primary dentition at the age of nine	(Stensson et al., 2014)
Children (4-12 years)	19	L. reuteri (ATCC PTA 5289 and DSM 17938)	$\geq 10^8$ CFU/5 drops	Drops (5 per day)	25 days	There was no significant decrease in the number of salivary S. mutans and Lactobacillus after 25 days of probiotic consumption	(Cildir et al., 2012)
Adolescent (12-17 years)	36	L. reuteri (ATCC PTA 5289 and DSM 17938)	10^8 of each strain	Tablet	3 months	There was no significant change in the number of S. mutans and Lactobacillus in the treatment group. It also seems that this probiotic does not affect adolescent decay lesions	(Keller et al., 2014)
Children (6-8 years)	191	L. brevis CD2	2×10^9	Lozenge	6 weeks	A significant decrease was observed in the count of salivary S. mutans, plaque acidogenicity, and bleeding on probing	(Campus et al., 2014)
Adults	42	L. reuteri (ATCC PTA 5289 and ATCC 55730)	10^8 CFU/gum	Chewing gum (One or two a day)	2 weeks	After consuming these strains, it was found that the volume of gingival crevicular fluid and bleeding in the probe improved significantly (p<0.05)	(Twetman et al., 2009b)
Adults (20 years)	40	L. reuteri	–	Yogurt (95 g once daily)	2 weeks	L. reuteri consumption significantly decreased the number of S. mutans compared to placebo (yogurt without probiotics)	(Nikawa et al., 2004)
The elderly	276	L. lactis and Lactobacillus helveticus	10^7 of each strain	Cheese (50 g)	16 weeks	Probiotics can control hyposalivation and oral Candida in older people.	(Hatakka et al., 2007)
Adults (average of 20 years)	60	–	–	Curd (200 mg) and toothpaste (twice daily)	30 days	The use of probiotics significantly reduces the count of S. mutans in the plaque formed around the bracket in orthodontic patients.	(Jose et al., 2013)
Adults (22-32 years)	22	Saccharomyces cerevisiae, L. casei subsp. Pseudo plantarum	–	Kefir drink (100 ml per day)	2 weeks	Consuming a probiotic Kefir drink can inhibit the number of salivary S. mutans. It may also be selected as an alternative to fluoride washing.	(Ghasempour et al., 2014)
Adults (20-25)	60	L. acidophilus	–	Curd (100ml)	7 days	In the short term, probiotic consumption reduced the number of salivary S. mutans and increased salivary pH.	(SrivaStava et al., 2016)
Adults	57	L. salivarius TI 2711 (LS 1)	2×10^7	Tablet	4 or 8 weeks	With probiotic consumption, the number of whole bacteria, S. mutans, and Lactobacilli did not change, but the number of P. intermedia, P. nigrescens, and P. gingivalis decreased.	(Ishikawa et al., 2003)

resistance is becoming a new issue worldwide, and new methods are needed to fight pathogenic fungi. Probiotic Lactobacilli have demonstrated different inhibitory effects against oral Candida during in vitro studies. Meanwhile, L. Rhamnosus GG has shown a strong prohibitory effect (Jiang et al., 2015). Haukioja et al. (2006) conducted a placebo-controlled study for the first time to examine

the effect of probiotics on the abundance of oral Candida. Consumption of cheese containing Propionibacterium freudenreichii ssp. shermanii JS and L. rhamnosus GG probiotics decreased the abundance of C. albicans by 75% in the elderly. Yakult drink containing B. breve and L. casei increases salivary secretory protein levels and causes a significant decrease in Candida and non-

TABLE 2 Human clinical studies on the effect of *Bifidobacteria* on oral health.

The studied community	Number	Probiotic strain	Dose of probiotics (CFU per ml/gram)	Carrier food	Study period	Result	Reference
Adults (18-22 years)	30	*Bifidobacteria*	10^6	Chocobar ice cream (42 grams once a day)	18 days	The number of salivary S. mutans decreased in contrast to salivary *Lactobacilli* (p < 0.05).	(Nagarajappa et al., 2015)
Adults (21-24 years)	21	*Bifidobacterium* DN-173010	$7×10^7$	Yogurt (200 grams daily)	2 weeks	decreased in the number of S. mutans in saliva, and no significant change in the number of *lactobacilli*.	(Çaglar et al., 2005)
Adults (mean age 20 years)	24	*Bifidobacterium* lactis Bb-12	–	Ice cream (53 grams daily)	10 days	The number of salivary S. mutans decreased in contrast to salivary *Lactobacilli* (p < 0.05).	(Caglar et al., 2008a)
Infants (1-2 months)	121	*B. animalis* subsp. lactis BB-12	10^{10} (daily dose)	Tablet (200-600 mg xylitol or sorbitol for control groups without probiotic)	2 years	It seems that the consumption of strain BB-12 in infants does not cause a change in the caries process until the age of 4 in the low caries population.	(Taipale et al., 2012; Taipale et al., 2013)
Children (12-14 years)	40	*B. lactis* Bb-12 ATCC27536, *L. acidophilus* La-5	10^6 of each probiotic strains	Ice cream (54 gram daily)	10 days	A significant decrease in salivary S. mutans levels was observed (p=0.003), unlike *Lactobacilli* levels.	(Singh et al., 2011)
Children (6-12 years)	60	*B. lactis* Bb-12, *L. acidophilus* La-5	10^6 of each probiotic strains	Ice cream (54 grams)	7 days	Within a week of consuming probiotic ice cream, a significant decrease in the number of S. mutans was observed (p<0.001).	(Ashwin et al., 2015)
Adults (18-30 years)	66	*B. lactis* Bb12	10^6	Yogurt (300 grams daily)	2 weeks	Consumption of probiotics decreased the count of salivary S. mutans and *Lactobacilli* in the treatment group, both compared to the baseline level and compared to the control group.	(Javid et al., 2020)
Children (average age of 15 years)	26	*B. animalis* subsp. lactis DN-173010	–	Yogurt (200 gram daily)	2 weeks	After 2 weeks, the reduction in the count of S. mutans and *Lactobacilli* was not significant.	(Pinto et al., 2014)
Children (8-10 years)	52	*B. bifidum* DN-173 010	10^{10}	Fruit yogurt (110 gram daily)	2 weeks	No significant difference was observed in S. mutans levels in dental plaque before and after treatment.	(Caglar, 2014)
Young adults	60	*B. animalis* subsp. lactis BB-12, *L. rhamnosus* GG	$2×10^9$ of each probiotic strains	Lozenge	4 weeks	Improvement of the periodontal condition was observed without affecting the oral microbiota after taking probiotics.	(Toiviainen et al., 2015)
Adults	70	*Bifidobacterium* lactis BB-12 and *L. acidophilus* La5	10^6/100 grams	Yogurt (100 grams daily)	2 weeks	A decrease in the number of salivary S. mutants was observed after consuming yogurt containing *B. lactis* Bb12 and *L. acidophilus* La5.	(Bafna et al., 2018)
Children (3-4 years)	363	*L. rhamnosus*, *B. longum*	$5×10^6$ L. rhamnosus, $3×10^6$ B. longum	Milk (200 ml daily)	9 months	The number of S. mutans in the probiotic consumption group was lower than in the control group, but this decrease was not significant (p=0.173).	(Villavicencio et al., 2018)
Children (3-5 years)	63	*B. longum*, *L. rhamnosus* GG	L. rhamnosus GG ($7.5 × 10^5$) and B. longum ($4.5 × 10^5$)	Milk (200 ml)	3 months (5 days a week)	Consumption of probiotic milk did not reduce the count of S. mutans, but it reduced the remineralization of tooth decay and saliva acidity.	(Angarita-Díaz et al., 2020)
Children (6-12 years)	49	*B. lactis*	10^6	Yogurt (200g once daily)	2 weeks	use of probiotic yogurt containing *B. lactis* could not decrease the levels of S. mutans and *Lactobacilli* in saliva, while normal yogurt	(Nozari et al., 2015)

(Continued)

TABLE 2 Continued

The studied community	Number	Probiotic strain	Dose of probiotics (CFU per ml/gram)	Carrier food	Study period	Result	Reference
						could decrease the count of *S. mutans* significantly	
Adults (19-27 years)	50	*B. bifidum* ATCC 29521, *L. acidophilus* ATCC 4356	1.5×10⁸	Yogurt (200 g daily)	3 weeks	On the first day, the seventh day, and one month after the intervention, the count of *S. mutans* was significantly lower than the baseline values (P < 0.05).	(Ghasemi et al., 2017)
Children (12-15)	33	*B. bifidum, L. acidophilus, B. lactis,* and *B. longum,*	–	Water (30 ml once daily)	3 weeks	Up to the second week, a significant decrease in the number of salivary *S. mutants* was observed (P<0.05).	(Yousuf et al., 2015)

Candida species in the oral cavity of the elderly (Mendonça et al., 2012). Also, the consumption of *L. reuteri* lozenge and probiotic cheese containing *L. rhamnosus* LC 705 and *L. rhamnosus* GG has reduced the number of oral yeasts correlated with caries (Ahola et al., 2002; Kraft-Bodi et al., 2015). During a randomized clinical trial that was conducted on 60 children, it was shown that a probiotic rinse for one week was as efficient as chlorhexidine digluconate 0.2% in decreasing the count of *C. albicans* (Mishra et al., 2016). It has also been reported that probiotic bacteria have an anti-biofilm effect against *C. albicans* (James et al., 2016; Matsubara et al., 2016) and against the ability to produce biofilms of two species of *C. albicans* and *S. mutans* (Krzyściak et al., 2017).According to these promising studies, it can be estimated that the expansion of research on the relationship between probiotics and oral yeast infections and the investigation of molecular means of probiotic activity may expand their potential applications in the future (Meurman and Stamatova, 2007).
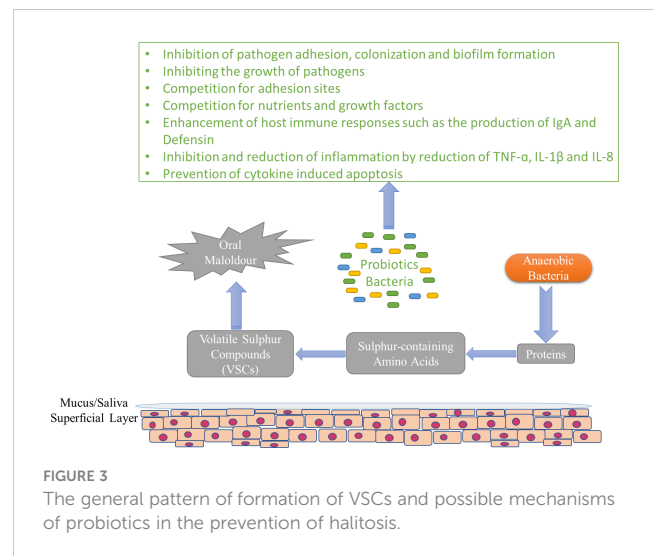
6 Probiotics and periodontal diseases

Periodontal disease is inflammation of dental support tissues, which comprises gums, the bony socket, the outer layer of the roots of teeth, and the associated connective tissue. This disease begins with the formation of plaque. Symptoms of periodontal disease are bleeding on probing, color alterations, swelling, pain, and in advanced stages, dental mobility. Probiotics prevent plaque formation by reducing the pH of saliva and producing antioxidants that use free electrons used in plaque mineralization because, in this condition, carcinogenic bacteria are not able to form plaque. Therefore, in this way, probiotics prevent periodontal disease. Also, encouraging results of the consumption of probiotics in the cure of plaque level, gingivitis, periodontitis, and significant reduction of periodontopathogens have been reported in various studies. Today, according to new knowledge, three factors are known to cause plaque-related periodontitis. These three factors are a vulnerable host, the existence of a pathogen, and the low extent or absence of advantageous microbiota (Slots and Rams, 1991; Socransky and Haffajee, 1992; Wolff et al., 1994). An unbalance between the pathogenic and saprophytic flora of the oral cavity

in a vulnerable individual may cause periodontal disease (Dye, 2012). Through scaling and root planing, and deep pocket debridement, which are considered the primary cure, it is possible to reduce invasive periopathogens significantly. Debridement treatment of periodontal disease is possible in two ways, surgical or non-surgical. Sometimes, systemic antimicrobial administration is also necessary. Although plaque removal using mechanical surface instrumentation is an effective treatment method, pocket recolonization is highly unpredictable (Morales et al., 2016; Meurman and Stamatova, 2018). Considering that the administration of these drugs gradually creates bacterial resistance, new alternatives are needed for them (Laleman and Teughels, 2015; Morales et al., 2016). Since a probiotic can modify the oral microbial flora, it is probably a purposive strategy in the clinical control of periodontitis in addition to other beneficial advantages it provides to the host (Saha et al., 2012). On the one hand, probiotics can compete with periodontal pathogens and modulate dysbiosis conditions, therewith decreasing the overall immunogenicity of the oral microbiota, and also, they can modulate immune/inflammatory pathways to decrease the destructive inflammation of periodontitis and result in immune homeostasis that can be retained by the individual for a long time (Allaker and Stephen, 2017). It has been shown that the existence of probiotics with a suitable concentration of 10⁸ CFU/mL in periodontal dressings reduces the number of periodontal pathogens, including *Actinomyces* sp., *Bacteroides* sp., *S. intermedius*, and *C. albicans* (Volozhin et al., 2004). The impact of probiotic *Lactobacilli* on inhibiting the growth of periodontopathogens in the oral cavity has also been shown (Sookkhee et al., 2001; Ishikawa et al., 2003; Kõll-Klais et al., 2005b). There is a straight relationship between periodontal inflammation and destruction and the reduction of LAB levels (Kõll-Klais et al., 2005a). It has been reported that bacteria such as *L. fermentum* and *L. gasseri* in the oral cavity of patients with chronic periodontitis had lower levels than in healthy people (Kõll-Klais et al., 2005b). The usage of *L. reuteri* has also shown a decrease in gum bleeding and a decrease in gum inflammation (Krasse et al., 2006; Meurman and Stamatova, 2007). In another study, *L. reuteri* was used as a supplement to conventional treatments for patients with periodontitis, and it caused a decrease in the number of *P. gingivalis, P. intermedia,*

and *Aggregatibacter actinomycetemcomitans* (Vivekananda et al., 2010). In addition to reducing the count of periodontal pathogens, the activity of probiotics has resulted in a decrease in the concentration of IL-17, IL-1β, and TNF-α in the gingival crevice fluid (Teughels et al., 2013; Szkaradkiewicz et al., 2014). It has been shown in mouse models that gut-based probiotics can have a protective effect on periodontitis through immune modulation (McCabe et al., 2015; Kobayashi et al., 2017). Therefore, this characteristic of probiotics can make them an alternative to antibiotics in periodontal cure to help decrease the overall burden of antibiotic resistance (Bidault et al., 2007; Rams et al., 2014). Meta-analyses also support the consumption of probiotics in the management of periodontitis (Gruner et al., 2016; Martin-Cabezas et al., 2016). However, before recommending the routine consumption of probiotics for the cure of periodontitis and gingivitis, various aspects and points should be considered. For example, the length of the treatment and how to do it so that the pathogenic microbiota does not prevail again after it ends, and also pay attention to the possible risks that the consumption of probiotics can cause in subjects with a weak immune system.

7 Probiotics and halitosis

Halitosis, or the nasty odor that comes out of the mouth, is a disease that depends on various factors, and its origin may be oral or non-oral (Van den Broek et al., 2007; Oliveira-Neto et al., 2013). Halitosis is usually attributed to biofilm in the interdental spaces, the back of the tongue, and chronic inflammatory diseases. The incidence of this disease in different populations is estimated between 22 and 50 percent (Miyazaki, 1995; Meningaud et al., 1999; Yaegaki and Coil, 2000; Quirynen et al., 2009; Akaji et al., 2014). Sulfuric gases such as dimethyl sulfide, hydrogen sulfide, and methyl mercaptan play an important role in causing bad breath. These gases are released in the oropharynx (tongue coating, tonsillitis, gingivitis, periodontitis) through bacterial degradation of sulfur-containing amino acids (Figure 3). *F. nucleatum*, *Treponema denticola*, *P. intermedia*, and *P. gingivalis* can be mentioned among the diverse range of bacteria that contribute to this disease (Corcoran et al., 2004). On the other hand, the levels of bacterial species that form the dominant microbiota in the oral of healthy people are not significant in people with halitosis (Kazor et al., 2003). Current treatments seek to eliminate these pathogenic bacteria using chemical or physical antibacterial agents. Antimicrobial treatment indiscriminately reduces the population of pathogenic bacteria and bacteria that are not involved in causing halitosis but are probably effective in maintaining a normal oral microenvironment. However, the result of this cure is to reduce the bad smell temporarily, and after some time, the bacteria causing halitosis appear again (Burton et al., 2005). Probiotics that are effective in maintaining periodontal health may also be useful for eliminating bad breath by helping to keep a healthy ecology of the tongue because in oral health, access to certain areas of the tongue, such as the dorsal posterior surface to the circumvallate papillae, which acts as a shelter for the large number of gram-negative bacterial species correlated with bad breath, is more difficult

FIGURE 3
The general pattern of formation of VSCs and possible mechanisms of probiotics in the prevention of halitosis.

(Allaker et al., 2008). Nevertheless, it is known that the tongue is a more palpable recess than the periodontal recesses in terms of species that normally colonize, suggesting the necessity of recess-specific conformity, and probiotic strains intended to colonize the periodontal recesses may not freely colonize the tongue to exert health-promoting impacts (Zaura et al., 2009; Eren et al., 2014). For the first time, Kang et al. (2006) sought a probiotic to prevent or treat halitosis using a scientific approach. In children, after gargling the rinsing solution containing *Weissella cibaria*, a significant decrease in H_2S (48.2%) and CH_3SH (59.4%) levels, and as a result, halitosis has been observed (Lima et al., 2005; Kang et al., 2006). A possible candidate to compete with bacterial species that increase the level of volatile sulfur compounds is *S. salivarius*, which has shown an inhibitory effect on volatile sulfur compounds (VSC). Rinsing with chlorhexidine followed by lozenges containing *S. salivarius* K12 strain decreased the respiratory levels of VSCs in most subjects and maintained their levels for at least 2 weeks. (Sullivan and Nord, 2005). This strain produces two lantibiotic bacteriocins that inhibit gram-positive strains involved in halitosis (Meurman and Stamatova, 2007). *S. salivarius* K12 seems to be able to reduce bad breath for a long time by replacing the bacteria involved in halitosis (Burton et al., 2006). In some other studies, the effect of this strain in eliminating bad breath has been reported (Horz et al., 2007; Wescombe et al., 2010; Masdea et al., 2012). In a study, it was shown that *L. salivarius* WB21 has a positive effect on the organoleptic test score and bad breath (Iwamoto et al., 2010). Chewing gum containing probiotics can also reduce the levels of non-sulfur odor-producing bacteria. In the study by Keller et al. (2012b), this was mentioned, and it was shown that the organoleptic scores were significantly decreased after the consumption of chewing gum containing *L. reuteri* compared to the placebo group. In contrast, there was no improvement in breath VSCs concentration or organoleptic scores after being treated with *L. brevis* CD2 lozenges (Marchetti et al., 2015). Also, no significant decrease in breath VSCs concentration or organoleptic scores was observed after consuming milk containing *L. casei* Shirota (Sutula et al., 2013). Anti-VSC effects by non-oral bacteria such as *S. thermophilus*, *E. faecium*, and *W. cibaria* have also been

reported in laboratory studies (Lee and Baek, 2014; Jang et al., 2016; Suzuki et al., 2016). It seems that the effect of probiotics, mostly used in commercial foods, has been less investigated in past studies. Therefore, it is recommended that future researches focus on such strains.

8 The application of postbiotics as novel biological compounds to improve oral health

During the past years, researchers have usually used different idioms such as cell-free supernatant, biogenic, abiotics, metabiotics, pseudoprobiotics, ghost probiotics, paraprobiotics, and postbiotics to introduce non-viable parts or metabolites of probiotic bacteria. In the meantime, postbiotic has been used the most (Abbasi et al., 2022). By definition, postbiotics are cell wall fragments, cytoplasmic extracts, or metabolites produced by gut-resident probiotics and fermented foods. However, because of the uncertain definition and broad bioactivity of metabolites produced by probiotics, the term postbiotic can be defined as follows: any soluble agent (products or metabolic by-products of microbial metabolisms or compounds produced by the action of LAB on culture or food ingredients) that is released by live probiotics or after their cell lysis during fermentations is secreted in food, microbiological cultures or gut. During the fermentation process, probiotics feed on prebiotics and produce a wide range of postbiotics. The functional mechanism of probiotics is related to the production of compounds like bacteriocins, organic acids, fatty acids, and hydrogen peroxide (Miles, 2007; Stamatova and Meurman, 2009; Takahashi, 2015; Żółkiewicz et al., 2020; Rad et al., 2020b; Moradi et al., 2021) (Figure 4). These compounds are currently produced by laboratory methods, and if they are consumed in sufficient amounts, they will have health effects (Aguilar-Toalá et al., 2018; Moradi et al., 2021). Also, due to their favorable antimicrobial effects, they are

considered a promising alternative to antibiotics (Johnson et al., 2019; Rad et al., 2020a). Organic acids are acknowledged as one of the most important and impressive components of postbiotics. Lactic acid produced during bacterial fermentation effectively controls pathogenicity (Baird et al., 2006). Bacteriocins are peptides that have antimicrobial activity. These compounds resist heat and pH and can prevent the development of pathogens in the gastrointestinal. The mechanism of function of bacteriocins is in the cytoplasmic membrane of bacteria (Gálvez et al., 2007; Šušković et al., 2010). Also, fatty acids, as one of the components of postbiotics, have shown good antimicrobial effects. Long-chain fatty acids like eicosapentaenoic acid are active against gram-positive bacteria. Fatty acids exhibit various antimicrobial mechanisms against bacteria, including increasing membrane permeability, lysing bacterial cells, disrupting the structure and activity of enzymes, disrupting the electron transport chain, and inducing morphological and functional changes in susceptible components like proteins (Desbois, 2012; Yoon et al., 2018). H_2O_2 (Hydrogen peroxide) is another antimicrobial agent whose antimicrobial effect is said to be due to its strong oxidizing action on the bacterial cell and the destruction it causes to the structure of proteins in its cytoplasm (Osborn and Akoh, 2002). Earlier, the advantageous effects of some probiotics in improving oral health and preventing oral diseases are mentioned. It is thought that the antimicrobial properties of probiotics are because of the production of antibacterial compounds, such as hydrogen peroxide and organic acids, and antifungal compounds, such as bacteriocins and fatty acids (Twetman et al., 2009a). Also, it has been reported that *L. reuteri* produces water-soluble antimicrobial compounds like reuterin (Talarico et al., 1988) and reutericyclin (Ganzle et al., 2000), which have antagonistic activity. These substances are resistant to lipolytic and proteolytic enzymes (El-Ziney and Debevere, 1998) and maintain their function in a wide range of pH (Rodriguez et al., 2003). The strain of *S. dentisani* isolated from the mouth of people without caries also can produce bacteriocin
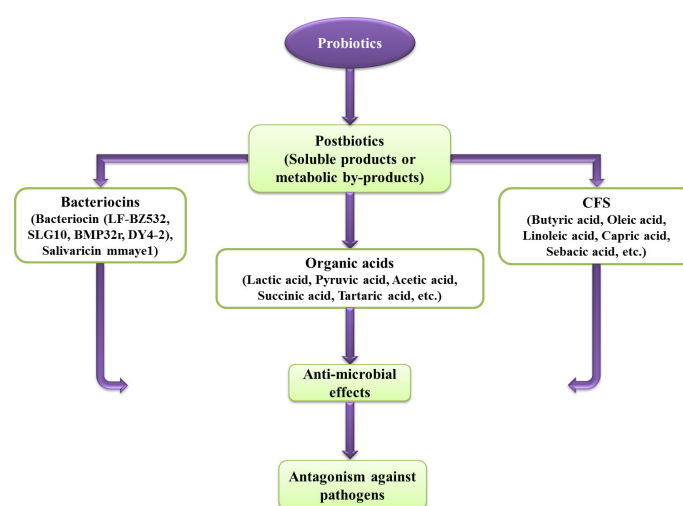

FIGURE 4
The indirect effect of probiotic bacteria through produced compounds.

and can be considered another useful probiotic spp. (López-López et al., 2017). Also, in a three-month clinical study, the results showed that the *S. salivarius* M18 probiotic strain, which also produces bacteriocin, can reduce the development of tooth decay in children (Di Pierro et al., 2015). It has been found that some bacterial spp., such as *S. sanguinis* (Trüper and De'Clari, 1997) and *S. uberis*, are not present in the subgingival plaque samples of people with refractory periodontitis and people with localized juvenile periodontitis. At the same time, they are present in the subgingival plaque samples of healthy individuals. It was shown that these strains prevent the growth of *A. actinomycetemcomitans* (Norskov-Lauritsen, 2006) and other periodontal pathogens (Hillman and Socransky, 1982; Hillman et al., 1985) through the production of hydrogen peroxide (Hillman and Shivers, 1988).

It has been stated that the decrease in pH level and tooth demineralization by bacteria (Kidd and Fejerskov, 2004) like *S. mutans*, *S. sobrinus*, and *Lactobacillus* spp. is because of the organic acids produced in the biofilm as metabolic byproducts produced during fermentation (Simon, 2007; Conrads et al., 2014). On the other hand, as mentioned, one of the mechanisms of probiotics to prevent the growth of pathogenic bacteria is the production of organic acids. Therefore, the question may arise whether the presence of these acids causes a further reduction in pH and an increase in tooth decay. In different studies, it was shown that salivary pH levels were significantly higher in the probiotic treatment group than in the control group. The results of this study are consistent with some other studies that have reported an increase in pH level after the use of yogurt (Shakovetz et al., 2013) and curd-containing probiotics (SrivaStava et al., 2016a). The increase in the pH level after the consumption of probiotics can be considered due to their competition with pathogenic bacteria and reducing their number. This reduction in the number of acid-producing pathogens causes the production of acid to decrease and, as a result, the pH level of saliva increases. Since tooth decay is affected by pH imbalance, these findings can be important. The issue of protection and security has been noticed in recent years due to the prevalence of probiotic food products. A probiotic strain to treat a bacterial disease must have some characteristics. For example, the probiotic bacteria should not cause disease or otherwise susceptible the individual to other disease states by disrupting the ecosystem in which it resides (Hillman et al., 2000). They should also be examined and screened for general safety, such as antibiotic resistance genes and those related to the potential invasion (Corcoran et al., 2004; Meurman and Stamatova, 2007). Considering these concerns about the consumption of live bacteria, we should consider a suitable and safe alternative that has the same biological health benefits as probiotics (Aguilar-Toalá et al., 2018). The evidence achieved from *in vitro* and *in vivo* studies indicates that postbiotics are clinically safe and have beneficial and therapeutic effects if used in appropriate amounts and duration (Patel and Denning, 2013; Dinić et al., 2017). With features such as a safe profile, long shelf life (up to 5 years), no toxic effects, standardization, and easier transportation, postbiotics can be safe and cost-effective alternatives for probiotics in the pharmaceutical and food industries (Homayouni Rad et al., 2021; Rad et al., 2021a).

9 Conclusion

Probiotics and their therapeutic effects in the control, prevention, and treatment of some diseases have been the subject of attention for many years. Therefore, people's desire to use probiotic food and pharmaceutical products is increasing day by day. Due to the problems that exist in the survival of probiotics in food until the time of consumption, as well as under adverse environmental and gastrointestinal conditions, the interest in using probiotic side products and secretions, especially postbiotics, has increased. Because there is no need for survival of probiotics, and also these compounds are kept unchanged for a long time and are easily included in different food formulations, therefore, postbiotics can be a suitable alternative to replace live probiotics. One of the new topics is the use of postbiotics in maintaining and improving the health of the oral cavity. Various studies have shown that the presence of probiotics in the oral cavity has significant effects in reducing abnormalities such as tooth decay, oral cavity fungus, infection, and swelling of the gums and palate. It seems that the use of postbiotics instead of probiotics has a similar effect and can be effective in the prevention and cure of many oral and dental infectious diseases caused by the presence of pathogens such as *S. mutans*, and the results of existing studies confirm this impact. However, there are still some challenges as to whether postbiotics are as durable as probiotics. Also, in order to prove these preventive and therapeutic effects, many animal studies and human clinical trials are needed, especially in the case of postbiotics of different types and species of probiotics, to be able to prove their effectiveness finally. Since probiotics are acidogenic like cariogenic bacteria such as *S. mutans*, future studies also could examine the issue of what differences exist between the amount and type of acids produced by probiotic and pathogenic strains. The results of these studies can provide clearer evidence and reasons for whether there is a difference in the cariogenic of these acids and the strains that produce them.

Author contributions

EM and AHR conceived the idea. EM wrote the first draft of the manuscript. HP wrote sections of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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