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Studies on the Oral Disease Improvement Effects of Probiotics : A Review

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프로바이오틱스의 구강질병 개선에 관한 연구 고찰

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Abstract This study is a review of research articles on the characteristics of probiotics. Probiotics are effective at ameliorating immune disease, alleviating glucose intolerance, and improving constipation and diarrhea. Furthermore, they have anticancer and antitumor effects, preventive effects against cardiovascular disease, antidiabetic effects, antioxidant effects, antibacterial effects, and they produce useful metabolites. It has been demonstrated that oral probiotics are effective in eliminating halitosis and forming a favorable oral ecosystem, by creating an environment that is not readily inhabited by harmful bacteria, such as Streptococcus mutans, which produces lactic acid and causes tooth decay, or Porphyromonas gingivalis, which causes gum disease.As a result, oral probiotics are being considered not only as therapeutics against diseases, but also as preventive agents for the maintenance of a healthy oral balance. In spite of some limitations, clinical trials are currently underway, and this study can provide evidence to support the use of probiotics to improve oral health conditions, including dental caries, periodontal disease, and Candida colonization.

Key Words : Probiotics, Disease management, Periodontal disease, Dental Caries, Bacteria

요 약 본 연구는 프로바이오틱스의 특성과 관련 연구에 대한 종설이다. 프로바이오틱스는 면역질환 개선 효과, 유당불내증 완화 효과, 변비 및 설사 개선 효과, 항암 및 항종양 효과, 심혈관계 질환 예방 효과, 항당뇨 효과, 항산화 효과, 항균효과, 유용 대사산물의 생산 등의 기능성을 입증하였다. 구강 프로바이오틱스는 젖산을 생성하여 충치의 원인이 되는 뮤탄스균과 잇몸 질환을 일으키는 진지발리스균을 비롯한 유해균이 서식하기 어려운 환경을 만들어 구강 생태계 조성과 구취 제거에 효과적이라는 연구가 입증되었다. 그 결과 질환 완화는 물론 건강한 구강 밸런스를 관리하는 예방법으로 주목받고 있다. 일부 제한점에도 불구하고 현재 유용한 임상연구가 진행되고 있으며, 본 연구는 치아우식증과 치주염, 칸디다의 집락화 등 구강상태를 개선하기 위한 프로바이오틱스의 근거가 될 수 있을 것이다.

주제어 : 프로바이오틱스, 질병관리, 치주질환, 치아우식증, 세균

1. Introduction

With the 'Human Microbiome Project', started by the U.S. National Institutes of Health in 2012, research on gut microbiota is being recognized as a new avenue to overcome the limitations of modern medicine, and has accelerated our understanding of the relationship between microbes

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and various diseases[1]. The human microbiome is a portmanteau of microbiota and genome, and a concept encompassing all microbial communities living in the human body as well as their genetic information. Recently, with rapid advances in next-generation sequencing technology, it has become possible to use genetic information from microbes in the body to not only manage health but also treat intractable diseases. Accordingly, the human microbiome is receiving attention as a solution to various problems relating to diseases and the human body.

Around 95 % of human microbiota are found in the colon and the rest of the digestive system, and the remaining 5 % have a broad distribution in the other parts of the body including the respiratory system, reproductive organs, oral cavity, and skin[2]. Although bacteria are the most common microbes in the human body, there are also a wide variety of viruses, archaea, molds, and protozoa. Most of the microbes are commensal microbes which cause no harm to the host, and some can be classified as beneficial microbes (probiotics) which produce health-improving metabolites or suppress pathogenic bacteria, or harmful microbes which are pathogenic, and harmful to health[3].

The human gastrointestinal (GI) tract is a complex ecosystem inhabited by hundreds of species of microbes, and it performs two roles, namely, nutrient absorption and prevention of invasion by pathogenic bacteria. While some intestinal microbes are recognized as disease-causing pathogenic bacteria, most intestinal microbes form a mutually beneficial symbiotic relationship with the host. Intestinal microbes not only affect the immune system and energy metabolism, but also, outside of the GI tract, affect the functions of the heart, lungs, and brain.

Our body is connected by a single tube from the mouth to the anus. This means that oral health is directly related to the health of not only the teeth, but also various other organs in the body including the stomach, and closely related to overall health management. In the mouth, there are around 100 million bacteria from 770 species, including both beneficial and harmful bacteria, and balancing the oral bacteria is very important in the maintenance of oral health[4].

Dysbiosis of the human microbiome is associated with several diseases, and hence, there has been a growing interest in research to isolate probiotics and analyze their functional effects, with the aim to prevent or treat diseases by regulating the microbiome[5].

Probiotics are live microbes that improve the balance of the host's intestinal microbiota, and have beneficial effects on health. When administered to humans at appropriate doses, probiotics have a positive effect on health. Although the actual mechanisms of action of probiotics are unclear, various studies have demonstrated that they alter intestinal microbe communities and the intestinal environment.

The role of probiotics in the prevention of dental caries has been suggested by studies that demonstrated that *Lactobacillus rhamnosus* GG[6] and *Lactobacillus reuteri*[7] decreased the number of *S. mutans,* a bacteria that causes dental caries. Similarly, it has also been shown that by ingesting probiotics, the oral Candida count can be reduced and that the oral yeast infections can be controlled[8]. However, probiotics are not being widely used in the improvement of oral health despite many such results. In this study, we aimed to summarize the findings on the functions of probiotics in the improvement of human health, and to explore the potential benefit of probiotics in the prevention of oral disease.

2. Methods

This study is a review of research articles on the characteristics of probiotics. In Stage 1, we

designed and planned research content related to the characteristics of probiotics, and in Stage 2 we performed a literature search. In Stage 3, based on the selected literature, we collated the research contents. In Stage 4, we objectively interpreted and derived conclusions from the analyzed data on content related to probiotics and human heath care. The period for the literature search and organization of results was from 1st January to 30th April, 2019.

For conducting online searches, we used global databases such as, PubMed, Google Scholar, and Google, and domeatic databases such as KISS, NDSL, DBPIA, KMBASE, and RISS. For search terms in the literature search, probiotics was used as the query term, and terms such as oral, efficacy, and functionalities were used as detailed items. The literature search included journals and books. Among more than 100 papers selected, the papers that mentioned the health improvement effects of probiotics were selected. The review was written by using recently published 10 plus papers among the selected papers; papers not related to dentistry, having no content regarding the improvement effects of probiotics, or having duplicate content were excluded.

3. Results

3.1 Definition of probiotics

Probiotics were first defined by Lilly & Stillwell as 'factors produced by microbes that promote growth,' and are defined by FAO and WHO as 'living organisms that provide benefits to the host when a sufficient quantity is consumed'[9]. The main probiotics genera are *Lactobacillus* and *Bifidobacterium*, while *Enterococcus, Streptococcus*, and *Leuconostoc* are also used as probiotics[5].

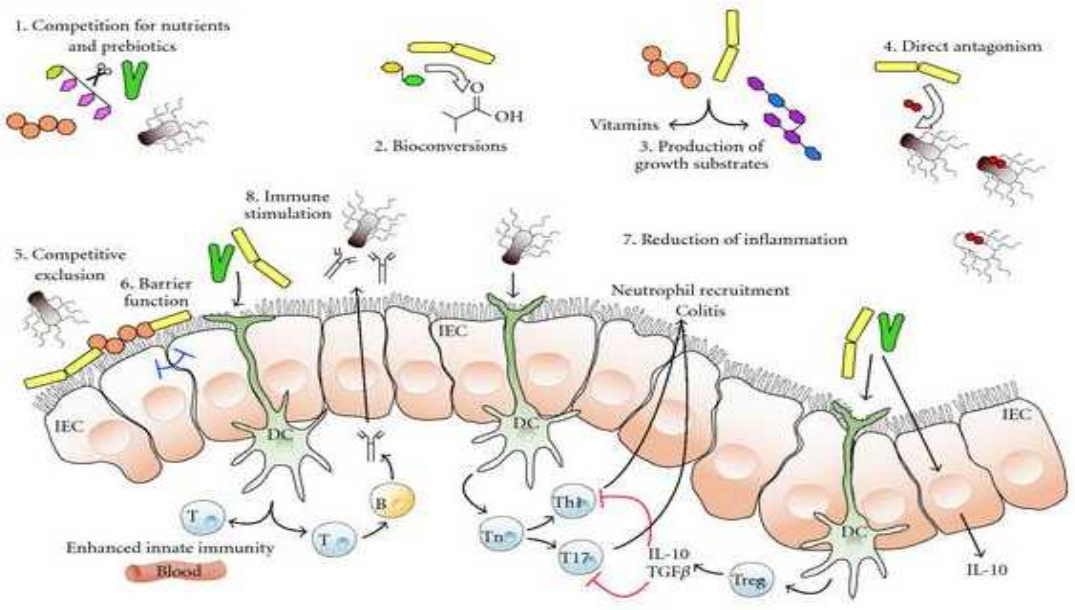
The major effects of probiotic strains are related to the prevention and relief of symptoms of GI and metabolic diseases, including the reduction of blood cholesterol, alleviation of the symptoms of inflammatory bowel disease, anticancer action, regulation of blood pressure, regulation of immune system, constipation relief, and improvement of allergies[10-13]. Changes in the intestinal microbiota composition as well as in the host's metabolic system and mucosal immune system due to probiotic consumption require successful colonization by exogenous microbes. In human experiments, probiotic strains are usually only capable of short-term colonization, and hence, probiotic products need to be consumed persistently to be effective[14].

In 2002, FAO/WHO published probiotics assessment guidelines, stipulating the criteria that need to be satisfied as follows[15]: (i) probiotics must be safe to consume. However beneficial it may be for our body, consuming a certain amount of live bacteria could, in some circumstances, cause unexpected adverse effects. Therefore, potential harmful effects to the host must be minimized, and fermented foods that have been left for a long time could be used as a suitable source of candidate microbes for probiotics. (ii) Probiotics should be resistant to gastric acid and pancreatic juice. The low pH of the stomach and the antibacterial agents and digestive enzymes secreted by the pancreas are defense mechanisms, protecting our body from exogenous microbes. Probiotics need to pass the stomach and pancreas and arrive in the intestines alive; they should be resistant to these defense mechanisms. (iii) probiotics should be able to colonize the epithelial cells and should have antimicrobial activity. The colon is already the part of the body with the highest concentration of microbes; hence, probiotics should have antimicrobial activity, and be capable of colonizing the intestinal epithelium alongside existing intestinal microbes. (iv) They should exhibit competitiveness with pathogenic bacteria. Probiotics and pathogenic bacteria are both exogenous microbes entering the body, and so they must compete with each other in order

to establish themselves among the commensal microbiota. If probiotics outcompete pathogenic bacteria for intestinal colonization, they will provide the body with some resistance against pathogenic bacteria. (ⅴ) They should be resistant to food additives, and be stable in food. Although microbes exist almost everywhere around us, the microbes that can be cultured and stored stably in a laboratory account for only 1% of all microbes. Thus, microbes demand specific culture conditions and are sensitive to the external environment. However, since probiotics are usually consumed as part of another food, and because commercial food products contain various additives to improve the taste and scent, probiotics should be resistant to food additives, in order to maintain their activity, and should be stable within a food matrix[16,17].

3.2 Mechanisms of action of probiotics

Although the actual mechanisms of action of probiotics have not been clearly revealed, the mechanisms demonstrated in animal models and in *in vitro* experiments are presented in Fig. 1[18]. These mechanisms include the following: (ⅰ) competition with food components as growth substrates, (ⅱ) bioconversion, such as glucose fermentation products with inhibitory effects, (ⅲ) production of growth substrates such as vitamins, (ⅳ) direct antagonism by bacteriocins, (ⅴ) competitive exclusion at binding sites, (ⅵ) improving function of the intestinal wall, (ⅶ) maintenance and persistence in the intestine due to reduced inflammation, (ⅷ) and immune stimulation[17].



These mechanisms include (1) competition for dietary ingredients as growth substrates, (2) bioconversion of, for example, sugars into fermentation products with inhibitory properties, (3) production of growth substrates, for example, EPS or vitamins, for other bacteria, (4) direct antagonism by bacteriocins, (5) competitive exclusion for binding sites, (6) improved barrier function, (7) reduction of inflammation, thus altering intestinal properties for colonization and persistence, and (8) stimulation of innate immune response (by unknown mechanisms). EPS: extracellular polymeric substances, IEC: epithelial cells, DC: dendritic cells, T:T-cells. Adapted from the article of Paul and Jakki (Interdisciplinary perspectives on infectious diseases, 175285, 2008)[18] in accordance with the Creative Commons Attribution (CC BY 4.0) license

Fig. 1. Schematic diagram illustrating potential or known mechanisms of the impact of probiotic bacteria on the microbiota.

3.3 Probiotics and systemic disease

Although probiotics have shown various functions in both *in vitro* and *in vivo* experiments, a number of conditions have made it difficult to verify these effects in clinical trials. The functions of probiotics are known to be strain-specific. In the future, even more research is needed to investigate the mechanisms through which probiotics express their functions in humans(see Table 1)[19].

3.3.1 Alleviation of diarrhea

Numerous studies have been performed using probiotics to prevent acute infectious diarrhea. In a large-scale randomized controlled trial, some probiotic strains were found to have protective effects against diarrhea[20]. In children aged 1 month to 3 years who had visited the hospital with acute diarrhea, those who consumed 10 billion cells of *L, rhamnosus* GG per day showed a diarrhea incidence of 7-10 %,

Table 1. Different types of probiotic microbial strains, and their usage.

Disease/Condition	Strain
Eczema	*Escherichia coli* *Bifidobacterium bifidum* *Bifidobacterium lactis* *Lactococcus lactis*
Food allergies	*Escherichia coli*
Immune-related diseases	*Bacillus circulans* PB7 *Lactobacillus plantarum* DSMZ 12028
Antibiotic effect removal	*Enterococcus mundtii* ST4SA *Lactobacillus plantarum* 423 *Lactobacillus brevis* KB290 *Lactobacillus* strains *Bifidobacterium* strains
Gastroenteritis	*Lactobacillus casei*
Intestinal hyperpermeability	*Lactobacillus plantarum species* 299 (LP299)
Vaginal candidiasis	*Lactobacillus rhamnosus* GR-1 *Lactobacillus reuteri* RC-14
Urinary tract infection	*Lactobacillus rhamnosus* GR-1 *Lactobacillus reuteri* RC-14
Lactose intolerance	*Lactobacillus acidophulus*
Non-steroidal anti-inflammatory drug	*Escherichia coli* strain Nissle 1917
Intestinal dysbiosis	*Lactobacillus johnsonii* La1 *Lactobacillus strain* *Lactobacillus* GG
Irritable bowel syndrome	*Bifidobacterium infantis* 35624 *Escherichia coli* DSM17252 *Bifidobacterium infantis* 35624
Traveler's diarrhea	*Lactobacillus* GG *Lactobacillus plantarum*
Radiation-induced diarrhea	*Lactobacillus casei* DN-114 001
Crohn's disease	*Escherichia coli* strain Nissle 1917
Colon cancer	*Enterococcus faecium* M-74 *lactic acid bacteria*
Ulcerative colitis	*Lactobacillus acidophilus* *Escherichia coli* Nissle 1917 *Bifidobacterium*
Peptic ulcer disease	*Lactobacillus acidophulus*
Atopy	*Lactobacillus rhamnosus* GG
Hypercholesterolemia and cardiovascular diseases	*Enterococcus faecium* M-74 *Lactobacillus plantarum* *Propionibacterium freudenreichii* *Lactobacillus plantarum* PH04

Adapted from the article of Amara and Shibl (Saudi pharmaceutical journal, 23(2), 107-114, 2015)[19] in accordance with the Creative Commons Attribution (CC BY 4.0) license.

which was significantly lower than that shown by the placebo group (33%)[21]. When caring for children with acute gastritis, in addition to fluid therapy, the probiotics *L. rhamnosus* GG and *Saccharomyces boulardii* can be considered, and *E. faecium* SF68 which reduced the risk of diarrhea lasting 4 or more days[22]. In a recent study, patients with symptoms of diarrhea associated with *Clostridium difficile* showed high mortality and recurrence rates, but the symptoms were reduced after the administration of probiotics[23]. Although there is no enough evidence, when *S. boulardii* was administered with antibiotics, it helped to reduce antibiotic-induced diarrhea and prevent recurrence; it is thought that other strains could also be effective[24].

3.3.2 Amelioration of immune disease

Among the immune modulating mechanisms of probiotics studied to date, well known mechanisms include stabilizing intestinal wall function, stimulating intestinal IgA production, and regulating inflammatory cytokine secretion. In addition, probiotics have also been reported to modulate the overall immune system by altering the composition or activity of other intestinal microbes[25]. Several *in vitro* and *in vivo* studies have demonstrated that probiotics help immune function, such as increasing the number of phagocytes, increasing NK cell activity, or stimulating IgA secretion[26]. In particular, probiotics increase the secretion of Th1 type cytokines such as IL-12 and INF-γ, and inhibit the expression of Th2 type cytokines via IL-10 secretion by Treg cells[27].

3.3.3 Antitumor effect

Compared to other forms of cancer, there has been more research on the preventive effects of probiotics against colorectal cancer. The mechanisms for suppressing colorectal cancer that have been revealed so far are as follows: (ⅰ) boosting the host's immune system, (ⅱ) binding to and degrading potential carcinogens, (ⅲ) qualitatively changing intestinal microbes that caused the production of carcinogens and cancer-promoting substances such as bile salt-degrading bacteria, (ⅳ) production of anticancer or antimutagenic compounds in the colon, and (ⅴ) changing metabolic activity in the intestines. One explanation for tumor suppression by lactic acid bacteria is that it is possibly mediated by the host's immune response. In addition, one study reported that lactic acid bacteria with antitumor effects play an important role in the host immune protection system through the enhancement of specific and non-specific mechanisms[28].

3.3.4 IBD (Inflammatory Bowel Disease) and IBS (Irritable Bowel Syndrome) treatment effects

The human GI tract contains a diverse, complex community of microbes[29], and these are known to modulate the inflammatory response in allergic reactions and inflammatory bowel disease[26]. When a problem develops in the normal interactions between the microbiome and the host, it results in a bowel disease, such as IBD or IBS. Therefore, maintaining the normal balance of the intestinal microbiome has emerged as a potential alternative method for the prevention and treatment of these diseases[29]. Niedzielin studied 20 IBS patients and found that *L.actobacillus plantarum* 299v reduced upper abdominal pain[30], and in a human study involving 360 IBS patients, *Bifidobacterium lactis* was effective in the treatment of IBS[31].

3.3.5 Preventive effect against cardiovascular disease

There are three known pathways through which lactic acid bacteria inhibit cholesterol absorption. In the first pathway, lactic acid

bacteria colonize the intestine and proliferate, they adhere to the intestinal wall and excrete cholesterol[32]. In the second pathway, lactic acid bacteria adhere to the intestinal wall and excrete bile salts. Cholesterol is a precursor to bile salts, hence, in order to supplement the insufficient bile salts, the bacteria use cholesterol, ultimately reducing the concentration of cholesterol in the body[33]. In the third pathway, lactic acid bacteria deconjugate conjugated bile acid[34]. Because bile salt hydrolase is able to deconjugate conjugated bile acid, bacterial strains with this function can inhibit cholesterol absorption in the small intestine[35].

3.4 Probiotics and oral disease

Oral disease is caused by imbalance among the millions of microbes living in the mouth, and can manifest as halitosis, calculus, inflammation, periodontal disease, or tooth loss[36]. Interest in oral probiotics has grown with the suggestion that harmful intraoral bacteria could affect the health of the whole body[37]. Oral probiotics colonize and are active in the oral cavity, helping oral health management by increasing the concentration of beneficial bacteria in the mouth, and controlling the growth and activity of harmful bacteria[38,39]. The mechanisms of action in the mouth are not yet completely known. However, it is thought that the same mechanisms as that of the GI tract are involved, and that there will be both systemic and local intraoral effects[40].

Overseas, probiotics are being developed to treat various oral diseases. Examples include replacement therapy, in which wild-type *S. mutans*, which is a pathogenic bacteria in dental caries and part of the normal intraoral microbiome, is replaced with bacteria that have deactivated lactate dehydrogenase gene[41], or the use of *S. mutans* which produces single chain antibodies to deactivate pathogenic bacteria, toxins, and cytokines[42].

3.4.1 Preventive effect against dental caries

Dental caries is the process of decalcification by acid produced by microbes in dental plaque. Starting with a study in 2001 by Nase et al.[43], there have been several clinical research on dental caries. In most studies, probiotics showed the suppression of *S. mutans* in the saliva, but in some, there were no changes after probiotic use[44,45]. Compared to other microbes, there has been more research on the characteristics of probiotics including *Lactobacilli*. In particular, *L. rhamnosus* GG has been the subject of several studies. Unlike other *Lactobacilli*, *L. rhamnosus* GG cannot readily ferment sugar, hence, it is considered to be a safe bacteria species for the teeth. However, it has been found that *L. rhamnosus* GG does not easily form clusters in the mouth[46].

In a study by Nase in 2001, *L. rhamnosus* GG was administered to 594 kindergarten students aged 1-6 years for 7 months through milk. Clinically, the group that consumed probiotic milk showed a decrease in dental caries compared to the group that consumed normal milk, and the probiotic group also showed lower levels of *S. mutans* in the saliva and dental plaque. Especially in children aged 3 to 4 years, the dental caries preventive fraction (PF) of *L. rhamnosus* GG was 56%; the prevention effect in this age group was higher than that in other age groups [43]. A similar study was conducted in Sweden, where milk containing *L. rhamnosus* LB21 and 2.5 ppm fluoride was provided to 1 to 5 year old infants every day. The resulting PF of this study was 75%[44]. In a recent study in Finland, artificial nipples were used as a new method for continuously providing *L. rhamnosus* LB21 to 0 to 12 months old infants. However, the PF of 4 year old infants was only 5%, which might be due to uncertain compliance[47]. Stensson et al[48]. showed a PF of 29% in 7 year-old children who were treated with 5 drops of *L. reuteri* ATCC for the first 12 months.

A study by Calgar in 2007 examined the effects of xylitol and probiotic chewing gums on *S. mutans* and *Lactobacilli* in saliva. In 80 healthy adults aged 21-24 years, *L. reuteri* was used to test the effects of probiotics on dental caries. Xylitol and probiotic chewing gum both decreased the concentration of *S. mutans* in saliva. However, when xylitol and probiotic chewing gums were used together, the *S. mutans* reducing effect was not improved[49].

Studies have also been conducted using other strains of *Lactobacilli* against dental caries: *L. casei* and *L. acidophilus* inhibited *S. mutans* in experimental or clinical studies[50,51].

A study on the growth inhibitory effect of probiotics on *S. mutans* and *S. sobrinus* was conducted in 2009 in Korea. This study experimentally observed the growth inhibitory effect of three standard lactic acid bacteria—*L. acidophilus*, *L. casei*, and *L. plantarum*—and commercially available yogurt products on *S. mutans* and *S. sobrinus*. The results showed that probiotic bacteria generally reduced the number of bacteria causing dental caries, although there were differences in the extent of reduction. When the bacteria causing dental caries and probiotic bacteria were cultured together, the 2 hour culture showed a larger decrease in bacteria causing dental caries as compared to the 1 hour culture, and a large inhibitory effect (higher than 50%) was observed when they were cultured for 24 h. Thus, the inhibitory effect increased with increasing culture time, when the bacteria causing dental caries and probiotics bacteria were cultured together. This implies that the exposure time of probiotics bacteria to the bacteria causing dental caries is important. The experimental results show that *the L. plantarum* lactic acid bacteria have a higher inhibitory effect than other bacteria[52].

3.4.2 Preventive effects against gingivitis and periodontitis

Gingivitis and periodontitis are diseases of the tooth-supporting tissues caused by intraoral bacteria and the host's immune response. One important cause of periodontitis is an increase in the number of Gram-negative bacteria and the absence of beneficial microbes in the periodontal microbiota[53]. Several studies have shown that probiotic *Lactobacilli* has the potential to inhibit the growth of major bacteria that causes periodontal disease, such as *P. gingivalis, P. intermedia,* and *A. actinomycetemcomitans*. Recently, Ricca studied the effects of *L. brevis* as a probiotic in patients with chronic periodontal disease. *L. brevis* improve periodontal disease through its anti-inflammatory action, mostly by reducing prostaglandin E_2(PGE_2) and matrix metalloproteinase(MMP). In this study, Ricca suggested that *L. brevis* lowered the levels of PGE_2 and MMP, which cause periodontal disease, by reducing nitric oxide production[54]. Shimauch et al.[55] performed a double-blind randomized comparative clinical trial, administering *L. salivarius* WB21 to 66 healthy individuals, and observed improved periodontal indices after 8 weeks. Mayanagi et al.[56] and Zahradnik et al.[57] observed a decrease in *P. gingivalis*, a causative bacteria for periodontal disease, in the saliva and gingival plaque of healthy individuals following lactic acid bacteria treatment. Burton et al.[58] administered *L. salivarius* M18 or placebo for 3 months to 100 individuals aged 5-10 years, and assessed changes in the dental plaque and gingival scores. The group treated with probiotics showed much lower dental plaque scores, but there was a little difference in the gingival scores. These results were also confirmed in a study by Karuppaiah et al.[59].

3.4.3 Effects at reducing halitosis

There have also been studies showing positive outcomes for the use of probiotics in reducing halitosis. *W. cibaria* isolated from the mouths of healthy children showed the potential to reduce halitosis. In an *in vitro* experiment, peroxide produced by *W. cibaria* reduced volatile sulfur

compounds produced by *F. nucleatum*, which are a major cause of halitosis. Participants who rinsed their mouths with a suspension containing *W. cibaria* also showed a reduction in the levels of volatile sulfur compounds due to the peroxide produced by *W. cibaria*[60].

3.4.4 Reduction of Candida

There have been studies that showed that probiotics have the potential to reduce intraoral yeast infections. Hatakka et al.[61] showed that probiotics can reduce intraoral *C. albicans*. This study was a double-blind randomized comparative clinical trial to assess the effects of probiotics on the prevalence of candidiasis. Probiotic cheese or placebo cheese was consumed for 16 weeks by 276 elderly individuals. The group that consumed probiotic cheese showed a 32 % decrease in the *Candida* count in saliva, while the placebo group showed a 21 % increase. In addition, probiotics therapy is effective at reducing the number of patients with *Candida*-related stomatitis[62], and the *Candida* count in elderly individuals with dentures and no candidiasis-related symptoms[63]. Recently, Kraft-Bodi et al[64] conducted a study in which 215 elderly people ingested the probiotic, *L. reuteri* twice a day. The study then evaluated the oral Candida count and prevalence. After 12 weeks, it was observed that *L. reuteri* treatment significantly reduced the salivary Candida count to below 104 CFU/ml in the treated subjects compared to the placebo group.

4. Conclusion

For a long time, probiotics have been consumed safely, in the form of dairy products, without any great risk. However, in order for more probiotics to be used clinically, more research on their safety is required. Most probiotic bacteria are used without significant risk, and hence, if probiotic consumption increases, leading to a higher concentration of intraoral probiotic bacteria, the risk of bacteremia will also increase. In particular, the risk of bacteremia increases in patients with immune dysfunction or severe diseases. Indeed, there have been cases of bacteremia caused by probiotic use in patients with impaired immune function or chronic disease[65]. There has also been a case of *Lactobacillus* endocarditis during dental treatment in a patient who consumed *L. rhamnosus* as a probiotic[66]. Thus, in order to use probiotics for the treatment of oral disease, it is important to not only select suitable bacteria, but also to consider the condition of the patient. It is also necessary to thoroughly study the possibility of antibiotic-resistance genes being transferred from the probiotic bacteria to other intraoral bacteria. Although we have discussed studies showing the possibility of using probiotics for effective treatment of dental caries, some bacteria used as probiotics have the ability to produce acidic substances through the fermentation of carbohydrates. These bacteria can cause damage if they come in contact with the teeth. Therefore, it will be safer to deliver these bacteria to patients using dairy products that also contain calcium and phosphorus. When acid-producing bacteria are used as probiotics, it is important to be careful so that they do not cause caries[67]. In order for probiotics to be used effectively against multiple oral diseases, including dental caries, we must have an accurate understanding of the basic oral microbial ecology. All probiotic bacteria do not have equal effects, but each possess unique properties; hence, the appropriate bacteria need to be selected for use as probiotics. Furthermore, it will be necessary to find the most effective probiotic bacteria for each disease. In the future, it will be necessary to investigate the appropriate doses and which mixtures of strains are effective, study mechanisms of action, and perform further clinical trials before using probiotics for therapeutic or preventive purposes.

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