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VARIOUS HEALTH BENEFITS OF PROBIOTICS

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Abstract

Unlike bacteria that cause diseases, probiotics are beneficial bacteria and yeasts that help various body systems, especially the digestive system and skin, to work in a balanced way. Beneficial bacteria, which also play a major role in eliminating the pathogenic effects of harmful bacteria, are found naturally in the body. While these communities that are formed are called "normal flora", they have been called "microbiota/microbiome" in recent years. Beneficial bacteria in this microbiome; are microorganisms that contribute to health in the human body, survive in internal organs, and are safe to consume. Due to these properties, they can be supplemented with supplements when their number decreases in the human body for any reason. Clinical and experimental studies reveal a strong link between the brain and the gut. In these studies, it is emphasized that changes in the microbiota may affect the metabolism, immunity, and hormone system in the body and this is closely related to the development of cancer, obesity, intestinal diseases, fatty liver, depression, and panic attacks. In addition, studies show that nutrition changes the microbiota and even affects our genes. Specialists have important responsibilities in raising the awareness of our society about healthy nutrition and quality of Life. Otherwise, we see that disease phobia, especially cancer, is created unconsciously by people who are not experts in the subject. Research shows that probiotics can be used as potential solutions for human health. The strains most commonly used as probiotics include lactic acid bacteria, *Bifidobacterium, Saccharomyces boulardii, and Bacillus coagulans*. This review examines the relationship between probiotics and the human gut microbiota and their role in intestinal diseases. It also discusses its benefits such as immune modulation, cancer prevention, inflammatory bowel disease.

Keywords: Microbiota, Intestinal Disease, Probiotics, Prebiotics, Synbiotics

PROBİYOTİKLERİN ÇEŞİTLİ SAĞLIK FAYDALARI

ÖZET

Hastalıklara neden olan bakterilerin aksine probiyotikler, başta sindirim sistemi ve deri olmak üzere çeşitli vücut sistemlerinin dengeli bir şekilde çalışmasına yardımcı olan faydalı bakteri ve mayalardır. Zararlı bakterilerin patojenik etkilerini ortadan kaldırmada da büyük rol oynayan bu bakteriler, vücutta doğal olarak bulunur. Oluşan bu topluluklar "normal flora" olarak adlandırılırken son yıllarda "mikrobiyota/mikrobiyom" olarak adlandırılmaktadır. Bu mikrobiyomda faydalı bakteriler; insan sağlığına katkıda bulunan, iç organlarda yaşayan ve tüketilmesi güvenli olan mikroorganizmalardır. Bu özelliklerinden dolayı insan vücudunda sayıları herhangi bir nedenle azaldığında takviyelerle desteklenebilirler. Klinik ve deneysel çalışmalar, beyin ve bağırsak arasında güçlü bir bağlantı olduğunu ortaya koymaktadır. Bu çalışmalarda mikrobiyotadaki değişikliklerin vücuttaki metabolizmayı, bağışıklığı, hormon sistemini etkileyebileceği ve bunun kanser, obezite, bağırsak hastalıkları, karaciğer yağlanması, depresyon ve panik atak gelişimi ile yakından ilişkili olduğu vurgulanmaktadır. Ayrıca araştırmalar, beslenmenin mikrobiyotayı değiştirdiğini ve genlerimizi etkilediğini gösteriyor. Toplumumuzun sağlıklı beslenme ve yaşam kalitesi konusunda bilinçlendirilmesinde uzmanlara önemli sorumluluklar düşmektedir. Aksi takdirde hastalık fobisinin özellikle kanserin, konusunda uzman olmayan kişiler tarafından bilinçsizce oluşturulduğunu görmekteyiz. Araştırmalar, probiyotiklerin insan sağlığı için potansiyel çözümler olarak kullanılabileceğini gösteriyor. Probiyotik olarak en yaygın olarak kullanılan suşlar arasında laktik asit bakterileri, *Bifidobacterium, Saccharomyces boulardii ve Bacillus coagulans* bulunur. Bu derleme, probiyotikler ile insan bağırsak mikrobiyotası arasındaki ilişkiyi ve bunların bağırsak hastalıklarındaki rolünü incelemektedir. Ayrıca bağışıklık modülasyonu, kanser önleme, inflamatuar bağırsak hastalığı gibi faydalarını da tartışmaktadır.

Anahtar kelimeler: Mikrobiyota, Bağırsak Hastalığı, Probiyotikler, Prebiyotikler, Sinbiyotikler

1. INTRODUCTİON

The term probiotic, which consists of two parts, "pro" and "biota", means "for life" and is the antonym of the term antibiotic. Probiotics are live microorganisms that positively affect the health of the host when taken orally in adequate amounts. Prebiotics are foods that are not digested but ferment in the gut and improve the health of the host by positively affecting the growth of bacteria in the colon. Probiotics are derived from a Greek word meaning "for life". Probiotics are friendly bacteria that open up innovations to scientists' unceasing researches on the dream of humankind's desire to live healthy for many years, whose effects on preventive treatments against diseases are tried to be evaluated, and that serves a healthy life for human beings. All diseases start in the gut. If the bowel is sick, the rest of the body is also sick. " Hippocrates' calling words are today the ideology of the food-conscious population (1).

Probiotics were first noticed in 1908 by Nobel Prize-winning Russian researcher Elie Metchnikoff. Russian researcher Metchnikoff noticed that Bulgarian peasants lived longer and he saw that these people eat plenty of yogurts. When he investigated the structure of yogurt, he encountered live bacteria and called them *Lactobacillus bulgaricus*. Metchnikoff reported that substances such as ammonia, amines, and indole formed by protein hydrolysis by intestinal flora bacteria cause autointoxication in the host, and the use of lactic acid bacteria that derive their energy from carbohydrate fermentation instead of protein hydrolysis yielded beneficial results (2). However, it was possible to scientifically identify these organisms in the early twentieth century. Lille and Stillwell redefined the probiotic concept they used in 1965 and Parker in 1974, and Fuller in 1989 redefined the microbial flora of the host as beneficial microorganisms for the host [3,4]. Nowadays, probiotics have attracted the public's attention in maintaining human gut health, and the addition of prebiotics in treatment has also been proposed as synbiotics. Studies have suggested that probiotic intake increases general health and immunity (5,6).

In addition, probiotic has been identified as living microorganisms that improve the homeostasis of the microbiota to protect human gut health by the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO) (7). According to these definitions, the results of various clinical studies and an impressive number of species and strains that are beneficial are listed Those considered probiotics are in Table 1. It will help to determine the most suitable ones for the prevention and/or treatment of some diseases that show the effect of probiotics in vivo. Nowadays, there have been many in vivo studies. However, it is known that the results obtained in animal models are not directly transmitted to humans. Therefore, it was preferred to use animals with almost the same genetic background as animals associated with the human microbiota.

A great interest in the molecular processes underpinning host-microbe interactions has led to a desire for a better understanding of how probiotics work. In this review, we investigate the relationship between the role of probiotics in human intestinal microbiota and intestinal diseases, and whether probiotics have a therapeutic or preventive effect in various systemic diseases in the future (8,9).

Table 1. Results of clinical studies on probiotics (9,15).

Disease	Probiotics	The studies
Colorectal cancer (CRC)	*L. paracasei, Leuconostoc mesenteroides, L. Plantarum, Pediococcus pentosaceus* Synbiotics (inulin, pectin, beta-glucan, and resistant starch)	*L. paracasei* was found in the highest number compared to groups A (53.8 times) and B (2.5 times) and group C. But *P. pentosaceus, L. Plantarum,* and *Leuconostoc mesenteroides* were not detected.
Crohn's disease (CD)	*L. rhamnosus, L. plantarum L. acidophilus*	no reduction in inflammation was observed.

Crohn's disease (CD)	VSL#3 (*Bifidobacterium, Lactobacillus, Streptococcus thermophilus*)	mucosal inflammatory cytokine levels had decreased
Antibiotic Associated Diarrhea (AAD)	*L. acidophilus, L. bulgaricus B. animalis, S. thermophilus*	The proportion of volunteers with antibiotic-associated diarrhea was 6.9% (bio yogurt), 11.0% (commercial yogurt).
Antibiotic Associated Diarrhea (AAD)	*Streptococcus thermophilus L. delbrueckii subsp. bulgaricus L. acidophilus*	The study showed that the percentage of 202 (105 yogurt groups and 97 control groups) patients with antibiotic-associated diarrhea were 12.4% in the yogurt group and 23.7% in the control group.
Inflammatory bowel disease (IBD)	*L. acidophilus La-5 Bifidobacterium animalis subsp. lactis Bb-12*	The study was performed in both the probiotic yogurt group (Bifidobacteria (B), 43.8% and Lactobacillus (L) 36.1%) and the control group (B, 11.0%; L, 16.2%) and, placebo (B = 4.3%, L = 3.3%) Bifidobacteria and Lactobacillus numbers showed increased compared to the group.

2. *LACTOBACİLLUS, BİFİDOBACTERİUM, AND STREPTOCOCCUS STRAİNS*

Recently, a commercial probiotic mix (VSL # 3) consisting of 8 live bacterial strains has been reported. Four strains of this combination, known as VSL # 3, are *Lactobacillus* (*L. acidophilus, L. plantarum, L. casei* and *L. delbrueckii*), 3 strains *Bifidobacterium* (*B. breve, B. longum*, and *B. rush*), and the remaining one strain consist of a mixture of *Streptococcus* (*S. salivarius*) strains. This probiotic mixture has become the only probiotic.

The gene clusters of S. thermophilus have been shown in studies to encode most of the defense systems. Bifidobacterium gene clusters encode a tight adhesion pilus to increase intestinal barrier integrity. It is also predicted that Lactobacillus genomes encode signaling proteins (16,17).

Recently, a commercial probiotic mix # 3, has been reported to have therapeutic or preventive effects in various systemic diseases such as digestive system diseases, allergic diseases, liver diseases, nervous system diseases, bone diseases, atherosclerosis, and obesity (18).

3. PROBİOTİC, PREBİOTİC, SYNBİOTİC, AND POSTBİOTİC CONCEPTS

In the studies conducted, the concepts of prebiotics and synbiotics are mentioned as well as probiotics. In addition to probiotics, the health benefits of prebiotics and synbiotics have been the focus of much research in recent days. These food supplements, called functional foods, have been shown to alter and restore pre-existing gut flora. Lactulose, inulin, and a variety of oligosaccharides are among the indigestible carbohydrates found so far as prebiotics. Some starches can also escape from complete digestion during the passage through the human small intestines and reach the colon as sources of fermentable carbohydrates that can be used by intestinal bacteria. Postbiotics are probiotics that come into play after digestion. Products that contain prebiotics and probiotics together are called synbiotics. Yogurt is a good example of synbiotic food. The effect of the synbiotic is greater than the effect of the prebiotic and probiotics alone. In general, prebiotics affects the flora in the large intestine, while probiotics affect the small intestine more. Prebiotics and probiotics together act synergistically, termed cinebiotic, and it is a product containing a useful agent for both the small intestine and the large intestine (1,19,20).

4. BENEFİTS OF PROBİOTİC AND PREBİOTİCS

Probiotic microorganisms should have features such as non-pathogenic and toxigenic, being of human origin, being resistant to gastric acid and bile, adhering to the intestinal cell epithelium, being able to colonize temporarily in the gastrointestinal system, adapt to natural flora secretion. The positive effects on the health of intestinal flora supplemented with probiotic bacteria consumption have been known for many years. In researches conducted in this direction; It has been proven by clinical trials that probiotic consumption is necessary to live a healthier life, increase body resistance,

and fight intestinal disorders and diseases. The fact that probiotics can be active in the gastrointestinal environment without damage is due to their resistance in a highly acidic environment. One of the most important yeasts known to have probiotic properties is *Saccharomyces boulardii*. In vivo and in vitro studies have shown that VSL # 3 helps stomach ulcers, irritable bowel syndrome (IBS), and ulcerative colitis (UC) (8,9,21).

Probiotics are effective in treating and preventing diarrhea caused by rotavirus, allergic diseases (atopic dermatitis, allergic rhinitis, asthma, etc.), *Helicobacter pylori* infection, and inflammatory bowel disease, increasing the age of onset of diabetes and reducing irritable colon symptoms and the rate of colon cancer. It has also been found to be effective in reducing the severity and incidence of pancreatitis due to sepsis and sepsis after major surgery (22,23). Prebiotics are defined as non-digestible food ingredients that are beneficial to the host by promoting the growth and/or activity of one or more bacteria in the colon. While prebiotics is selectively used by the beneficial microflora in the colon (such as *Lactobacillus*, *Bifidobacterium*), toxin-producing *Clostridium* prevents the proliferation of potentially pathogenic microorganisms such as proteolytic *Bacteriodes* and toxigenic *Escherichia coli*. Prebiotic mixtures of specific galactooligosaccharides (GOS) and fructooligosaccharides (FOS) have been identified in the infant formula, which is similar to oligosaccharides in breast milk and stimulates the growth of bifidobacteria and lactobacilli. Supplementing newborn formulae with these particular GOS and FOS blends has been proven to increase the number of bifidobacteria and total lactobacilli, decrease the number of pathogens, and induce a short-chain fatty acid profile comparable to that of adults (24, 25).

Some of the important properties of probiotics are that they are active at low doses, lack side effects (beneficial bacteria selectively and efficiently digest it without creating gas), and their ability to control microflora modulation (26). Recently, many plant and bacterial sources have been investigated for their benefits as prebiotics and probiotics. Some new prebiotics and probiotics are listed in table (1,27).

Table 2. Some novel probiotics and prebiotics (27).

New Probiotics	New prebiotic	Source
L. plantarum	Inulin type fructans	Traditional Chinese medicinal Morindaof Officinalis or Indian mulberry roots
	Oligosaccharide	**White and red dragon fruit**
	Oligosaccharide	*Smallanthus sonchifolius* or yacon root
Faecalibacterium prausnitzii	A low molecular weight polysaccharide	Agar and algae Gelidium CC2253 alginate
	Ulvan B-glucan	Green algae-Ulvarigida *Pleurotus spp*. (pleura) mushroom

5. THE MAİN MECHANİSM OF THE PROBİOTİCS

The accepted beneficial effects and possible mechanisms of action of probiotic microorganisms have been shown in studies (28).

Mainly, probiotics have been proven to contribute to the strengthening of the epithelial barrier, adhesion to the intestinal mucosa, and combined inhibition of pathogen adhesion, production of anti-microorganisms, and modulation of the immune system (29).

It has also been found that probiotics can stimulate immunity by increasing the secretion of immunoglobulin-A (IgA) (31). Increased phagocytic activity of a high number of natural killer cells or macrophages (32).

Increased secretory IgA secretion can decrease the number of pathogens in the gut, thus better the composition of the microflora (33). Because of these immunomodulatory effects, some

researchers believe probiotics can be used to treat inflammatory bowel disease (IBD), pouchitis, food allergies, and immunization in addition to fighting gut and urogenital infections. (34).

Probiotics also compete for nutrients to be used by pathogens. Clostridium difficile, a potentially dangerous bacteria that rely on monosaccharides, causes this disease. A sufficient number of probiotic organisms use most of the monosaccharides available, resulting in the inhibition of *C. difficile* (32).

In one study, significant interleukin-10 (IL-10) production from dendritic cells in the intestinal mucosa was noted after a while in individuals consuming prebiotic and probiotic mixtures. In another study performed on *L. rhamnosus*, an interaction between probiotic and breast milk and cells secreting Ig was shown. In the same study, probiotics regulate intestinal immunity by increasing the number of cells that secrete IgM, IgA, and IgG during the breastfeeding process (35).

5.1. Adhesion To The İntestinal Mucosa

Probiotics are thought to reduce the degree of attachment of epithelial cells to these microorganisms by creating intestinal harmful bacteria that are blocked by this barrier. Various surface determinants enable the adhesion of lactic acid bacteria with intestinal epithelial cells. Passive forces, electrostatic interactions, hydrophobic and steric forces, unique structures coated with lipoteichoic acid, and lectins are all involved in lactic acid bacteria adherence (36).

Probiotics have also been shown to be beneficial for immune system regulation (37) and pathogen antagonism (38). As a result, one of the most important selection criteria for new probiotic strains has been adhesion. (36,39,40) and is closely related to some of the beneficial effects of probiotics (41,42,43).

Mucus binding protein (MUB), generated by *L. reuteri*, is the most well-studied example of bacterial adhesins that target mucus (44,45). Lactobacilli secrete proteins that are implicated in the mucosal adhesion phenotype, and these surface-bound proteins are either attached to the membrane or lodged in the cell wall (46,47).

In *B. animalis subsp lactis* and *B. bifidum*, surface proteins have been linked to interactions with human plasminogen or enterocytes. These proteins help bacteria colonize the human intestine by allowing them to make close contact with the epithelium under certain conditions (48,49). MapA (the protein that promotes mucosal adhesion) has been reported to mediate binding of *L. reuteri* and *L. fermentum* to mucus (42).

It has also been reported in studies that probiotics such as *L. plantarum* inhibit the adhesion of enteropathogenic *E. coli* to MUC2 and MUC3 (extracellular mucin secretion) secretions (38,50,51).

One study evaluated the adhesion of B. catenulatum and B. longum strains to human intestinal mucus. The study compared the results with control experiments with acid-sensitive strains. The acid-fast strain investigated in the study was reported to have a greater ability to adhere to human intestinal mucus than the original strain (52).

Inducing acid tolerance in Bifidobacteria could be an approach for selecting strains with improved stability and surface features, which could help them work as probiotics against specific infections. Probiotics have been shown to stimulate the production of cell surface mucins and the expression of the modin gene, allowing bacteria to cling to the intestinal epithelium (29,40,53).

Pathogens are prevented from sticking to the mucosa by some Bifidobacteria and Lactobacillus strains, which operate as "colonization barriers." This effect was observed in *L. rhamnosus* and *L. plantarum* strains. Both of these organisms have demonstrated the ability to inhibit *E. coli* from binding to human colon cells (32,54).

5.2. Antimicrobial Production Of Probiotics

Probiotics compete with pathogenic bacteria for a limited number of locations in the mucus layer and epithelial cells. At the same time, they prevent pathogenic bacteria from multiplying by absorbing the resources they require for reproduction. Antimicrobials such as hydrogen peroxide, organic acid, and bacteriocin are produced by them. By changing the fatty acid profile in the colon, they can alter the intestinal microflora. Probiotic strains have been found to convert linoleic acid to conjugated linoleic acid, which has anti-inflammatory and anticarcinogenic properties. The release of these chemicals by probiotic organisms positively alters the microflora (56). Organic acids, especially acetic and lactic acids, have a high inhibitory impact on Gram-negative bacteria and have been identified as the major antimicrobial chemicals responsible for probiotics' pathogen-inhibiting activity (57). Bacteriocins are antimicrobial compounds produced by probiotic microorganisms. Bacteriocins are defined as "bactericidal chemicals generated by bacteria that contain a physiologically active protein fragment. (55).

Some experiments published by the antimicrobial activity of selected probiotics are shown in Table 3. In the studies shown in the table, the most frequently investigated probiotic strains are *Lactobacillus* and *Bifidobacteria*. S. aureus, L. monocytogenes, E. coli, Vibrio spp., Aeromonas spp., Salmonella spp., and Pseudomonas aeruginosa were the most common pathogens used in the experiments. Probiotics' antagonistic efficacy against Herpes simplex virus types 1 and 2 was also investigated in one study. They also investigated the antibacterial activity of probiotics against Giardia lamblia (58, 59).

Table 3. A series of analyzes of the successful antimicrobial activity of probiotics was selected in some experiments (59, 60, 73).

Probiotics	Pathogens
L. plantarum PZ01 Oth: P. acidilactici JM241 ve JH231, P. pentosaceus JS233, E. faecium JS11. L. salivarius JM41, JK21V, JM31, JS2A, JM14, JK22, JM2A1 ve JM32	G -: *E. coli* K88, 25922 ve 1569, *S.* Enteritidis ATCC 13076, *S. Typhimurium* ATCC 14082 G +: *S. aureus* ATCC 29213,
L. acidophilus, L. fermentum, L. plantarum, L. rhamnosus, L. reuteri, B. animalis subsp. lactis, B. longum subsp. longum	G-: *E. coli* ATCC 25922, *P. aeruginosa* ATCC9027, fangi: *C. albicans* ATCC 10231 G+: *S. aureus* ATCC 6538, *E. faecalis* ATCC 29212,
L.casei, L. plantarum, L. acidophilus	G-: *E. coli* C17, *S. enterica* ser Typhimurium CECT4156, *Y. enterocolitica* IP383 G +: *L. monocytogenes*
B. longum ATCC15707, *L. acidophilus* La - 5	G-: *E. coli* O157: H7 G +: *L. monocytogenes, S. aureus*
Lactobacillus MSMC64-1	G-: *S.* Typhi DMST 5784, *V. parahaemolyticus* DMST 5665, *S. dysenteriae* DMST 15111 G +: MRSA DMST 20651, 20654
L. plantarum NA7, *L. plantarum* WCFS1	G-: *E.coli* O157:H7ATCC 43888, *S. enterica* ser Enteritidis CIP 81.3 G +: *L. monocytogenes* CIP 81.3 ILSI NA 39
L. plantarum P164, L. acidophilus P106	*Giardia lamblia*
B. amyloliquefaciens	Herpes simplex
B. amyloliquefaciens	*A. hydrophila, V. Parahaemolyticus, V. harveyi, E. tarda*
L. casei	*G-: S. sonnei, S. flexneri*
L. ramnosus	G-: *H. pylori*
L. salivarius, L. plantarum	G-: *E. coli* ATCC 8734, *S. Enteritidis* ATCC 13311, *Riemerella anatipestifer* ATCC 11845, *Pasteurella multocida* ATCC 43137 G +: *S. aureus* ATCC 6538S, *Clostridium Perfringens* ATCC 13124,
L. brevis DT24	G-: *E. coli* MTCC 729
B. subtilis, L. mesenteroides MTCC 5442	G-: *V. Cholerae*

6. PROBIOTICS AND CANCER

Epidemiological studies show that dairy products such as fermented milk and cheese have a protective effect against cancer. It is considered that the main preservatives in dairy products are milk fat components such as calcium, milk proteins, conjugated linoleic acid (CLA), butyric acid, is palmitic acid, and sphingomyelin, and lactic acid bacteria and their metabolites in the products (74).

In addition, human clinical studies have demonstrated that probiotics have inhibitory effects on the development of cancerous and precancerous lesions and have properties to manage cancer treatment side effects (75).

Probiotic bacteria have been found to lessen the risk of cancer in animal experiments and in vitro investigations., possibly due to their inhibition of mutagenic and genotoxic effects. However, although there is a general opinion about many health-beneficial effects of probiotic bacteria, the most controversial effects of probiotics are their anticarcinogenic effects. To confirm clinical results, recent translational studies have shown that specific application of selected bacterial bowel strains can improve the clinical outcome of immune checkpoint immunotherapy. *L. rhamnosus* GG (LGG), a probiotic widely studied in oncology, has proven beneficial when administered during anticancer therapy (76).

Probiotics are thought to be responsible for the detection and degradation of potential carcinogens and the production of short-chain fatty acids known as signaling molecules that affect cell death and proliferation in the immune system (77).

Anti-inflammatory cytokines play a key role in avoiding carcinogenesis, and probiotic bacteria have the potential to both boost and decrease their production. It can also activate phagocytes to eliminate early-stage cancer cells. To date, many studies have been evaluated, investigating the relationship between gut microbiota and carcinogenesis. For the potential application of probiotic strains in cancer prevention and treatment, a growing body of research has been examined and reviewed (78).

Many studies have focused on the effect of probiotics on gut microecology and cancer. *L.casei* strain has been shown to have an inhibitory effect on chemically induced tumors (79). Consequently, more in-depth studies should be conducted to better understand the interaction between host and pathogens associated with colorectal carcinogenesis. Although in vivo results show the beneficial effect of probiotics in alleviating the side effects of anticancer treatments, more randomized, placebo-controlled clinical studies are needed to fully understand the effect of probiotics and recommend their routine use as an adjunct.

7. PROBİOTİCS AND ORAL CAVİTY

Probiotics were previously a source of research on gut flora, but in recent years, it has shifted its focus to oral and dental health. Although several randomized controlled trials have been conducted in this area, the research on probiotics and oral health is still in their cradle. Probiotics can form a biofilm in the oral cavity as a protective layer for oral tissues against oral diseases. This biofilm does not allow bacterial pathogens to get close to the oral tissues. Probiotic bacteria; can release various antimicrobial agents such as organic acid, hydrogen peroxide, carbon peroxide, diacetyl, bacteriocin, and adhesion inhibitors. Their ability to adhere to surfaces in the mouth is important for the long-term probiotic effects of bacteria. The adhesion model of different probiotic strains to oral epithelial cells and hydroxyapatite was tested in one study and it was shown that *Lactobacillus* can adhere to hydroxyapatite (80, 81,82).

Some bacteria cannot be detected by the culture method, and PCR-based methods should be used to identify them. External factors (such as food, drink, temperature, and humidity) have a significant impact on the composition of the microbiota (83,84).

It has been reported that the oral microbiocenosis of elderly people differs from that of young people. Prostheses, hormones, long-term drugs, and age-related dental hygiene is all of the factors that can affect the composition of oral microbiocenosis (80,85). In addition, dental caries is one of the most common diseases found in humans (86).

According to studies, *Streptococcus mutans* is the main cause of dental caries, affecting more than 80% of the world's population [87,88]. Studies have shown that caries lesions include members of *Actinomyces, Bifidobacterium, Lactobacillus, Propionibacterium, Veillonella, Selenomonas*, and *Atopobium*, primarily Streptococcus mutans (89,90).

Oral microorganisms can also function as opportunistic pathogens and cause serious illness in other body compartments (91,92). Various systemic disorders, such as cardiovascular disease, bacterial pneumonia, diabetes mellitus, and low birth weight, can be influenced by these microorganisms. Oral microorganisms can also act as opportunistic pathogens and cause various systemic disorders in other body parts other than the mouth (Cardiovascular, pneumonia, diabetes mellitus low birth weight) (80, 91,92,93).

A microorganism must be able to cling to and colonize surfaces in the mouth to be considered an oral probiotic. Because probiotic microbes do not naturally live in the mouth, their usefulness in improving dental health is debatable. In a study, they reported the diversity of approximately 500-600 species in the oral cavity (82,94,95). In another study, they isolated *Lactobacillus* (*L. fermentum, L. rhamnosus, L. salivarius, L. casei, L. acidophilus, and L. plantarum*) species from saliva using polymerase chain reaction techniques [96]. In addition, 3790 lactic acid bacteria they isolated from 130 people with a healthy mouth were reported in a study (97).

8. PROBİOTİCS AND SKİN DİSEASES

Our bodies are home to trillions of microorganisms, many of which are found on our skin. These microorganisms also include good and bad bacteria. Research shows that probiotics are particularly beneficial for the skin. Probiotics act as a natural barrier against pathogenic bacteria on the skin.

However, many factors can reduce the level of probiotics, resulting in an increased risk of developing skin-related problems such as acne, rosacea, eczema, psoriasis, stretch marks, and skin aging. Few clinical studies are investigating the benefit of probiotics for the prevention and treatment of dermatological diseases. Current clinical studies show positive results with improvement of skin conditions after the probiotic intervention. Probiotics, both oral and topical, appear to be useful in treating some inflammatory skin conditions, as well as wound healing and skin cancer. However, further research is needed to corroborate these findings (98). Probiotics, according to research, are a direct way to affect the skin microbiota and immune response in a variety of disorders (99,100).

In one study, oral administration of *L. casei* in mice reduced hypersensitivity to a hapten in the presence of CD4 T cells (101). The cutaneous immune system of mice was protected against the immunosuppressive effects of ultraviolet B radiation when they were given *L. johnsonii* as a dietary supplement (102,103).

In a comparable in vivo investigation in people, probiotic bacteria were found to have a favorable effect on the skin, and it was hypothesized that oral ingestion of probiotic bacteria could be a novel way to protect the skin immune system from ultraviolet radiation (104).

Probiotics were compared with a placebo product in a randomized clinical trial. S ignificantly reduced transepidermal water loss to the skin in female volunteers and thus strengthened the stratum corneum barrier function (103,105).

Disorders in the skin microbiome are found in a variety of cutaneous neoplasms and play a role in promoting carcinogenesis. The probable significance of the Staphylococcus super genome in carcinogenesis is one example of the relationship between S. aureus infection and the severity of cutaneous T-cell lymphoma illness (106). A healthy microbiome, on the other hand, can inhibit carcinogenesis by regulating the immune system and managing inflammation through the activation of anti-cancer or immuno-surveillance pathways. Oral lipoteichoic acid from *Lactobacillus*, for example, is linked to less UV damage and a lower risk of skin cancer. Recently, it has been found that *S. epidermidis* strains selectively produce a nucleobase molecule that inhibits tumor proliferation and delivery (100,107,108).

9. EFFECTS OF PROBİOTİCS ON BONE

The ability of probiotics and prebiotics to increase calcium absorption and to improve bone density levels in children has been demonstrated in clinical trials. Inaddition, probiotics can induce the production of immunosuppressant cytokines that activate the regulatory T-lymphocyte community and lead to the maintenance of bone integrity (109,110).

In one study, bone mineral density was observed in stool samples of healthy menopausal women who consumed tablets containing the probiotic Bacillus subtilis (C-3102). These changes in gut populations showed significantly reduced proinflammatory responses. As a result, the study reported that *B. subtilis* C-3102 supports its inhibitory potential on bone loss. However, more research is needed to validate the strain's positive effects on osteoporotic individuals (111,112). Finally, osteoporotic men who consumed kefir, a fermented milk product enriched with probiotics, had increased bone mineral density in the femoral neck (113) (Table 4).

Table 4. Studies investigating the positive effects of probiotics on bone (109, 113, 116).

Probiotic	Number of patients	Regime	Clinical Results
L. casei	417 patients with acute distal radius fracture	Oral administration for 6 months	Rehabilitation
L. casei, L. acidophilus, B. bifidum	60 patients with rheumatoid arthritis	One capsule a day for 8 weeks	Inflammation reduction
L. casei	537 knee osteoarthritis patients	Oral administration for 6 months	Inflammation reduction
Kefir fermented milk	40 osteoporosis patients	Kefir fermented milk consumption for 6 months	Increased femoral neck bone mineral density

10. RESULTS

Studies show a detailed understanding of the pharmacokinetic and pharmacodynamic properties of probiotics makes their use in foods widespread. The critical point in the use of probiotic strains is their functional identification by genotypic and phenotypic methods. Only after this stage can be decided for safe use in foods. Adhesion to epithelial tissues, antimicrobial resistance characteristics, persistence in the gastrointestinal system, and long-term colonization are critical control steps in the selection of probiotic strains (117,118,119).

Although antibiotics such as penicillin and streptomycin save millions of human lives, there is always secondary damage as the commensal microbiota is affected (120). During the deterioration of the intestinal microbiota balance due to antibiotics, probiotics help the persistent microbiota restore this balance (121,122,123).

These day, most probiotic products are used for broader scenarios where their efficacy has not been fully determined when selling them. Therefore, probiotics should be largely based on scientific evidence with scientifically based clinical studies on the target population (124).

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