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EFFECTS OF PROBIOTICS IN PREVENTION AND TREATMENT OF MICROBIOTA RELATED DISEASES (1)

MİKROBİYOTA İLİŞKİLİ HASTALIKLARIN ÖNLENMESİ VE TEDAVİSİNDE PROBİYOTİKLERİN ETKİLERİ

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Öz: Mikrobiyota ile ilgili hastalıkların önlenmesi ve tedavisi için faydalı mikroorganizmaların veya "probiyotiklerin" kullanımına ticari ve bilimsel ilgi artmştır. Bu yararlı mikroorganizmalar, patojenik bakterilerin kolonizasyonunu engeller ve mikrobiyal dengeyi sağlar. Mikrobiyotadaki mikrobiyal denge, bağışıklık sisteminin gastrointestinal sistem dengesi, enerji homeostazı, lipid ve karbonhidrat metabolizması, beyin fonksiyonları ve davranışlarında önemli rol oynar. Probiyotikler çeşitli hastalıklarda enfeksiyon hastalıklarında ve hatta atopik hastalıklarda ve kolorektal kanserde kullanılmıştır. Bu nedenle probiyotik içeren besinleri tüketmek ve probiyotik mikroorganizma içeren besin takviyelerini kullanmak belirli sağlık problemleriyle karşılaşma riskini azaltabilir veya önleyebilir. Probiyotiklerin besinler üzerinde suşa bağlı koruyucu etkisi ve farklı hastalıkları tedavi etme potansiyeli vardır. Diğer yandan hastalıkların önlenmesi ve tedavisinde probiyotikler için etki mekanizmasını somut bir şekilde açıklayan ve olumlu sonuçları klinik denemelerle kanıtlanan birçok çalışmanın yapılması gerekmektedir. Bu derlemenin amacı, hastalıkların önlenmesi ve tedavisinde kullanılan probiyotiklerin belirlenmesi ve probiyotiklerin terapötik potansiyelini ve suş seçim kriterlerini belirlemektir.

Anahtar Kelimeler: Probiyotikler, Lactobacillus, Bifidobacterium, Microbiota, Besinler

Abstract: There is an increasing commertial and scientific interest in the use of benefical microorganisms, or ''probiotics'', for the prevention and treatment of microbiota related diseases. These benefical microorganisms prevent the colonization of pathogenic bacterias and provide the microbial balance. The microbial balance in the microbiota plays an important role in the function of the gastrointestinal tract balance of the immune system, energy homeostasis, lipid and carbohydrate metabolism, brain functions and behaviors. Probiotics have been used in various diseases to infection diseases and even to atopic diseases and colorectal cancer. Therefore, consuming foods containing probiotics and using food supplements containing probiotic microorganisms can reduce or prevent the risk of encountering certain health problems. Probiotics have strain dependent protective effect on food and potentials for treatment of different diseases. On the other hand, many studies which explain mechanism of action concretely and proven positive results with clinical trials need to be done for probiotics in the prevention and treatment of diseases. The purpose of this review is identification of probiotics which have been used in the prevention and treatment of diseases and determine the therapeutic potential and strain selection criteria of probiotics.

Keywords: Probiotics, Lactobacillus, Bifidobacterium, Microbiota, Nutrients

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INTRODUCTION

World Health Organization (WHO): Health is not just the absence of disease and disability; it has been defined as a physical, spiritual, and social well-being. Human health is under the influence of many factors like nutrition, heredity, and environmental conditions. There is a strong relationship between nutrition and health. Malnutrition reduces body resistance, the probability of contracting diseases increases, and diseases are more severe (Canbulat ve Özcan, 2007: 69-79). It is important that the gastrointestinal system is structurally and functionally normal for a healthy life. Microbiota which consist of a wide variety of bacteria, viruses, and other single-celled in the digestive system has a very important role on the health of people and animals. Human Microbiome Project (HMP) is a study project initiated in 2008 to determine the characteristics of the factors affecting the distribution and evolution of microorganisms that make up the human microbiome and microbiota. Other purposes of the project are to better understand human nutritional needs and to set microbiome-based targets for the production, consumption, and distribution of nutrients. Today, more than 10,000 bacteria and fungi and more than 3000 virus species have been detected in human body. Microbiota has an important role in human, disease and health conditions. The digestive system constitutes a large part of the microbiota, especially colon due to its large surface area and rich nutrients for microorganisms. The colon contains more than 70% of the microorganisms in our body. The flora of the gastrointestinal tract affects many biochemical, physiological and immunological features of the host (Doğan, 2012: 20-27). In general, the optimum balance in the microbial population in the digestive system is related to good nutrition and health. However, when this balance is disrupted for certain reasons, health problems that may require treatment may arise (İkinci, 2011: 80-83). Studies have reported that probiotic microorganisms positively affect health by restoring intestinal microflora balance and have a therapeutic or protective effect in many diseases (Gülmez ve Güven, 2002: 83-89).

Microbiota

In recent years, the terms microbiota and microbiome are used frequently. Microbiota refers to all the special species that live with humans. Therewithal, microbiome refers to the genes carried by microorganisms living commensally with humans. Human microbiota consists of viruses, fungi and many eukaryotic microorganisms, especially bacteria (Tuğ vd., 2002: 56-57). Also, the bacterial genome is 150 times more than the human genome in the human body . This association of human and microbial genome is called hologenoma. The number of microorganisms is 10

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times higher than the number of human cells in the human body (Whitman et al., 1998: 6578-6583). Most of the human microbiota is colonized in the digestive system, the skin, reproductive organs, and respiratory system. The digestive system, especially the colon is the largest part of the microbiota. Because it provides appropriate conditions for microorganisms. Intestinal microbiota plays a role in many biochemical processes such as synthesis of some vitamins and cofactors, destruction of short chain fatty acids, conjugated linoleic acid production, digestion of complex polysaccharides, and modulation of the immune system. Disruption or change of the balance in the microbiota for any reason is called dysbiosis. This process has been found associated with many diseases (Altunbaş ve Batman, 2017: 286-296).

Formation of Intestinal Microbiota

Intestinal microbiota is individual spesific. Microbiota varies depending on factors such as geographic origin, genetics, mode of delivery, age, lifestyle, nutrition, antibiotic usage, and diseases passage. At birth, the intestines are considered sterile. In recent years, the presence of bacteria has been determined in the intrauterine environment and it is assumed that this colonization is caused by meconium colonization. There are many factors that affect the type and number of bacteria that make up the baby's intestinal flora. External factors such as whether the mother consumes foods and foods containing probiotic bacteria, the types of birth [vaginal or surgical], gestational age and the initial feeding style of the baby [breast milk or formula], low birth weight babies, antibiotic therapy, preterm birth, geographic region affect the development of bacteria. In addition, internal factors such as the health condition of the newborn baby, immunological status, transit time of the gastrointestinal tract, pH and stress affect the development of bacteria (Dominguez-Bello et al., 2010: 11971-11975). The type of birth is very important in the variation of the intestinal microbiota. Babies born with Caesarean do not pass through the birth canal. So their microbiota development is late and includes more microorganisms from the environment. Bacterias of Klebsiella, Enterobacter and Clostridium genus are dominant. Bifidobacterium amount is low. Therefore, they are more prone to gastrointestinal and immunological disorders (Ventura et al., 2012: 467-476). In the intestinal microbiota of babies, bacterias appear to be similar to the vaginal microbiota in vaginal birth. Diet [breast milk, formula], antibiotic using in the infantile period and hygiene conditions are very effective in shaping the microbiota in the early colonization period after birth (Wall et al., 2009: 4554). In the intestinal flora of breast-fed babies in the first weeks of life, the number of Bifidobacterium increases significantly while the number of E.

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coli and Streptococcus decrease. The intestinal microbiota begins to resemble the gastrointestinal tract microbiota of a young person after the first year of life. The maturation of the gastrointestinal tract microbiota towards the adult-type is reached by the age of 3 years (Özdemir vd., 2017:25-33).

Probiotics and Probiotic Microorganisms

Probiotics are living microorganisms that have many beneficial effects on health when taken in a certain number by digestion. Probiotics were first described by Lily and Stillwell in 1965. The probiotic is derived from the Latin roots "pro" and "bios" and means "for life". Digestive tract microorganisms or products belonging to these microorganisms that are beneficial to the host's health. Among the benefits of probiotics; preventing the development and reproduction of pathogens, balancing the intestinal and urogenital system flora after antibiotic treatment, ensuring their reconstruction, relieving lactose intolerance, decreasing serum cholesterol level, preventing colon cancer and activating the immune system (Roberfroid, 2000: 162-168). Microorganisms that are generally included in the scope of probiotics are divided into 3 groups as bacteria, fungi, or yeast. The most common lactic acid bacteria used as probiotics are divided into 6 groups in classification. These are Lactobacillus, Streptococus, Enterococcus, Leuconostoc, Pediococcus and Bifidobacterium. Other microorganisms used as probiotics besides lactic acid bacteria are Bacillus, Saccharomyces, and Aspergillus (Başyiğit, 2004: 96). Among these, Bifidobacterium and Lactobacillus species are the safest and widely used probiotic microorganisms (Blackstone et al., 1981: 366-374). Probiotics used in the clinic consist of Lactobacillus, Bifidobacterium, Streptococcus and Sacchoromyces boulardii (Yeşilova, 2010: 49-56). In some products, a few microorganisms are combined. For example, in the product named VSL # 3, four separate Lactobacillus strains [L. casei, L. plantarum, L. acidophilus and bulgaricus strain of L. delbrueckii], three separate Bifidobacterium strains [B. longum, B. breve and B. infantis] and the thermophilus strain of Streptococcus salivarius.

Features of Probiotic Microorganisms

The properties sought in microorganisms used as probiotics must be reliable. They should not cause side effects on humans and animals. They must be stable to metabolized in the intestine without environmental conditions such as low pH, bile salts. Probiotic microorganisms must stick to intestinal cells and colonize. Also, they should have antagonist effect to the carcinogenic and pathogenic bacteria. Therefore, they must produce antimicrobial agents. They must be capable of generating beneficial effects such as increased resistance to diseases in the host. They should

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be resistant to antibiotics; It can be used to fix the intestinal flora in patients with antibiotic associated diarrhea. Therewithal, they must be suitable for industrial treatment, remain alive and stable for a long time in storage conditions. When added to foods, they should not decrease quality and contain highly live microorganism [16].

Complementary of Probiotics: Prebiotics

The development of probiotics depends on the presence of complex carbohydrates known as oligosaccharides in the environment. Oligosaccharides [short-chain carbohydrates] are known as prebiotics. Prebiotics are defined as low-energy foods that can reach the colon without digesting in the upper gastrointestinal tract, limit the number of pathogenic bacteria in the colon and support the development of probiotic bacteria, can be fermented but not digestible (Gibson and Roberfroid, 1995: 1401-1412).

Postbiotics

Postbiotics are metabolic by-products of probiotics. These metabolites affect health positively, such as short-chain fatty acids. Each of the short chain fatty acids [propionate, acetate and butyrate] have different functions. There are more detail about s ome postprobiotic and their potential local and systemic possitive effects in the host (Aguilar-Toalá, et al., 2018: 105-114). Propionic acids contributes to the lowering serum LDL levels by inhibiting hepatic fatty acid synthesis. It has important role in controlling hyperlipidemia which is known that the increase in the rate of blood lipid levels because of diabetes and providing healthy blood lipid levels. The low lipid level in the blood reduces the risk of heart disease. Acetate lowers intestinal pH because of it is a strong acid. Pathogenic microorganisms cannot multiply in the acidic environment, while beneficial microorganisms can multiply. Butyrate is the fuel of colon cells, it suppresses the proliferation of cancerous cells, affects colon carcinogenesis, and increases apoptosis of these cells (İkinci, 2011: 80-83).

Use of Probiotics in Microbiota Related Diseases

Many years, it has been known that the probiotic bacterias play an important role in supporting and strengthening the immune system, improving the microbiota. In a research, it has been proven by clinical experiments that probiotic consumption is required to lead a healthier life, increase body resistance and combat intestinal irregularities and diseases (Gülmez vd., 2002: 83-89).

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CLINICAL RESEARCH CONSEQUENCES

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a common disorder that affects the large intestine. Signs and symptoms include cramping, abdominal pain, gas, bloating, and diarrhea or constipation, or both. Intestinal microflora in IBS patients was found to be different from healthy individuals. Several studies have shown the efficacy of different probiotic species on IBS, Lactobacillus plantarum 299v was found to reduce abdominal pain and gas accumulation in IBS. Another study has investigated the effect of L. plantarum MF 1298 on IBS treatment. There are no positive effects of L. plantarum MF 1298 on IBS symptoms were detected. The recovery time of symptoms was significantly higher in the placebo group than in the L. plantarum group (Ligaarden et al., 2010: 6-10). Most randomized, placebo-controlled studies have suggested that Bifidobacterium have beneficial effects on IBS symptoms. In a trial with 77 IBS patients, ingestion of Bifidobacterium infantis 35624 reduced pain and bowel movement difficulty for 8 weeks (O'Mahony et al., 2005: 541-551). In a different study, the beneficial effects of Bifidobacterium animalis DM 173010 (contained in fermented milk) were determined. It has been shown that the quality of life increases in 6 months, and the frequency of defecation increases in individuals who have less than 3 defecations per week (Guyonnet et al., 2007: 475-486). In a double-blind placebo-controlled study by Kim et al., VSL#3 treatment for IBS Bifidobacterium (B. longum, B. infantis, and B. breve); Lactobacillus (L. acidophilus, L. casei, L. delbrueckii ssp. Bulgaricus , and L. plantarum); Streptococcus (salivarius ssp. Thermophilus) efficacy was investigated. VSL#3 had no effect on gastrointestinal and colonic transit or other individual symptoms but reduce abdominal distansion (Kim et al., 2003: 895-904).

Infectious Diarrhea

The most fully documented probiotic intervention is the treatment of acute infectious diarrhea. It is viral origin and its incidence is directly related to sanitation and hygiene. The purpose of treating infectious diarrhea are prevent dehydration, shorten the duration of diarrhea and prevent electrolyte imbalance. Therefore, probiotic treatment widely used besides antibiotics, oral and intravenous fluid treatments. Numerous publications on different populations have substantiated the success of specific probiotic strains (Gismondo et al, 1999: 287-292). The European Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends the evaluation of probiotic administration as well as rehydration for the treatment of acute gastroenteritis in children (Sánchez et al., 2017:

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1-8). In the guidelines developed by the ESPGHAN Working Group (WG) on Probiotics and Prebiotics provide recommendations of probiotics usage for the treatment of acute gastroentrit, in infants and children. Using of L. rhamnosus GG ve S. boulardii CNCM I-745 has been suggested in the treatment in addition to early rehydration and avoidance of dietary restrictions. These probiotics have been confirmed to be effective in reducing the duration and severity of symptoms by 50% (Allen et al., 2010: 11)

Antibiotic Associated Diarrhea

Antibiotics can be a very powerful factor causing imbalance of the intestinal microbiota. Antibiotic using is disrupt balance of colonization. As a result, clinical findings such as diarrhea and abdominal pain. The severity of clinical findings depend on the type of antibiotic, its dosage and its effects on the immune system. Therefore, long-term antibiotic treatment causes the development of diarrhea by decreasing the beneficial bacteria and the multiplication of pathogenic bacteria (Erdeve et al., 2005: 1508-1509). In patient with antibiotic associated diarrhea, Clostridium difficile multiplies excessively. Two probiotic types such as Saccharomyces boulardii CNCM I-745, a mixture of three Lactobacilli strains [L. acidophilus CL1285 + L. casei Lbc80r + L. rhamnosus CLR2] and another single strain probiotic (L. casei DN114001) had strong evidence for the prevention. Saccharomyces boulardii is effective by binding toxins of Clostridium difficile (Erdeve et al., 2005: 1508-1509).

Traveler's Diarrhea

Traveler's diarrhea (TD) is the most predictable travel-related illness. Diarrhea can be seen in travelers who goes to countries with low hygiene and sanitation standards. There are data that probiotics can prevent travelers' diarrhea. Efficacy of the probiotic varies on the strain, traveled region, and the agent that caused the diarrhea. Various studies have been conducted to evaluate prevention of traveler diarrhea with probiotics. In most of these, Lactobacillus GG was used, and traveler diarrhea significantly reduced the incidence. In a double-blind, placebo-controlled trial with S. boulardii, travelers that taking active yeast preparation, experienced a modest but statistically significant reduction in diarrhea (Goossens et al., 2003: 15-23).

Constipation

Constipation can happen for many reasons, such as when stool passes through the colon too slowly. The slower the food moves through the digestive tract, the more water the colon will absorb and the harder the feces will become. Bifidobacteria, Bacteroides and Clostridia decreased in the fecal flora of individuals with constipation. Therefore, pro-

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biotics are thought to be beneficial in constipation by balancing the flora (Gürsoy et al., 2005: 136-148). There are data that lactic acid bacteria regulate intestinal motility and relieve symptoms of constipation by lowering intestinal pH. Studies have found that the usage of L. acidophilus NFCM 1748, L. casei and Lactobacillus GG (in the fermented whey) has positive effects in treating constipation and alleviating its symptoms. Another studies has been conducted with 45 children with chronic constipation between the ages of 1-10, L. rhamnosus was found to be effective in preventing constipation. Organic acids produced by bifidobacterium are thought to promote peristaltic movement of the intestine and support normal bowel movement. It has been observed that patients with constipation, bowel movement improved and the amount of water in the stool increased when they consumed milk and dairy products containing Bifidobacterium. In the intestines of the elderly individuals, lack of Bifidobacterium population is one of the factors causing constipation (Arunachalam, 1999: 1559-1597).

Inflammatory Bowel Disease (IBD)

Inflammatory Bowel Disease (IBD) is chronic and recurrent inflammations that usually occur in the colon and small intestines. Crohn's disease and ulcerative colitis are examples of IBD. The etiology of IBD has not been precisely defined yet. The intestinal microbiota is considered to be the begining and center of the disease. It has been reported that probiotic can be used easily. Chronic inflammatory bowel diseases are divided into ulcerative colitis and Crohn's disease (Oktay, 2001: 199-206). Ulcerative colitis: Ulcerative colitis is a chronic disease that causes long-term inflammation of mucosa of the rectum and colon. The dysregulation of the gut microbiota plays an important role in the pathogenesis of UC. Defects in renewal and formation of the inner mucus layer allow bacteria to reach the epithelium and have implications for the causes of colitis. Human-Animal studies show that the rate of beneficial microorganisms decreases in inflammatory bowel diseases. However, benefical bacteria such as Lactobacillus spp. promote inflammation (Bullock et al., 2004: 59-64). Tamaki et al.(2016: 67-74) conducted a randomized, double-blinded, placebo-controlled trial to investigate the efficacy of Bifidobacterium longum 536 supplementation for induction of remission in patients with active ulcerative colitis.56 patients with mild to moderate UC were enrolled. 17 had proctitis, 3 patients had pancolitis and 36 had left-sided colitis. They treated 56 cases with Bifidobacterium longum 536 suplementation 3 times a day for 8 weeks. In total, 63% of patients receiving BB536 showed clinical remission at week 8 compared to 52% of those receiving placebo. Overall, this study demonstrated that giving BB536, in addition to standard

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treatment, improved clinical symptoms (rectal bleeding, stool frequency, mucosal findings etc.) and endoscopic findings in patients with mild to moderately active UC (Tamaki et al., 2016: 67-74)

Crohn's disease: Type of inflammatory bowel disease and chronic condition that may recur at various times over a lifetime. It usually involves the small intestine, lower part called the ileum. However, in some cases, both the small and large intestine are affected. Sometimes, inflammation may also affect the entire digestive tract, including the mouth, esophagus, stomach, duodenum, appendix or anus. Symptoms often include diarrhea, fever, weight loss, abdominal pain, anemia, skin rashes, arthritis and tiredness (Wang et al., 2012: 2405-2410). Bacterias are very different in the intestines of individuals with Crohn's disease from normal individuals. Therefore, studies have been considered to bring the flora closer to that of normal individuals using probiotics. The results obtained were not possible in reaching a definitive judgment. After Saccharomyces boulardii and antibiotic treatment, VSL # 3 has been able to maintain the remission in some cases. Successful results could not be achieved with L. rhamnosus GG (Penner et al., 2005: 1-8). Although there are some studies showing that probiotics have a positive effect on Crohn's patients, it has been shown that they are ineffective in preventing the acute period. For this reason, probiotics are currently not recommended according to ESPEN guidelines (Ateş-Özcan ve Yeşilkaya, 2019: 309).

Helicobacter Pylori Infection

Helicobacter pylori (H. pylori) is a gram (-), microaerophilic bacterium, located in various areas of the stomach and duodenum. H. pylori spreads through the contaminated food and juices, saliva, direct mouth-to-mouth contact. Duodenal ulcer, stomach ulcer and stomach cancer may develop because of this (Eshraghian, 2014: 17618-17625). In recent years, Helicobacter pylori infection affects more than half of the world's population. Resistant of strains have been developed for common antibiotic using. L. acidophilus and Bifidobacterium stay alive as they pass through high-acid (pH: 3.0) areas such as the esophagus, stomach, and duodenum. Thus, they can prevent the development of H. pylori, which causes peptic ulcer. It has been concluded that it is possible to restore microbial balance and strengthen the immune system by taking probiotics containing Bifidobacterium and Lactobacillus species (Turgut, 2006: 168). In a meta-analysis evaluating fourteen studies, H. pylori positive 1671 adult cases were treated. It was concluded that adding probiotics to the treatment increases the success rate and reduces the side effects of antibiotics. Some trials have examined the potential role

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of different probiotics in children and yielded conflicting results. In studies, Bifidobacterium animalis, L. Casei and L. Reuteri ATCC 5573 positively affected the treatment, while L. Acidophilus and S. Boulardii were not successful in treatment (Gotteland et al., 2005: 1747-1751).

Oral Health

The main features required for a microorganism to become a mouth probiotic are its ability of stick to the oral cavity and to colonize. Lactobacilli constitute about 1% of the cultivable oral microbiota in humans. The species most found in saliva for instance Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus salivarius, Lactobacillus rhamnosus and Lactobacillus fermentum (Teanpaisan and Dahlen, 2006: 79-83). Probiotic bacteria should be able to stick to the tooth surfaces and join the bacterial communities that make up the biofilm To be useful in preventing or slowing tooth decay. As an example, it has been conducted to help support that cheese can help increase the pH level in the oral cavity by reducing bacteria which in the long term could reduce decay and support remineralization. In a study of 23 bacterial species used in dairy products, it was reported that Streptococcus thermophilus NCC1561 and Lactobacillus lactis NCC2211 bacteria were able to stick to biofilms on the hydroxyapatite surface and prevent the development of the cariogenic species of S. sobrinus (Comelli et al. 2002: 218-224). In some other studies, it has been shown that L. rhamnosus and L. casei bacteria can suppress the development of two important pathogens, S. mutans and S. sobrinus, in vivo and in vitro (Meurman et al., 1995: 253-258). Krasse et al. (2006: 55-60) investigated whether L. reuteri has beneficial effect on gingivitis. In this study, the action mechanism of L. reuteri cannot be explained but the researchers focused on three possible causes. First, L. reuteri can secrete Reuterin and Reutericycline stop the development of many pathogens. The second reason is L. reuteri competes with pathogenic microorganisms due to its strong adhesion to the hard tissues of the tooth. The third reason, L. reuteri prevents the secretion of inflammatory cytokines on the intestinal and oral mucosa due to its anti-inflammatory effect. It has the potential to provide beneficial effects to individuals with periodontal disease (Krasse et al., 2006: 55-60).

Lactose Intolerance

Lactose intolerance (LI) is a common digestive disorder which is due to the inability to digest and absorb dietary lactose caused by decreased β-galactosidase activity in the intestine. Lactose consists of two monosaccharides known as glucose and galactose. It is a carbohydrate of milk and cannot be easily metabolized. This causes problems such

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as gas, abdominal pain, cramping, bloating, nausea, vomiting, diarrhea and fluid loss. Lactose-intolerant individuals can often tolerate yogurt. The reason is beta-galactosidase activity in bacterias of yogurt. There is beta-galactosidase [lactase] enzyme in S. thermophilus and Lactobacillus delbrueckii subsp. bulgaricus, which improves lactose digestion in yogurt. These bacteria are not resistant to bile and stomach acidity. Therefore, they are not expected to live and grow in the intestines. However, it provides the release of β-galactosidase enzyme that will increase bile cell permeability and hydrolysis of lactose because they are resistant to bile salts. L. acidophilus and Bifidobacterium species can be colonized in the intestines and metabolize lactose easily. Probiotic bacteria such as L. acidophilus and B. bifidum can reduce the sensitivity to dairy products by creating the enzyme β-galactosidase (Zubillaga et al., 2001: 569-579). Roskar et al. (2017: 1-8) randomized double-blind, placebo-controlled study, probiotic supplements were tried in 44 (test:22, plasebo:22) individuals with lactose intolerance. Participants in both groups consumed a capsule containing Bifidobacterium animalis IM386 (at least 5 × 109 CFU) and Lactobacillus plantarum MP2026 (at least 5 × 109 CFU) twice daily during 6 weeks of treatment. After the 6 weeks of treatment, both groups tended to improve on all symptoms. This result showed a strong placebo effect on the severity of symptoms during treatment (Roskar et al., 2017: 1-8).

Colorectal Cancer

In Turkey, colorectal cancer is placed in the diagnosis of cancer ranks at the second. The greatest effect of probiotics mechanism is in the intestines. Therefore, studies usually concentrated on colorectal cancer. The findings of some animal studies and in vitro studies have shown that probiotic bacteria reduce the risk of cancer because they prevent mutagenic and genotoxic effects. Diet plays an important role in the development of colorectal cancer. the diet which is poor in fiber and rich in animal source fat, changes the colon flora. Bifidobacterium strains are decreasing, while Clostridium and Bacteroides strains are increasing. Studies in animals have shown that some of L. acidophilus and Bifidobacterium species can reduce the level of enzymes responsible for the activation of procanserogens and consequently reduce the risk of tumor formation. In a study, it was observed that the bacterial activity changed in the intestines by taking L. acidophilus and Bifidobacterium in humans. It has been demonstrated that the activity of bacterial enzymes associated with the conversion of procanserogens into carcinogens is reduced. Lactic acid bacteria and fermented milk products have anticarcinogenic activity. Also, B. longum and B. infantis have antitumor effect (Sağdıç vd., 2004: 221-228).

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Serum Cholesterol

Cholesterol is an organic substance found in the cell membrane of all living things in the animal. High level of blood cholesterol is an important risk factor for cardiovascular diseases. The most accepted opinion: probiotics are rapidly removed from the intestinal system by breaking bile salts into free acids. Lactic acid bacteria have been found to lower LDL cholesterol and fibrinogen levels, which increase the risk of cardiovascular diseases. There are anti-cholesterol effects of many probiotic bacteria such as L. acidophilus, L. bulgaricus, L. reuteri, B. bifidum, B. longum, B. breve, B. animalis and S. thermophilus have been demonstrated (Eren, 2009:). Hypercholesterolemic mice were given a low dose of L. reuteri for seven days. While cholesterol and triglyceride levels decreased by 38% and 40%, respectively, HDL / LDL ratio increased by 20%. L. sporogenes were given to hyperlipidemic patients for three months. Serum cholesterol levels decreased by 32%, LDL levels decreased by 35%. When overweight individuals were given yogurt containing S. thermophilus and E. faecium for eight weeks (450 ml / day), LDL level decreased by 8.4% (Asgerholm-Larsen et al., 2000: 288-289).

Allergy

An allergy is immune system reacts to a foreign substance, called an allergen. It could be food, something inhale into the lungs, inject into the body or touch. This reaction could cause coughing, sneezing, itchy eyes, a runny nose and a scratchy throat. In severe cases, it can cause rashes, hives, low blood pressure, breathing trouble, asthma attacks and even death (Thomsen, 2015: 24642). Allergic symptoms and signs can be controlled more quickly when allergic children are given food with Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb-12 as well as standard allergy treatment. When L. rhamnosus GG was given to pregnant women and newborn babies, there was a 50% reduction in atopic eczema compared to those given placebo (Kalliomaki et al., 2001: 1076-1079). Atopic dermatitis is an allergic skin disease called eczema. This condition, disease which is seen in 1-3% of children, is 27% in newborns with an allergic disease in their mother. Some studies have suggested that supplementation of food with L. rhamnosus GG may prevent or improve atopic dermatitis in children and cow milk allergy in first 1 year. When pregnant women and newborn babies were given L. rhamnosus GG, the rate of atopic dermatitis decreased by 50% in the following period (Capurso, 2019: 1-41).

CONCLUSION

Changing dietary habits and metabolic disorders are becoming more common problems in the world. The most important factor that determines the survival fight against acute

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and / or chronic diseases is the inflammatory and immune response. The most important immunomodulator in both responses are the large intestine and its flora. Conditions that threaten flora integrity (antibiotics, fiber-free diet) affect the form and degree of the immune response inevitably. The World Health Organization recommended limiting the use of antibiotics in Geneva in 1994 to speed up growth in animals. In humans, vaccines, bacterial relationships, serum therapy and the use of macrophages have been suggested preventing infections by increasing immunity. It has been proven that human and animal model studies that probiotics have many beneficial effects in the organism, especially in the gastrointestinal system. For this reason, the place of probiotic bacteria has become indisputable for treatment of disease and healthy life. Especially, probiotic species belonging to Bifidobacterium and Lactobacillus genus, prebiotics as inulin and oligofructose show significant anticarcinogenic effect. There are clinal studies that include positive results in the prevention of cancer, control of side effects and complications related to cancer treatment. It has been reported that only certain probiotic bacteria show potential activity in the prevention and / or treatment of colorectal cancer. Proven data about probiotic using is very few. However, depending on food and environmental factors, they can repair the damage that occurs in the flora and resist for infections. More studies are needed for probiotics to be widely used in therapeutic medicine.

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