NEW CONCEPTS IN FOOD ENGINEERING

Conceptualizing gut microbiota, biotic, probiotics, postbiotics, paraprobiotics, psychobiotics, synbiotics and prebiotics with new approaches

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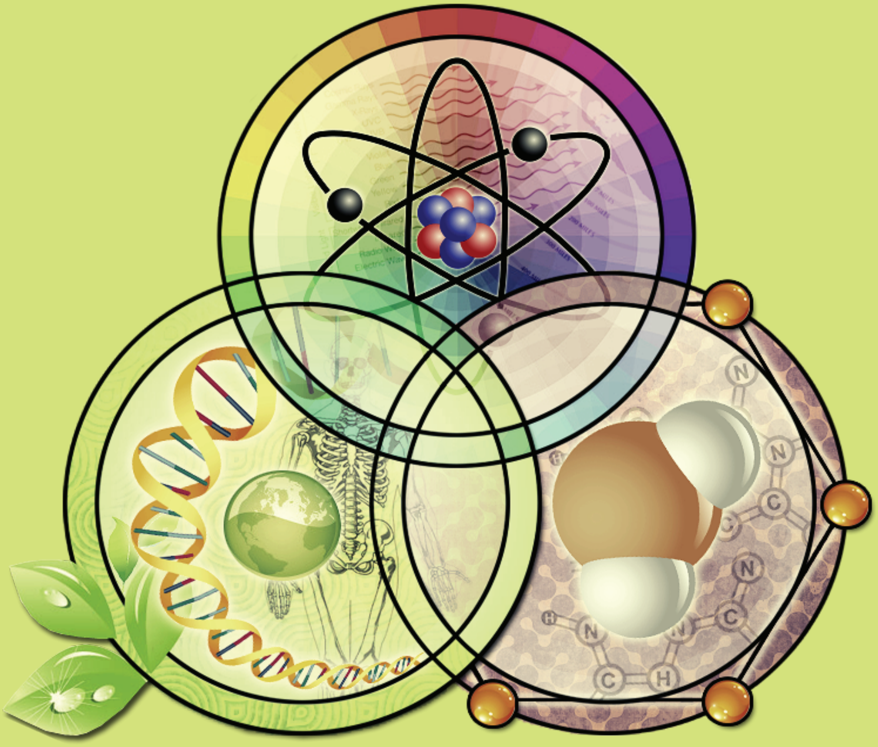

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PREFACE

An active and balanced immune system is extremely important in maintaining health. In order to the immune system for function properly, the necessary structural components must be taken on time and at an adequate level. The effects of nutrients and nutritional factors on human health are known through their effects on nutritional metabolism, intestinal microbiota and the immune system. At the same time, nutrition plays an important role in ensuring growth and development, preventing diseases, slowing down aging processes, emotional state, physical and mental functions, in addition to its importance in regulating the immune system. At this stage, the foods that are included in the daily diet without the need for medication to keep the immunity in balance and that have a regulating effect on the immune functions through some bioactive components in the body are called "functional foods".

All foods are of course highly functional in terms of taste, aroma and nutritional properties. However, foods are being studied extensively for additional physiological benefits, particularly those that may reduce the risk of chronic disease or optimize it in a way that contributes to maintaining health. It is assumed that changing dietary intake throughout life plays an important role in the development, management, follow-up and treatment of noncommunicable diseases including some chronic diseases (allergic, cancer, diabetes and cardiovascular, etc.). Although the importance of foods in therapeutic medicine has remained in the background with the rapid development of modern pharmacology, the relationship between nutrition and microbiota of many diseases whose pathogenesis has been understood in recent years has been revealed in a striking way. Intestinal microbiota consists of many bacteria and its composition differs from individual to individual. Dietary components, especially macronutrients, are one of the key factors in shaping the intestinal microbiota and are very important in decreasing or increasing beneficial bacteria. Today, the results of practices involving humans directly, such as the use of biotics and prebiotics in the treatment of various diseases and the monitoring of these patients, studies with cell culture, and stool transplantation, are shared in the scientific world and shed light on the developments in this field. This book is designed to share current knowledge in the field of the new microbiome-based approach and to discuss possible answers to questions.

Filiz YANGILAR

Erzincan, Turkey

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INTRODUCTION

It is a fact that the population, which will reach 9.8 billion in 2050 due to the increasing world population, will bring along food-based problems that will lead to very difficult risk factors such as energy crises, toxic gas emissions, climate changes, greenhouse effect and global warming (Alishah Aratboni et al., 2019). Today, sudden fluctuations in the population, which has increased with the effect of more widespread diseases such as pandemics, various environmental parameters, individual concerns have compelled researchers to search for alternative food sources. At the same time, a mass of consumers concerned about their health and becoming increasingly conscious has emerged. Foods are evaluated by these consumers not only for their taste and nutritional content but also for their positive health benefits.

Today, with the rapidly increasing population, preventive medicine has greater importance than curative medicine. Microorganisms are found in all living multicellular organisms, including humans. The human body is the habitat of many bacteria, mites, viruses and single-celled eukaryotes. For this reason, increasing studies and activities are carried out in the treatment and nutrition fields related to probiotics, which have protective effects on human health, especially with their defensive properties against undesirable bacteria. Today, foods containing prebiotics and probiotics have come to the forefront in protecting and improving health, increasing the quality of life and especially in the fight against diseases, depending on their properties. These probiotic microorganisms are added to various foods in pure culture or are available in the market as food supplements in various forms such as powder, tablet, and capsule.

Because of their similar effects on fermented foods, most of the initial research in the food field focused on the isolation and characterization of probiotic microorganisms from fermented foods.

The mechanisms of action of these organisms, which have versatile functions such as health-promoting effects, immunostimulating properties, inactivating pathogens and strengthening intestinal barriers, are partially known. This book aims to share the views on the details of the studies on probiotic and new concepts by evaluating the studies and proposals on new microbiome-based applications in all areas of daily life from a scientific point of view.

INTESTINAL MICROBIOTA

Humans try to adapt to a common life with microbes that make up the most abundant life-forms on Earth since ancient times (Whitman et al., 1998). The microbiota is considered an “organ” that carries approximately 150 times more genes than those found in the entire human genome (Wang et al., 2017). Microorganisms (microbiota/microflora and their collective genomes–the gut microbiome, which represent the bulk of the metagenome) are found to colonize almost all parts of the body, such as the skin, respiratory tract, urogenital, oral cavity, and gastrointestinal tract, and peacefully interact with the host (Dethlefsen et al., 2006). All of these microorganisms found and living in our body are called "microbiota", and this genome carried by microorganisms living commensal with humans is called "microbiome". Human is a super-organism consisting of roughly 90% microbial cells with 10% human cells settled in this macroscopic host (Belkaid and Hand, 2014; Karatay, 2019). To date, more than 10.000

bacteria and fungi and more than 3000 virus species have been detected in humans (Tuğ et al., 2002).

Microbiota composition varies depending on host-related factors such as the genetic structure of the individual, diet, disease status, geographical location and existing bacterial species (Pelzer et al., 2017). Dietary habits changing with modern life, on the other hand, are accepted as one of the factors contributing to the diversity of the gut microbiota, and it is accepted that diet has a more dominant role in shaping the gut microbiota than other possible factors such as ethnicity, hygiene, geography and climate (De Filippo et al., 2010).

Microorganisms play an important role in the continuity of healthy body and sometimes appear as infectious agents (Ley, 2010; Çetinbaş et al., 2012). It has been accepted for many years that bacteria are harmful to our bodies and cause diseases. The greatest importance of microorganisms is that they can affect our lives in health and disease; they are present in the gastrointestinal (GI) system, which provides various functions in order to the host in terms of immune, physiological, developmental and nutritional properties (Drasar and Hill, 1974; Guarner and Malagelada, 2003; Nicholson et al., 2005).

It is expressed as the ecological community of 10^{13} - 10^{14} CFU/g symbiotic microorganisms found in the gastrointestinal tract and whose content varies according to individuals (Burokas et al., 2015). In the intestinal system (Figure 1) a large number and variety of bacteria are resident (Tok and Aslım, 2007; Ceyhan and Alıç, 2012). It is shared that the microbiota of the intestine, which is expressed as the second brain, is formed in the prenatal period, with the presence of microorganisms located in the endometrial lining, fetal membranes, amniotic fluid, placenta, cord blood, meconium and urogenital regions, as well as the patterns of the foods consumed by the mother (Walker et al., 2017). The taxonomic classification of bacteria is made as Strain-Species-Genus-Familya-Ordo-Classis-Phylum. Although there are more than 160 types of microorganisms in the intestine, which is a very important organ and expressed as the second brain of our body, there are only a few Phylum. While a total of 6 bacteria, Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicrobia, formed the intestinal flora of healthy people and provided colonization, Bacteroidetes and Firmicutes constitute a very large part (90%) of the intestinal microbiota (Rinninella et al., 2019).

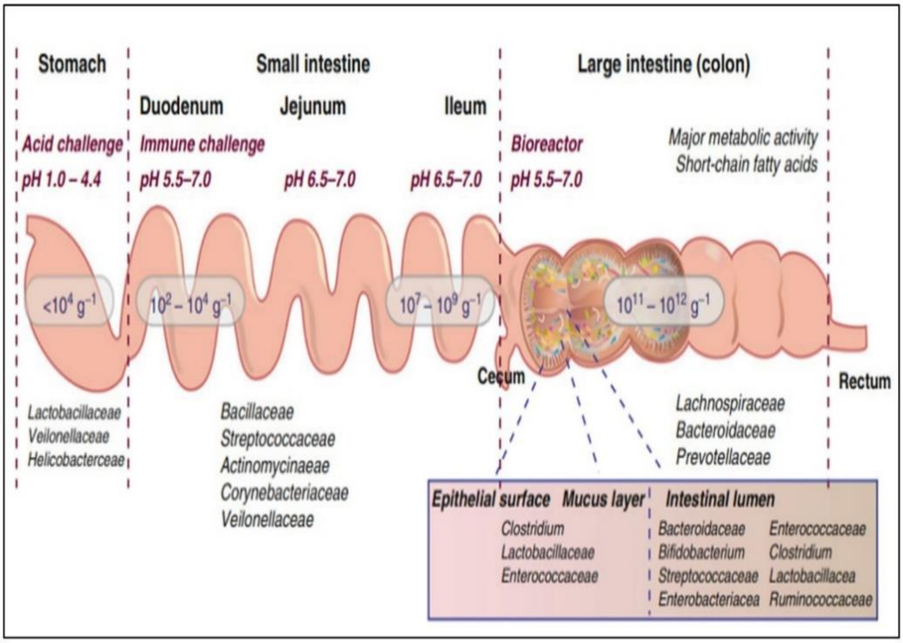

Figure 1. Variations in gut microbiota composition and numbers throughout the gastrointestinal tract (Kovatcheva-Datchary et al., 2013)

It is stated that microorganisms in the gastrointestinal tract (GI) contribute to many metabolic processes such as nutrition, vitamin synthesis, energy production mechanism, inflammatory regulation, immune system of the host, contribution to short chain fatty acids of the indigestible carbohydrate group and lipid metabolism (Cheng et al., 2019).

These contributions are mostly due to their association with commensal bacteria, their role in the extraction, synthesis and absorption of most dietary nutrients and metabolites (acids, lipids, amino acids, plant polyphenols, vitamins and short chain fatty acids) and indeed intestinal system, this is the result of this microorganisms are the main regulators of digestion throughout the gastrointestinal tract (Rowland et al., 2018). However, the gastrointestinal tract is in constant warfare against harmful agents (pathogenic microorganisms, chemical agents), antigens consisting of nutrients and antigens originating from normal gastrointestinal flora (Özden, 2005; Taşdemir, 2017). Food additives called prebiotics, probiotics and symbiotics are used to protect this microflora against pathogens and to fulfill its function (Sezen, 2013). In addition, changes in living conditions and diet bring about changes in natural flora, which is associated with increased obesity, inflammatory diseases and the prevalence of specific cancer types (Commane et al., 2005; Bakır, 2012). Since the strong relationship between nutrient intake and microbiota has been understood, the effects of probiotic foods on human health have gained importance and have been a subject of serious discussion. The term 'biotic' refers to a thermonology used for viability to bring the gut microbiota into a state conducive to host health. The word is derived from the Greek "biōtikós". It refers to the elements formed by living organisms (Salminen et al., 2019). Prebiotics, probiotics and symbiotics regulate intestinal microbiota diversity and activity. It also provides an immune function (Wegh et al., 2019; Dışhan et al., 2022). Although studies are still carried out in society, there is the confusion of information about probiotics, prebiotics and symbiotics. The concepts of these terms are not known or are known incorrectly or incompletely. In addition, the definition of the term probiotic has changed over the years and has been further expanded.

The initial definition of probiotics approved by WHO and FAO has been expanded over the years. In recent years, in addition to this concept, new definitions such as 'paraprobiotics', which means dead/inactivated cells of probiotics, and 'postbiotics', which are considered healthy metabolites, have been added. The study findings share that cell metabolite as well as dead cells (lysed/extracts) can have significant health effects on human health (Di Lena et al., 2015; Zendeboodi et al., 2020). It has been determined by studies that paraprobiotics and postbiotics have an effect similar to probiotics in improving both the health and balance of the intestinal microbiota (Wegh et al., 2019). Therefore, the use of paraprobiotics and postbiotics as an alternative to probiotics has become popular. Servi and Ranzini (2017) concluded that selected different probiotic strains compete with pathogenic microorganisms in vitro models of the intestinal mucosa, preventing their adhesion to the mucosa, increasing paracellular permeability, forming membrane integrity, and protecting intestinal cells. In addition, they contributed to the literature that the pathogenic bacterium *Escherichia coli* infection protects cells by affecting cytokine gene expression.

With the advances in molecular technology, it has emerged that the deterioration of the intestinal microflora is associated with many diseases and its importance has begun to be understood more. In terms of nutrigenomics, the effects of nutrients on genes occur in three ways:

i) Nutrients interact with receptors to provide gene variation, such as a transcription factor that can bind to DNA,

ii) Nutrients can create epigenetic mechanisms (such as DNA methylation and chromatin remodeling) that affect gene expression,

iii) The response to the diet may vary due to genetic variations [single-nucleotide polymorphisms (SNPs)] between individuals (German et al., 2003). All individual responses to diet can be illuminated by assistive technologies (genomics, transcriptomics, proteomics, metabolomics, and epigenomics) and microbiota in the field of nutrigenomics.

THE MICROBIOTA-GUT-BRAIN AXIS

The gut microbiota and the brain are two important systems that communicate with each other in two ways. Recent literature reviews have revealed that the microbiota on human health has a bidirectional interaction with the brain, which is expressed as the gut-brain axis, and thus has an effect on the health or disease states of individuals. In addition to stress, it is known that there is a direct link between anxiety and mood disorders and gastrointestinal (GI) dysfunction. The coexistence of such gastrointestinal problems with mental disorders and psychological problems such as depression and anxiety is evidence of the connection between the gastrointestinal and the central nervous systems known as the gut-brain axis (Villares et al., 2017). This new perspective on the brain and microbial communities have been the subject of many studies showing their functions in development (e.g. autism spectrum disorder), mood (e.g. depression and anxiety), neurodegeneration diseases such as (Parkinson's, Alzheimer's, multiple sclerosis) and chronic pain. (Martin and Mayer, 2018; Morais et al., 2021).

The gut microbiota-brain axis refers to the neurohumoral communication network in the basal ganglia, which includes many biological systems, allowing two-way communication between gut bacteria and the brain. This communication network is essential for maintaining homeostasis of the digestive system, central nervous system (CNS), and microbial system. The aim of communication is how the signals created by the intestinal microbiota can affect the actual brain functions, as well as how the brain can affect the microbial activity and gastrointestinal environment in response to these messages. This communication is provided by neuroendocrine and neuroimmune mechanisms. The most important function of the brain at this point is to regulate intestinal properties through the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. For example, norepinephrine, one of the neurotransmitters that act as hormones, is released by the brain during stress and controls the proliferation of pathogenic microorganisms in the intestines (Mart'yanov et al., 2021). In addition, the importance of the microbiome in the gut-immune-brain pathway and general physiological effects is also valuable in terms of strengthening the immune system and continuity of the mechanism. As seen in Figure 2, signal transmission mechanisms are quite complex and include neuronal, immune, endocrine and metabolic pathways, although not fully explained.

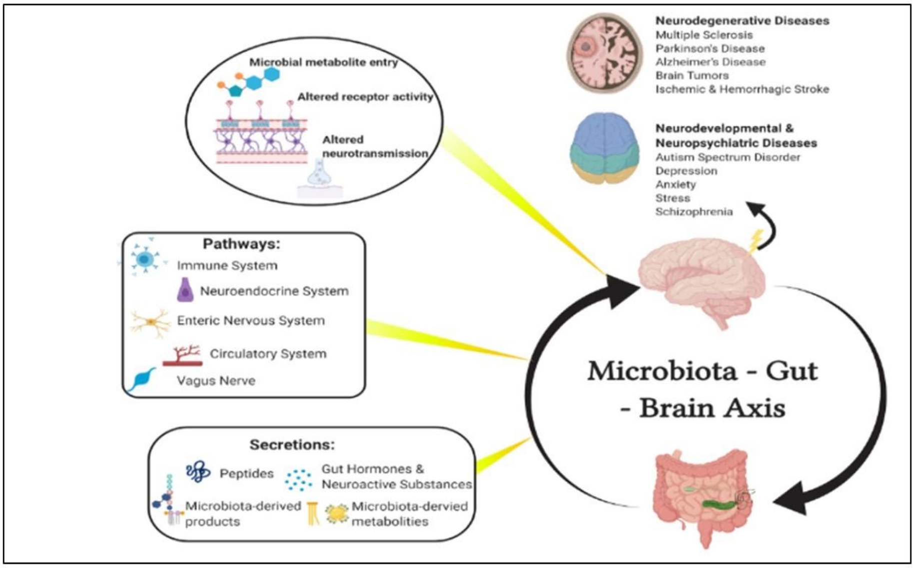

Figure 2. Microbiota-gut-brain axis (Liu et al., 2022)

The existing bidirectional communication between the brain and gut microbiota is accompanied by various pathways (immune, neuroendocrine, enteric nervous system (ENS), circulatory system and vagus nerve stimulation etc.). These ways are very important because once they reach the brain, they can affect the neurodevelopment and neurodegeneration of many disease states such as Parkinson's, Alzheimer's, multiplesclerosis, depression, schizophrenia, autism, anxiety and stress. Intestinal bacteria can synthesize gamma amino butyric acid (GABA), 5-Hydroxytryptamine (5-HT), dopamine, and short chain fatty acids (SCFAs). In particular, intestinal cells can produce many 5-HT, which has an effect on the brain (Yoo and Mazmanian, 2017). Most neurotransmitters necessary for the body are produced by the gut microbiota and exert effects on the living body, including the brain (Dinan et al., 2013). It is also reported that peripheral inflammation markers can increase the blood-brain barrier permeability and thus directly affect the brain (Mccusker and Kelley, 2013). It can also affect social behavior by secreting metabolites that function as olfactory pheromones in the microbiota (Figure 3)

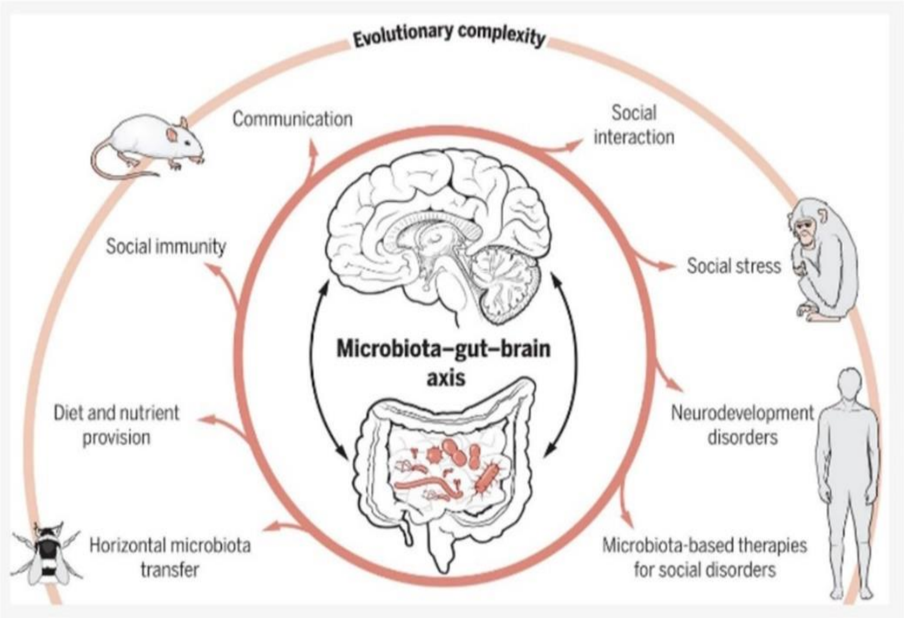

Figure 3. Mechanism of interaction between the microbiota-gut-brain axis and social behavior (Sherwin et al., 2019).

The dynamic relationship between the gut microbiota and the human host extends to a trophic relationship of the microbe that can range from both commensalism and gut symbiosis. In addition to dietary practices, it is also known that the intake of biotic such as probiotic, post/paraprobiotic, and prebiotic preparations positively affects the intestinal flora.

PROBIOTICS

The word "probiotic" refers to living microorganisms that are formed by the combination of the two words "pro" and "bios" and the meaning of “for life”. It can provide the expected benefits on host health and is used as a food additive (Hill et al., 2014) the opposite of the term antibiotic (Coşkun, 2006). The therapeutic doses of probiotics are also very important, and it is known to provide positive effects on health when consumed more than 5 billion colony forming units (CFU) per day for children and more than 10 billion CFU per day for adults (Naidu et al., 2012; Hill et al., 2014; Ullah et al., 2019). In addition, probiotics are also called "biotherapeutic agents". Treatment with probiotics is also named “bacterial replacement therapy”, “bacteriotherapy” and “treatment of pathogenic microorganisms with non-pathogenic microorganisms” (Gibson and Roberfroid, 1995; Markowitz and Bengmark, 2002; Reid et al., 2003; Ötleş et al., 2003; Gill and Guarner, 2004; Isolauri et al., 2004; Coşkun, 2006). For centuries, probiotics have been used as a safe product (Figure 4), but their economic value has been recognized in recent years. In the late nineteenth century, French biochemist Louis Pasteur made a major scientific breakthrough in fermentation. In the technological process in the last decades, important studies have been carried out in the fields of examination, classification and characterization of different concepts related to probiotics. Of course, the establishment of the International Scientific Society for Probiotics and Prebiotics (ISAPP) was also important in the success of these studies. The concept of postbiotic as a new biotic term was first formalized in 2012 by Tsilingiri et al. (2012) at the ISAPP workshop (Salminen et al., 2021).

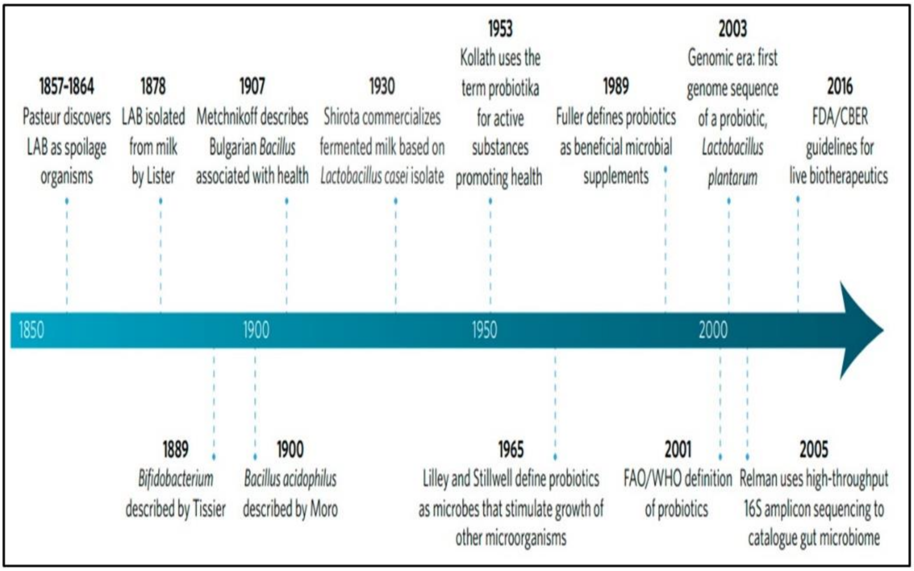

Figure 4. Timeline of the history of probiotics and new generation probiotics. *LAB: lactic acid bacteria (O'Toole et al., 2017)

Probiotic bacteria should be able to survive in sufficient numbers in the product and should not be pathogenic and toxigenic. However, probiotic bacteria; its clinical effects have been demonstrated, they can be easily identified in the microbiota, it is resistant to storage conditions, it does not adversely affect the taste and taste of the product, they can multiply by clinging to the intestinal mucosa, secrete antimicrobial properties, temporarily colonize in the digestive system, provide immunological sensitivity in the host, systemic toxicity and resistant. It is important to cause the development of microorganisms and to control the irregularities in the gastrointestinal tract. In order for all these effects to occur, strains of human origin should be selected and microorganisms that should be able to regulate metabolic activity should be preferred (Baysal, 2000, Delikanlı and Özcan, 2014, Ceyhan and Alıç, 2012; Yılmaz and İpek, 2021).

PROBIOTIC MICROORGANISMS

Most types of bacteria have probiotic properties; however, *Lactobacillus* and *Bifidobacterium* species are the most common among these groups (Table 1; Daliri et al., 2015; Collins et al., 2017). These strains have generally considered safe (GRAS) status (O'Toole et al., 2017). The most common microbial genera that exhibit functional characters associated with probiotic properties include *Lactobacillus, Bifidobacterium, Streptococcus*, *Enterococcus*, *Leuconostoc*, and *Lactococcus* (Choi et al., 2015; Şahin and Şenel, 2020).

Table 1. Probiotic microorganisms

Genus	Species	Genus	Species	Other
Lactobacillus	*acidophilus*	***Bifidobacterium***	*adolescentis*	*Bacillus cereus*
	casei		*animalis*	*Bacillus subtilis*
	crispatus		*bifidum*	*Enterococcus faecalis*
	fermentum		*breve*	*Enterococcus faecium*
	gasseri		*infantis*	*Escherichia coli (strain Nissle 1917)*
	johnsonii		*lactis*	*Lactococcus lactis*
	paracasei		*longum*	*Propionibacterium freudenreichii*
	plantarum			*Saccharomyces cerevisiae*
	reuteri			*Streptococcus thermophilus*
	rhamnosus			
	salivarius			

THE EFFECT MECHANISMS OF PROBIOTIC BACTERIA

Probiotics have the following mechanisms of action:

1. *Reduce the Number of Pathogenic*

The majority of probiotic microorganisms reduce intestinal pH by producing organic acids such as acetic and formic acid, especially lactic acid. With this decrease in pH, the environment turns into a state that prevents the growth of pathogenic gram-negatives (Vanbelle et al., 1990). It has been stated that these beneficial effects of probiotics occur through three mechanisms: changing the enzymatic activity, reducing the number of pathogenic microorganisms and improving the immune system (Gültekin, 2004).

It is known that probiotic microorganisms activate important mechanisms for host health. Pathogen inhibition mechanisms include the production of antimicrobial substances such as bacteriocin from its metabolites, hydrogen peroxide with organic acids (Patel and DuPont, 2015) and/or stimulation of mucosal immunity (Servin and Coconnier, 2003; Castro-Bravo et al., 2018). Probiotic strains compete with pathogens for adhesion to intestinal epithelium and mucus. The potential to inhibit pathogens and spoilage microorganisms is an important criterion to selection of probiotic microorganisms. Many probiotic strains fulfill this function by producing one or more antimicrobial substances containing hydrogen peroxide (H_2O_2), organic acid, diacetyl, biosurfactant substances, bacteriocin or bacteriocin-like molecules, or by preventing the attachment of pathogenic bacteria to intestinal epithelial cells (Gibson, 1998; Ouwehand et al., 1999).

In many studies, it has been reported that lactobacilli have effects that inhibit the proliferation of periodontal pathogens including *Porphyromonas gingivalis, Prevotella intermedia/nigrescens* and *Actinobacillus actinomycetemcomitans* (Sookkhee et al., 2001; Kim et al., 2017). In a study, it was reported that the use of probiotics containing *Lactobacillus reuteri* in addition to the initial periodontal treatment may be beneficial in patients with moderate pockets (İnce et al., 2015).

2. Adhesion to Intestinal Surfaces

The lactic acid bacteria to intestinal epithelial cells results from their interactions with various surface determinants (electrostatic attraction, hydrophobicity, steric forces, lectins, lipoteichoic acid, etc.) (Servin and Coconnier, 2003). Adhesion to epithelial cells means that it can provide immunological modulation of probiotic microorganisms. The selection of probiotic bacterial strains is very important, and their ability to destroy pathogenic and spoilage microorganisms is considered a very important criterion. Most probiotic strains perform these important functions by producing one or more antimicrobial substances containing hydrogen peroxide (H_2O_2), organic acid, diacetyl, biosurfactant substances, bacteriocin or similar molecules, or by preventing the attachment of pathogenic bacteria to intestinal epithelial cells (Markowiak and Śliżewska, 2017; Önal et al., 2005). It has been shown that probiotic microorganisms can detoxify the host with these effects, and reduce their absorption in the intestine by binding some toxins to their cell walls by adsorption. It has also been reported that mycotoxins (such as aflatoxin) can be detoxified by probiotic microorganisms (Nikbakht Nasrabadi et al., 2013). It is stated that probiotics in the gastrointestinal tract reduce the adhesion of both pathogens and their toxins to the intestinal epithelium (Vanderpool, 2008). Studies have shown that by preventing pathogens in this way, probiotic bacteria can protect the host against pathogenic microorganisms and strengthen the host’s immunity (Scott et al., 2015). In fact, although it is known that mechanisms such as the stimulation of host factors such as mucin and competitive binding to receptors are effective in preventing the adhesion of probiotic microorganisms and toxin binding and pathogens, serious studies are still needed on the inhibition mechanisms (Rastall et al., 2005).

3. Competition for Nutrients

Probiotic organisms are in a constant race to bind to the receptors against pathogens. This effort is also made for the nutrients in the intestinal lumen. The nutrients in the environment are consumed by probiotic microorganisms and there are no nutrients required for pathogenic bacteria to survive (Coşkun, 2006). Thus, the development of pathogenic bacteria is prevented (Castagliuolo et al., 1999). Probiotics can prevent the growth of pathogens by competing for some nutrients they need. For example, *Saccharomyces boulardii*, a probiotic yeast species, prevents reproduction by consuming the monosaccharides needed for the metabolism of *Clostridium difficile* bacteria, which are included in the human normal intestinal microbiota and can cause serious gastrointestinal infections after antibiotic treatment (Castagliuolo et al., 1999; Önal et al., 2005).

4. Enzyme Activity

Thanks to their resistance to enzymes, which is one reason for the most important selection criterion of probiotic microorganisms, they can survive in the acidity of the stomach and reach the intestine (Şengün, 2011). Probiotics show enzyme activity by increasing the lactase, maltase and sucrase activity of the intestine. It is also known that *Saccharomyces boulardii* has effects on polyamines and aminopeptidases (Matheu et al., 1993). Compared to probiotics, yogurt bacteria show the most β-galactosidase activity (Shah and Jelen, 1990; Shah, 1994). When yogurt bacteria are used together with probiotic bacteria, since they grow faster than probiotic bacteria, their proteolytic and β-D-galactosidase activities are higher (Shah, 2001; Sağdıç et al., 2004). It has been reported that lactobacilli and bifidobacteria probiotic strains reduce the amount of microbial enzymes such as nitroreductase, urease and β-glucosidase, which have mutagenic and carcinogenic effects in the fecal environment (Roberfroid, 2000; Noble et al., 2002). It has been shown that clinical Bifidobacteria and some probiotic bacterial preparations are given to lactose-intolerant patients for a long time, reducing or completely eliminating symptoms in patients (Heyman and Menard, 2002).

5. Toxin Receptors and Responses

Probiotics, which have the effect of disrupting the intestinal toxin receptor enzymatically, can also prevent this way of diseases with their ability to modify or block the toxin receptors. *Saccharomyces boulardii*, which acts by disrupting the toxin receptor in the intestine in this way, may protect the host against *Clostridium difficile* intestinal disease (Bajaj et al., 2015). It has been emphasized that probiotic microorganisms may be associated with reducing metabolic reactions that lead to toxin production, as well as stimulating pathways that lead to the production of antimicrobial substances along with vitamins and natural enzymes (Oelschlaeger, 2010).

6. Immune System

Recently, "immunostimulant" is among the important effects of probiotics. All of the epithelial cells, B/T lymphocytes, blood leukocytes and the remaining auxiliary cells of the immune system in the intestinal structure can be affected by probiotic microorganisms. Peptidoglycans, lipoteichoic acids and endotoxic lipopolysaccharides are bactericidal products with immunomodulatory properties. In addition, especially lipoteichoic acids of gram-positive bacteria show high affinity for epithelial cell membranes, while at the same time having a role for antigens, they can stimulate the immune response (Koçak et al., 2016). Immunological stimulation provided by probiotics can also be achieved by the increase in macrophage and lymphocyte activities together with the death of immunoglobulins and the stimulation of interferon production. Congenital and stimulated immune system probiotics can also affect host specific cells with their metabolite, cell wall components and DNA. Cell walls of lactic acid bacteria stimulate macrophage activity (Markowiak and Śliżewska, 2017). Probiotics help the mucosal immune system through Toll-like receptors to promote the differentiation of type 1 T-helper cells. As a result, antibody production, phagocytic and natural killer cell activity become enhanced (Quigley, 2019). Briefly, macrophage activation, mucus induction, increase in secretory IgA, peripheral Ig and neutrophil counts, and inhibition of cytokine release with inflammatory effect can be given with the signaling of lactobacilli to the environment by the changes caused by probiotics in the immune system (Fukushima et al., 1998). In a study conducted with the probiotic *Lactobacillus plantarum* ATCC 14917 and *Lactobacillus johnsonii* JCM 2012, which are used in milk and dairy products, it was stated that they have immune-enhancing effects in humans (Lebeer et al., 2010).

7. Antibiotic-associated Diarrhea

The probiotic bacteria and their products can also be used in the treatment of colitis caused by antibiotics on the intestinal system (Marteau et al., 1997). Probiotics are also effective in the treatment of acute diarrhea. In fact, studies show that *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* CNCM I-745 probiotic bacteria can reduce the severity and duration of acute infectious diarrhea in children. Overall, it has also been determined that there is a decrease of approximately 1 day in the acute disease process due to the use of probiotics (Szajewska and Skórka, 2009; Szajewska et al., 2013; Szajewska et al., 2014; Cremon et al., 2018).

8. Inflammatory Bowel Diseases

Treatment of Inflammatory Bowel Diseases is carried out by first creating a change in the immune response. In the etiopathogenesis, changes in the intestinal microbiota content have been prioritized in recent years. New treatment methods are aimed at regulating intestinal microflora. It has been found to be effective that probiotics are effective in both adjuvant and maintenance treatment of inflammatory bowel diseases (Madsen, 2006).

(i) ***Ulcerative Colitis (UC):*** UC is an inflammatory disease that extends from the rectum to the colon and shows an incessant mucosal inflammation (Seksik et al., 2008). In a study, the probiotic microorganisms *Saccharomyces boulardii* were used in addition to mesalamine in the treatment of ulcerative colitis in 25 cases, and it was reported that the incidence of the disease decreased by 68% (Guslandi et al., 2003). Individuals with low *Clostridia*, *Bacteroides* and *Bifidobacterium* ratios in their microbiota generally suffer from constipation, and consumption of *Lactobacillus* strains with food has been found to have positive effects in the treatment of constipation and alleviating complaints related to discomfort (Coşkun, 2006; Gürsoy et al., 2005). Ishikawa et al. (2003) reported that there was a significant reduction in relapse rates in patients with ulcerative colitis in remission who consumed *Bifidobacterium*-prepared dairy products compared to the control group. In addition, many studies have identified the positive effects of probiotics in the prevention of lactose intolerance (Montalto et al., 2006), irritable bowel syndrome (IBS) and peptic ulcers (Lesbros-Pantoflickova et al., 2007).

(ii) ***Irritable Bowel Syndrome (IBS):*** IBS, which is one of the most common gastrointestinal system diseases, shows various symptoms such as distension, diarrhea, constipation and abdominal pain (Kajander et al., 2005). Administration of *Saccharomyces boulardii* yeast to patients with acute, watery diarrhea resulted in a decrease in such complaints and improvement in patients in the following two months (Billoo et al., 2006). One of the probiotic bacteria, *Lactobacillus gasseri* CECT5714 and *Lactobacillus coryniformis* CECT5711 strains containing fermented products consuming 30 healthy volunteers in a study of 30 healthy individuals without any adverse events, short-chain fatty acids production, stool frequency and volume, and improved bowel functions were reported (Olivares et al., 2006).

(iii) Helicobacter pylori: Especially, it is known that *Lactobacillus* is the most effective species in preventing the binding of *Helicobacter pylori* (*H. pylori*) to the mucosa (Lesbros-Pantoflickova et al., 2007). In a study done in the USA, it was determined that the reproduction of all *H. pylori* strains kept for one day in yogurts containing lactic acid bacteria in their natural flora was stopped. Many microorganisms such as *Lactobacillus ferentoshensis*, *Lactobacillus crispatus*, *Lactobacillus kefiri* have been obtained from this yogurt and it has been found that the microorganisms found to inhibit the growth of *H. pylori* in various ways (Oh et al., 2002). It has been reported that the group fed with *Lactobacillus* and *Bifidobacterium* probiotic yogurt in the group fed with triple antibiotic therapy among *H. pylori* positive patients achieved greater success (78-91%) in the treatment of infection (Cats et al., 2003). In combination with standard triple therapy on *H. pylori* positive patients, in the study investigating the effects of *Lactobacillus acidophilus*; according to the urea breath test results, significant regression of the disease was detected in the probiotic group (88%) compared to the placebo group (72%) (Canducci et al., 2000; Malfertheiner et al., 2002). It has been stated that probiotics can be used successfully as adjuvant in the treatment of *H. pylori* infection, and that after 8 weeks of use, gastric mucosa inflammation decreases and successful results can be obtained with antibiotic-probiotic combined application. According to Cremonini et al. (2001) argued that although it increases the rate of *H. pylori* eradication, its place in treatment is controversial because the type, dose and time of probiotics are not standardized. It was stated that the urease activity of individuals using probiotic drinks decreased by 64% compared to the control group.

(iv) ***Crohn's Disease:*** Crohn's disease is defined as an inflammatory bowel disease that can lead to thickening and ulceration in these places, including the esophagus and intestinal tract, of individuals. In a study of 32 patients suffering from this disorder, it was observed that the rate of recurrence of the disease was reduced by administering *Saccharomyces boulardii* additionally to mesalamine (Guslandi et al., 2003). They found that the recurrence rates were low in the group that received eganomine and *Sacchoromyces boulardii* in 32 (20 male, 12 female) patients in clinical remission followed up with the diagnosis of Crohn (Guslandi et al., 2000, Gupta et al., 2000; İnanç et al., 2005). Probiotic microorganisms can also help treat inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, which really negatively affect the quality of life for individuals. The origin of these diseases is not fully understood; however, it is clear that they are associated with chronic and recurrent infections or intestinal inflammation (Markowiak and Śliżewska, 2018).

9. Effect on Liver Function

Hepatic encephalopathy is a disease characterized by a series of neuropsychiatric effects without neurological or metabolic disturbances in individuals with advanced liver disease (Solga, 2003; Hotten et al., 2003). The use of probiotics can improve the symptoms of hepatic encephalopathy by shifting the pH to acid, reducing blood NH_3 (ammonia) levels, reducing the functionality of the urease enzyme synthesized by bacteria, reducing the absorption and uptake of toxic substances in the villous structure of small intestine (Solga, 2003). Probiotic bacteria can remove cancer-causing enzymes or cancer-causing sources from the environment. Removal of precancerous carcinogenic effects by probiotic bacteria may include reducing the proportion of nitrosamines. In a study, it was observed that probiotic bacteria greatly reduced the mutagenicity of nitrosamines (Shah, 2001; Sağdıç et al., 2004). Probiotics also have an effect in the prevention of breast cancer, which is one of the hormonal cancer types. Probiotic consumption contributes to the treatment of breast cancer by regulating the intestinal microbiota balance. In addition to, it is reported that the increase in cells that affect the immune system is also caused by the mechanism of action of probiotics on breast cancer cells. At the same time, probiotics that reduce cancer cell proliferation also have an effect by promoting some apoptotic genes (Rea et al., 2018). It has also been shown to inhibit the negative growth of cells in leukemia and to have anti-cancer effects in liver cancer (Han et al., 2013).

Probiotics show their effects on body health through four main mechanisms in the host lumen, mucus layer, epithelial layer, and gastrointestinal-associated lymphoid tissue (GALT) levels. These living microorganisms show positive effects on health by competing with pathogenic microorganisms in the environment, improving barrier properties, regulating the release of some excitatory-neurotransmitters and increasing the modulation of the immune system (Sánchez et al., 2017). It has been proven as a result of studies that taking probiotics at the appropriate dose and frequency has many positive effects for on human health (Buran, 2020). In recent clinical studies, it has been determined that *Lactobacillus paracasei*, one of the probiotic bacteria, has beneficial effects on human health such as hypocholesterolemia, antihypertensive, antiosteoporosis, antimutagenic, antioxidant, anticancer, and anti-inflammatory (Araújo et al., 2022).

Cohen et al. (2005) emphasized in their study that capsule-shaped probiotics consisting of *Lactobacillus acidophilus, Bifidobacterium lactis, Bifidobacterium longum* and *Bifidobacterium bifidum* bacteria, used for 8 weeks by people with generalized anxiety disorder, reduced anxiety symptoms. There are studies showing that probiotics tend to decrease significantly in the case of depression and that even in healthy individuals, probiotics can reduce the risk of depression (Huang et al., 2016).

The prebiotics and probiotics with mental health are examined and it is stated that probiotics can positively affect mental health by modulation of brain activity. In addition, it has been reported that it produces neuroactive components and has behavioral effects, especially in stress-related such as anxiety and depression disorders (Liu et al., 2019; Peirce and Alviña, 2019; Huang et al., 2016).

In line with the research, due to the relationship between intestinal dysbiosis and acne pathogenesis; in acne treatment, the appropriateness of a probiotic-based complementary therapy to provide microbial diversity comes to the fore (Dagnelie et al., 2019; Fabbrocini et al., 2016; Gündüz and İrkin, 2022). In most studies, it has been shared that the intestinal dysbiosis before the onset of necrotizing enterocolitis (NEC), especially in preterm babies, is caused by increasing *Proteobacteria*, *Firmicutes* and *Bacteroidetes* species among the effective microorganisms (Pammi et al., 2017). Among the known benefits of probiotic microorganisms are the prevention of intestinal dysbiosis and the provision of by-products necessary for intestinal health by using nutrients. For example, *Bifidobacterium longum* subspecies *infantis* supports a healthy gut microbiota by consuming human milk oligosaccharides (Underwood et al., 2015). Under healthy conditions, the gut microbiota is in a normobese state. The composition of the gut microbiota, eczema, asthma and nutritional allergic conditions and intestinal dysbiosis are important (Bisgaard et al., 2011; Abrahamsson et al., 2012; Abrahamsson et al., 2014; Ling et al., 2014; Sestito et al., 2020). The recent increase in allergy prevalence is predicted to be a consequence of early intestinal dysbiosis (Cukrowska et al., 2020). In addition to all these, allergic diseases are considered as a result of the complex genome-environment interaction with the change of the immune system (Figure 5). All of the above has an impact on the microbiota, which growing evidence claims to play a fundamental role in shaping the normal structure and content of the immune system (Sommer and Backhed, 2013). The interaction between a low dietary fiber diet and allergic disorders on noncommunicable diseases is also important (Ellwood et al., 2013). An appropriate diet program to be determined by regulating the intake of foods containing these products or supplementing with prebiotics is one of the most correct practices to strengthen the intestinal microbial population (Gibson et al., 2004; Scott et al., 2013).

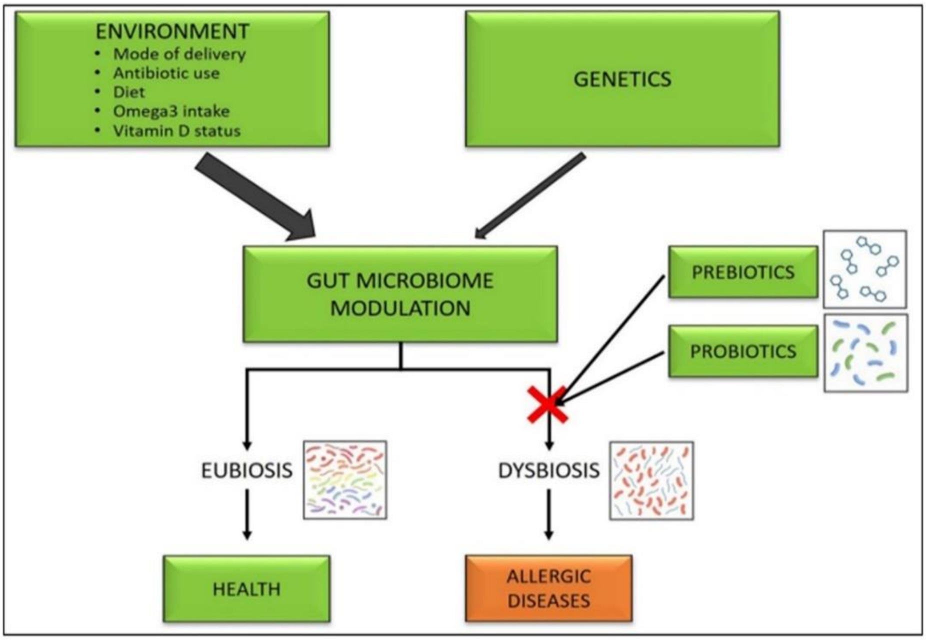

Figure 5. Intestinal microbiota that contributes to the causes and prevention of allergic diseases (Prescott, 2013; Ke, 2012).

Probiotics have a positive effect on alleviating allergy symptoms due to these properties (Zhang et al., 2003). Probiotics actually can be used to prevent allergic diseases. The therapeutic effects of probiotics in allergic diseases are due to their suppressive effects on lymphocyte proliferation and interleukin-4 in vitro for the first time (Sütas et al., 1996). In addition, probiotics are used to control respiratory allergic conditions such as asthma (Gorbach et al., 2002).

There are studies evaluating the use of probiotics in individuals with atopic eczema (Kalliomaki et al., 2001). *Acne vulgaris*, which seriously affects almost all of the adolescents (80-90%) and about half of the adults, is a chronic inflammatory skin disease that has devastating effects on the quality of life of the individual (Chernyshov et al., 2018; Tuchayi et al., 2015). Probiotic-rich fermented milk and yogurt have been traditionally used in many societies since ancient times; the fact that it has been used in the treatment of various conditions such as skin allergies, stomach disorders, especially diarrhea has increased the perception that these foods are beneficial and facilitated the prevalence of these foods (Senok et al., 2015).

Pouchitis which is a complication that may develop as a result of surgical operation of individuals with ulcerative colitis is an important disease with bloody diarrhea, abdominal pain and low-grade fever, among the symptoms that can be encountered when the balance of the intestinal flora changes. Kuisma et al. (2003) investigated the effects of *Lactobacillus* GG, which has edoscopic and histological inflammation, on the sac mucosa of patients. The researchers stated that there are changes in the microflora of the pouch with the application of probiotic microorganisms. Next-generation-probiotics (NPGs) clearly fit the normal definition of a probiotic, but this discussion is primarily focused on a U.S. Food and Drug Administration (FDA) definition of a low back pain (LBP) that has not hitherto been used as a health-promoting agent and is most likely within a drug regulatory framework is also suitable (Figure 6).

New generation probiotics,

(i) includes living organisms such as bacteria,

(ii) can be applied to prevent, treat or cure a disease or condition,

(iii) they are not vaccinated (O'Toole et al., 2017).

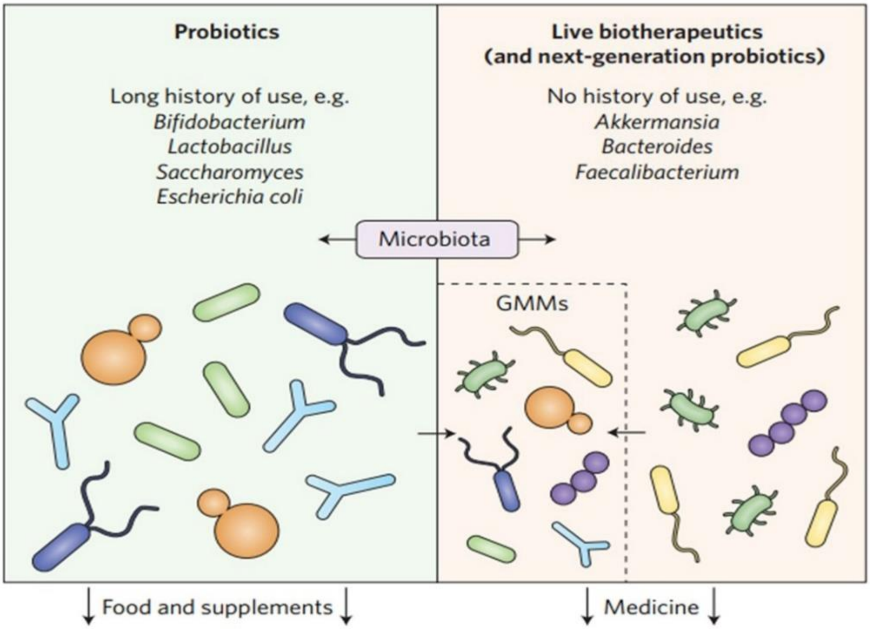

Figure 6. Schematic diagram of probiotics, next-generation probiotics and live biotherapeutic products (O'Toole et al., 2017)

The results of most studies on probiotics, which offer a wide range of health benefits and effects, reveal that various health problems such as infective endocarditis, sepsis, tissue-to-blood bacterial translocation and bacteremia may develop as a result of their molecular mechanisms, strain-specific behaviors, and antibiotic resistance mechanisms that may develop against horizontal gene transfer in the direction (Ayichew et al., 2017; Suez et al., 2019). In addition to this information, although the situation created by pathogens that provide resistance to multidrug use of probiotics in humans has shown promising results against various health problems such as diabetes, irritable bowel syndrome (He et al., 2017; Abdelhamid et al., 2018; Majeed et al., 2018) nevertheless, there is a need for studies on most of the subjects, including nutrition and each of the not illuminated areas of health (Galdeano et al., 2019).

Probiotics for Weight Loss

In randomized controlled studies investigating the effect of probiotics on body weight, it is stated that the use of probiotics suppresses body weight gain and body fat storage and provides a significant decrease in body mass index (BMI) (Kondo et al., 2010; Zhang et al., 2015; Ermumcu et al., 2022). Short chain fatty acids, which are released as a result of the fermentation of probiotics with prebiotics, activate G-protein-coupled receptors (GPR41 and GPR43) in intestinal epithelial cells and increase the release of some hunger/satiety hormones such as peptide YY and glucagon-like peptide-1. In addition, by changing the expression of genes involved in satiety regulation such as AGRP and POMC, they can be effective in controlling hunger and satiety, and in body weight (Thomas and Versalovic, 2010; Arora et al., 2013; Yadav et al., 2013). However, when the mechanism underlying its effectiveness in the treatment of obesity is examined, it has been suggested that it is due to the difference in the microbiota of obese individuals (Duca and Lam, 2014). It has also been reported that probiotics may be one of the anti-obesity agents to improve lipid metabolism (Tang et al., 2021). In normal-weight women, when a dairy product fermented with lactic acid and propionic acid bacteria is consumed half an hour before eating, it significantly reduces the desire to eat and increases the feeling of satiety, compared to the unfermented product; however, no difference in energy intake was reported at the ad libitum meal (Ruijschop et al., 2008).

In a randomized placebo-controlled study, when obese women and men were given probiotic support [*Lactobacillus rhamnosus* CGMCC1.3724 (LPR)] together with a weight loss diet program, it was stated that probiotic supplementation facilitated weight loss and appetite control in women compared to the control group, and reduced the desire to eat (Sanchez et al., 2008). Sanchez et al. (2017) reported that probiotic and dietary intervention in obese individuals resulted in greater weight loss in obese women than placebo. In addition, it has been stated that women who lose more body weight have positive improvements in eating behavior characteristics and cause less hunger.

Probiotics in Cosmetic

The skin, which is accepted as the largest organ of the human body, expresses a very complex and dynamic ecosystem. The stratum corneum, which is the outer epidermal layer, provides a physical barrier that prevents the entry of chemicals or pathogenic microorganisms, the amount of water lost by evaporation and the loss of body heat (Robinson, 2014). For this purpose, the cosmetics industry has gained momentum in order to emphasize the negativities that the skin will face as it is affected by various factors. The processes of developing products related to skin protection and anti-aging as well as beautiful appearance constitute the researches that cosmetic product developers are constantly working on. In recent years, cosmetic products containing "probiotics" or "probiotic ingredients" generally contain non-living bacteria, cell lysates or bacterial fermentation products that do not need much change in the preservative content system (Sfriso et al., 2019). Probiotics are used in a wide variety of product categories such as pharmaceuticals, cosmetics, dietary supplements, food and food additives, as well as to protect skin health. In the light of technological developments, the fact that the concept of micro-ecological skin care has entered people's lives at the application stage is considered an indicator of a new era in skincare. The main criterion of in this application is to improve skin health by improving skin barrier properties by supplementing with probiotics or prebiotics and shortening the regeneration time of the skin by improving cell combination (Gong, 2020). In addition, probiotics have an effect by reducing transepidermal water loss (TEWL), preventing skin dryness and improving skin hydration (Yu et al., 2022). Today, cosmetic products containing a lot of probiotics are on the market. It is important to monitor the functions of these products, which contain probiotic products, with clinical research as infections or allergies to the products are common in individuals who use cosmetic products.

Strains included in common cosmetic probiotics include *Bacillus subtilis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactococcus lactis*, and *Lactobacillus plantarum*. In particular, studies have shown that these probiotics provide effective moistening in the production and production of lipids in the epidermis. Among the benefits they provide: Enabling the development of unwanted pathogens, reducing the production of toxic metabolites, increasing the production of antibodies, and helping cytokine synthesis to establish homeostasis of the immune system (Reisch and Cosmetics, 2017; Fuchs-Tarlovsky et al., 2016;

Nowicka and Grywalska, 2019; Nowicka et al., 2022; Chilicka et al., 2022). Cosmetic product formulations containing probiotics and postbiotics create benefits such as blocking the effect of UV radiation and maintaining the cutaneous microbiota balance by creating an antioxidant and/or anti-inflammatory effect (Ngoc et al., 2019). It has been shown that the use of highly studied antioxidants (ascorbic acid, carotenoid, polyphenol, astaxanthin, etc.) together with probiotics as an oral supplement has an effect on protecting the skin against damage caused by UV radiation (Krutmann, 2009; Morifuji, 2019; Souak et al., 2021). In order to know exactly the mechanism of the use of probiotics in skin health applications, it is important to know what actually causes skin problems such as rosacea and acne. Not only the chemical products used but also the skin contact with irritating substances or pathogenic bacteria should also be evaluated in a stimulus that can be obtained from the environment. The immune system of the skin shows a defense mechanism against these microorganisms, but the skin in this case shows symptoms such as abscesses, redness, itching, pain, and swelling. For this, it is necessary to use a product containing natural probiotics, which is not harmful (Porubsky et al., 2018). As a result of a study conducted in Brazil, a patent was obtained for a cosmetic product containing the band M4 of *Weissella paramesenteroides*, which is provided antimicrobial effect against the effects of *Propionibacterium acnes* (Patel et al., 2022).

According to the U.S. Food and Drug Administration (FDA), cosmetic terminology defines only non-soap products designed for use in the human body to cleanse, beautify, increase attractiveness, or alter its appearance (US Food and Drug Administration, 2020; Puebla-Barragan and Reid, 2021). This definition does not include any health claims (Hill et al., 2014; Chilicka et al., 2022). Studies on it still have not established a definitive definition of probiotic in cosmetic products. While there is no problem with their use in oral preparations, there are still regulations for their use in cosmetics. It has been revealed in the literature review that there is still no legal regulation on the use of probiotics for cosmetic purposes (Lee et al., 2019; França, 2021). In addition, these products only contain the statement that they must comply with the European Cosmetics Regulation 1223/2009 (Conseil, 2009). The probiotic market with such functionality is expected to grow by 12% in the next ten years.

Probiotic Supplements

Some problems arising from inadequate and unbalanced nutrition lead individuals to supplementary foods in order to meet the macro/micro nutrients that the body needs and cannot obtain with a routine daily diet (Coşkun and Velioğlu, 2020; Kazaz and Gençyürek, 2020). It is seen that the use of supplements in the society has become a trend under the idea of healthy life and the popularity of supplements has increased thanks to some marketing and sales strategies (Baltacıoğlu, 2019).

In the global market, probiotics have become a billion-dollar industry by gaining great importance. The fullness of probiotic content also enables the production of a range of products in a wide variety of fields such as foods, baby food, animal feeds, pharmaceuticals, dietary and supplements (Zuccotti et al., 2015). These products are especially applied in the development of various formulations in commercial food-based products such as cheese, yogurt, milk and cream, along with capsules and powders (Govender et al., 2014; Lugli et al., 2019). Bacteria species used in such formulations include *Lactobacillus*, *Limosilactobacillus* (formerly *Lactobacillus*), *Lactiplantibacillus* (formerly *Lactobacillus*), *Ligilactobacillus* (formerly *Lactobacillus*), *Lacticaseibacillus* (formerly *Lactobacillus*), *Lactococcus*, *Bifidobacterium* and *Enterococcus* (Ullah et al., 2019; Zheng et al., 2020; Kim et al., 2022).

Dietary support comes from the mechanisms of action of nutraceuticals against diseases, the stability of their current active ingredients, their bioactivity and bioavailability (Fang and Bhandari, 2010). In addition to phytochemicals, it is important to widely use probiotics among the methods to be applied to strengthen the natural intestinal flora. These methods, which are generally applied, are characterized by conventional (pharmaceutical formulations) and non-traditional (mainly food-based) products. Consuming live bacteria of functional character, which has an effect on the GI system, is mainly effective in improving health status. For this purpose, probiotics have increasingly been used (Champagne and Fustier, 2007). In addition to the benefits of applying the encapsulation technique in living cells, it is known that allows the incorporation of most bioactive compounds such as vitamins, prebiotics, bioactive peptides, non-nutritive carotenoids, phenolic compounds, phytoestrogens, glucosinolates, phytosterols, fatty acids or structured lipids into food systems without loss, and also development in new cells (Chen et al. al., 2006). These products are considered functional foods. Due to formulation differences, products produced with lactic acid bacteria are considered the best examples of functional food.

Fermentation products obtained in this way are determined as three groups (Mitsuoka, 2014):

(i) Probiotics: These bacteria create an effect by regulating the existing flora balance in the intestine and by affecting the living microorganisms such as lactobacilli and bifidobacteria, nutritional food supplements and intestinal mucosa, which benefit the host. Probiotic bacteria that contribute to health are used for this purpose in the preparation of most products (yogurts, cheeses, ice creams, milk powders and frozen dairy desserts, etc.) (Brannon-Peppas, 1995; Desmond et al., 2005),

ii) Prebiotics: This group consists of indigestible food group components such as oligosaccharides and/or dietary fiber, which include compounds that accelerate the development of probiotic bacteria and nutrients that support the development of microorganisms in the gut with their metabolic activities. These compounds are obtained through the extraction processes of plants and enzymatic hydrolysis (Gurib-Fakim, 2006);

iii) Biogenics: These bioactive compounds such as peptides, flavonoids and carotenoids, which contribute to host health, have vital effects such as initiating reactions against antigens, suppression of mutation, tumor formation, peroxidation or intestinal rot, also known as intestinal gangrene (da Silva et al., 2016).

The International Society of Sports Nutrition (ISSN) concluded that the use of strain-based probiotics in athletes is important (Jäger et al., 2019). Probiotic microorganism supplement products are accepted as an important complementary food component for athletes. Lactic acid bacteria, bifidobacteria, *Pediococcus*, *Leuconostoc*, *Streptococcus*, *Saccharomyces*, *Bacillus* and *Enterococcus* are commonly used probiotic strains. Today, consumption of probiotic products is widely recommended in order to protect and maintain our health (Pugh et al., 2018; Bozdoğan and Tazeoğlu, 2022). All studies on athletes and recreational subjects reported that the use of supplemental probiotics would prevent episodes of respiratory disorders and further alleviate their symptoms (Wosinska et al., 2019). In addition to the importance of consuming adequate amounts of dietary fiber, various protein sources and unsaturated essential oils (especially ω-3 fatty acids), it has also shown that pre, pro and synbiotic supplement products can protect the health of the athlete and get good results by optimizing the intestinal microbiota (Mancin et al., 2021)

Today, the consumer tends to consume products in the form of tablets or capsules, along with products that use probiotics in their preparation, instead of a product that is not a probiotic product. Especially freeze-dried products available in the market (e.g. Multibionta, Enterogermina, Reuteriana, Ultra Levure, Florastor) are among the most preferred products (Schrezenmeir and de Vrese, 2001; Canani et al., 2007 Rivera-Espinoza and Gallardo-Navarro, 2010). Another very important issue that emphasized by scientific studies is that foods prepared using probiotic live have a minimum live bacteria content of 10^6 - 10^7 CFU/mL at the time of consumption (FAO/WHO, 2001). In order to see the effect of probiotic bacteria in individuals, the minimum amount of ingested probiotic microorganisms are required to be 10^8 - 10^9 CFU/mL (Tripathi and Giri, 2014). In order for 10^9 CFU/mL probiotic bacteria to pass into the digestive system, it is recommended to consume 100 grams of probiotics product or products per day (Akan and Kınık, 2015). In the Turkish Food Codex Regulation on Nutrition and Health Claims, it is stated that in order for a food product to have a probiotic declaration, it must contain at least $1.0x10^6$ CFU/g live probiotic microorganisms (TGK, 2017). Therefore, while preparing the supplements, it is extremely important to ensure the number of living things in terms of their therapeutic effects. In addition, the increase in use is reflected in the value of the rapidly growing probiotic market worldwide. Its value was $32.06 billion in 2013, with projections for the worldwide probiotic market to reach $73.8 billion in 2024 are shared (Zucko et al., 2020). In the United States, microorganisms used for consumption must have a GRAS (Generally Regarded as Safe) statement issued by the Food and Drug Administration (FDA, Food and Drug Administration) (Anonymous, 2022a). As a similar terminology in Europe, the European Food Safety Authority (EFSA, European Food Safety Authority) introduced the concept of "Qualified Presumption of Safety" (QPS). The QPS statement states that safety assessments of bacteria-supplemented should have additional criteria, including the safe use of the product and the development of resistance to antibiotics (Anonymous, 2022b).

Probiotic-fortified foods and product label

In addition to anticarcinogenic, antioxidative, anti-inflammatory, antimicrobial, antiobesity and antidiabetic effects, probiotics are reported to have positive effects on the host's metabolism, respiratory system and brain functions (Kandylis et al., 2016; Gibson et al., 2017; Bingöl and Şengün, 2022). For this reason, the use of probiotics by food authorities, producers and consumers in the food industry is important. The food industry, which operates in the field of probiotic food day by day, continues to appear in the market with different products such as capsules, powder, milk, yogurt, ayran, diet yogurt, kefir, and cheese according to people's preferences. Functional foods containing probiotic microorganisms, which are scientifically supported for people's increasing healthy life preferences and reduce the possibility of disease, have been on the market for a long time (Çakır and Çakmakçı, 2004; Kanak et al., 2022). Different from the definition made by the WHO in 2001, the definition of probiotics is now defined by the International Scientific Society of Probiotics and Prebiotics (ISAPP) as 'live microorganisms that provide health benefits to the host when administered in adequate amounts' (Hill et al., 2014). ISAPP did not recommend that they be considered as probiotics in this group because the number of living organisms in the matrix could not be differentiated exactly as in fermented products with live organisma content related to probiotics. The microbial content of traditional fermented foods needs to be identified by strain-based assessment (Hill et al., 2014; Zucko et al., 2020).

Fermented products include yogurt, kefir, boza, tarhana, fermented foods, vinegar, fermented cheeses, fermented milk products (Yağcı, 2002). The health benefits of probiotics are generally revealed by adding them to milk and their products. It has been shown that probiotic bacteria can be used successfully in the production of many cheese varieties. In addition, the fact that dairy products such as yogurt and cheese can play a positive role in supporting the viability and/or development of probiotic cultures is also effective in enriching these products. The use of probiotic cultures in cheese production is enriched by increasing its positive effect on health and improving its quality, as well as providing the potential to increase the diversity of probiotic products (Araújo et al., 2012). In particular, probiotic yogurt is one of the most important functional dairy products and is widely consumed all over the world (Abdel-Hamid et al., 2020). Probiotics are not only found in natural food products such as kefir (Hikmetoğlu et al., 2020), yogurt (Azizkhani et al., 2021), but also in various bakery products (Erem, 2019), different fruit juices (watermelon, strawberry, chervil, grape juice, etc.) (Perricone et al., 2015; Oruç and Çakır, 2019) and plant-based milks (coconut milk, soy milk, almond milk, etc.) (Erk et al., 2019). It is also used in other foods (chocolate, cereals, pickles, raw sausage, bread, etc.) (De Vos et al., 2010; Sezen, 2013; Erik and Ormancı, 2022). *Lactobacillus reuteri* and *Bifidobacterium longum* probiotic bacteria with alginate microencapsulation are also used in the fermentation of sausage (Lücke, 2015).

It is known that the absorption of mineral substances is done thanks to the active transport mechanisms of the small intestine (Diaz de Barboza et al., 2015). The process of incorporating mineral substances such as musclelium is also important. As a result of fermentation of prebiotics, it causes the production of short-chain fatty acids, which affect the PH of the lumen. This environment in particular increases calcium solubility, providing a greater impetus for passive uptake. It is important to increase calcium bioavailability that most calcium salts in food supplements and foods are affected by its solubility depending on pH conditions and that it provides higher calcium solubility than the initial pH (Goss et al., 2007; Sanders et al., 2019). It is known that the use of probiotic bacteria in the production of foods has an effect on mineral substance absorption with these mechanisms.

Considering that individuals with lactose intolerance and high cholesterol cannot consume very valuable food groups such as dairy products in the results of scientific research, it is shared that this problem can be solved by developing new products. Recent information is that there is a need for research on the application of probiotics in product development and the probiotic properties of fermented foods. At the same time, besides all these, obstacles arising from food processing (high temperature, high pressure, drying, freezing, acidic or alkaline environment), obstacles arising from metabolism after consumption (digestive system enzymes, highly acidic environment and bile salts) and obstacles arising from the microorganism itself (anaerobic growth conditions and the need for rich nutrients, oxygen, temperature, pH, and stress conditions caused by inhibitors and competitive microorganisms) are the factors that limit the production of foods containing probiotic microorganisms (Desmond et al., 2005). Since probiotics have a very sensitive structure, encapsulation is an important process that supports the protection of these creatures, their stability as a therapeutic dose in the food matrix, and the activity of their mechanism of action in the gastrointestinal tract. The aim is to maintain the viability of probiotics against adverse environmental conditions by forming a protective film layer around the microorganisms with various substances (Çakır, 2006; Sedefoğlu et al., 2022). Especially, the viability of *Bifidobacterium* *pseudolongum* and *Bifidobacterium longum* in simulated gastric fluid (SGF) media has been improved by encapsulation technology. It has been reported that encapsulated bacteria are more active against applications where some microorganisms are more affected, such as freezing or freeze-drying processes. It is also shared that provides a very effective effect for lactic acid bacteria, especially when stored with capsules in dairy products (Rao et al., 1989; Lee and Heo, 2000; Shah and Ravula, 2000; Huq et al., 2013). Microencapsulation (ME) is the technology used to extend shelf life by preserving functional properties for many years by packing solids, liquids and gases in small capsules. Although this technology attracted great attention for the pharmaceutical industry at first glance, its application in the food industry was accepted later on. In industrial food production, it is generally recommended to include functional compounds in the production line. In this case, continuous control of the prepared product in terms of taste, color, texture and shelf life is required (Champagne et al., 2005). With this application, compounds with known potential health benefits are more preferred. It is valuable for the development of functional products by bioactive substances in terms of stability and application in carrier phases in the processing and storage stages (Champagne and Fustier, 2007). The use of bioactive compounds in the production of foods by microencapsulation method provides positive contributions to this effect.

In medicine, cosmetics, agriculture and food applications, the trend is now towards nanoparticles applications and has formed a key role for most technologies (Kingsley et al., 2013). Nowadays, people prefer the synthesis of metal nanoparticles (MtNPs) using microorganisms and plants applications with a green method approach (Singh et al., 2016). It is also known that green synthesis of MtNPs using natural microorganisms has many advantages when compared to traditional (known) methods. Among these advantages, it can be given that the synthesis of MtNPs is faster in terms of size, shape, composition and physicochemical, the lower cost, a cleaner technology, not provide toxic effects and an environmentally friendly application (Shah et al., 2015; Ovais et al., 2018). The use of probiotic microorganisms for the synthesis of MtNPs shows that it is an environmentally friendly practice as well as commercially important (Kulkarni and Muddapur, 2014). Probiotic microorganisms either directly affect living systems and are beneficial, or they provide indirect effects on a wide variety of metabolites. In addition, as in other bacterial groups, probiotics have a negative electrokinetic force that freely attracts cations, and these effects are accepted as the starting point for the nanoparticles (NP) biosynthesis process (Khosravi-Darani et al., 2019).

Sharing the label information of probiotics, which is so important for their use in the food industry, is also extremely important. As given in Figure 7, all strain information, genus and species descriptions entered into production should be included on a probiotic product label (FAO/WHO, 2002). Classification of probiotics in the relevant area of the label and arranging their names in the light of up-to-date scientific information and providing the most accurate information from the producers for the best service to consumers can be achieved. In the light of this information, experts, healthcare providers or consumers can verify the formulated product and use it for its intended purpose. One of the most controversial issues on a probiotic product label is whether to include the phrase health benefit on it. When consumers see this statement, they rightfully feel confident about their product demands. Different regions' regulatory frameworks apply different standards of evidence to support claims. It is also seen that some regions require pre-approval of their claims. For example, the European Union (EU) is sensitive to this issue and considers it appropriate for all claims to be approved by their regulatory authorities, and they have also received the approval of the probiotic claims they have submitted so far. In addition, it was accepted in the reviews that a cause-effect relationship could not be established between a probiotic product and the claimed health effect of the files submitted to support the claims. The EU's standard is considered to be the 'highest possible standard of evidence' and confirms that all studies are performed on healthy subjects. In the USA, this practice is carried out somewhat differently (Sanders et al., 2018).

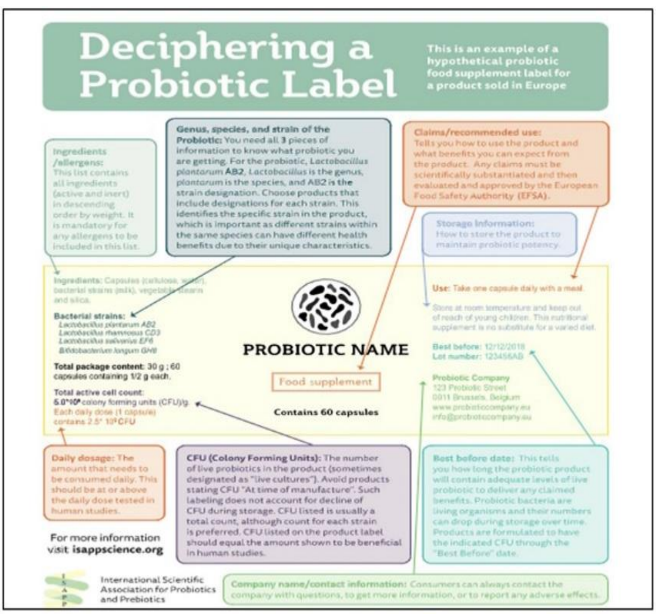

Figure 7. How to read the label information on the probiotic food supplement offered to the markets in the European Union? (Anonymous 2022c; Sanders et al., 2019)

NEW CONCEPTS ABOUT PROBIOTICS

Nowadays, in addition to probiotics, postbiotics (Nataraj et al., 2020), psychobiotics (Marx et al., 2020), para-probiotics, gerobiotics (Tsai et al., 2021), biotherapeutics, new generation probiotics (O'Toole et al., 2017) and designer probiotics (Paton et al., 2006) have taken their place in the literature. The differences between these new concepts and postbiotics Figure 8.

ISAPP (International Scientific Association for Prebiotics and Probiotics) was founded in 2000. This association organized a meeting (workshop) in Amsterdam in 2004 with the participation of 120 experts (Nutrition, Gastroenterology, Biology, Microbiology and Immunology). At this meeting, it was reported that the number of clinical and experimental studies on probiotics reached 1400, and 97 of them (7%) were randomized controlled studies on humans (İlkgül, 2005). Increasing the number of research, including new concepts emerging with the continuous development of science, will provide more contributions to the literature in this field, and will provide an opportunity to determine the conditions for the protection of our metabolism and the continuity of our health in quality.

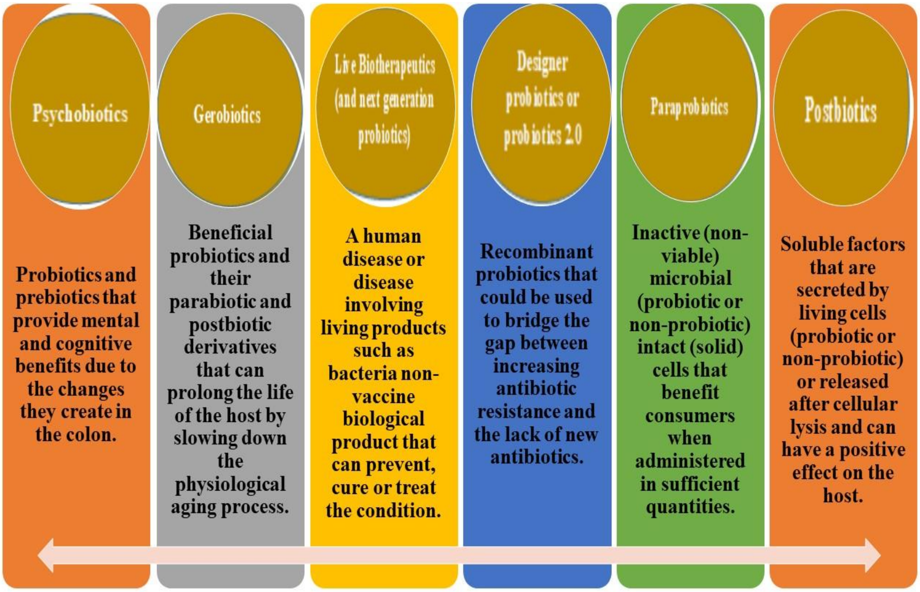

Figure 8. New concepts associated with probiotics (O'Toole et al., 2017; Singh et al., 2017; Sarkar et al., 2018; Cuevas-González et al., 2020; Tsai et al., 2021; Gökırmaklı et al., 2021)

POSTBIOTICS

Postbiotic products do not contain live bacteria, and the International Scientific Association of Probiotics and Prebiotics (ISAPP) defined the term "postbiotic" with a range of nomenclature in 2021 (Salminen et al., 2021). Compared to probiotics, prebiotics and synbiotics, this definition is a new concept that has been developing in recent years (Malashree et al., 2019). Postbiotics have antioxidant anti-infective, and antibacterial properties such as modulation of immune cell response, regulation of intestinal microbiota environment and epithelial barrier function, as well as inhibitory effect against pathogens (Aguilar-Toalá et al., 2018; Açar and Kaya, 2021). Although it is known that different postbiotics such as lactate, various peptides, short chain fatty acids (SCFAs), galactooligosaccharides (GOS) are produced by the strains of *Lactobacillus* and *Bifidobacterium* bacteria by fermentation in the intestine or food systems, it is known that metabolites that can be considered postbiotic are produced by many bacteria or yeasts such as *Streptococcus* and *Faecalibacterium* (Aguilar-Toalá et al., 2018; Collado, et al., 2019).

Although it has been reported that postbiotics produce compounds such as lactate, peptides, SCFAs, galactooligosaccharides by the fermentation of foods by strains of *Lactobacillus* and *Bifidobacterium* bacteria, it is also known that most bacteria and yeasts such as *Streptococcus* and *Faecalibacterium* can synthesize metabolites that can be considered postbiotic (Aguilar-Toalá et al., 2018). Metabolites synthesized as a result of the symbiotic effect of probiotics (*Bifidobacterium bifidum*) and prebiotics (fructooligosaccharides) are examples of postbiotics (Klemashevich et al., 2014).

Postbiotics are especially important in pediatric practice, mainly because they do not pose a risk of intestinal translocation or local inflammation (Nataraj et al., 2020; Morniroli et al., 2021). Postbiotics are part of a pathway that allows the gut microbiota to act both locally and at a distance via communication axes between the gut and target organs (Shen et al., 2021). In order to obtain postbiotics, methods such as ultrafiltration or chromatography are generally used for fermentation of probiotic strains, separation of the cell-free culture supernatant after fermentation and purification of the desired target molecule, and the resulting postbiotic is powdered in freeze-drying or spray-drying (Aguilar-Toalá et al., 2018; Barbieri et al., 2019; Moradi et al., 2021).

Postbiotics are defined as cell metabolites, biogenics, cell-free supernatant, functional proteins/enzymes, extracellular polysaccharides (EPSs), teichoic acid, pili-type structures, metabiotics (microbiota metabolites) and metabolic wastes of probiotic activity (Malashree et al., 2019; Wegh et al. al., 2019). The main components of postbiotics are given in Figure 9.

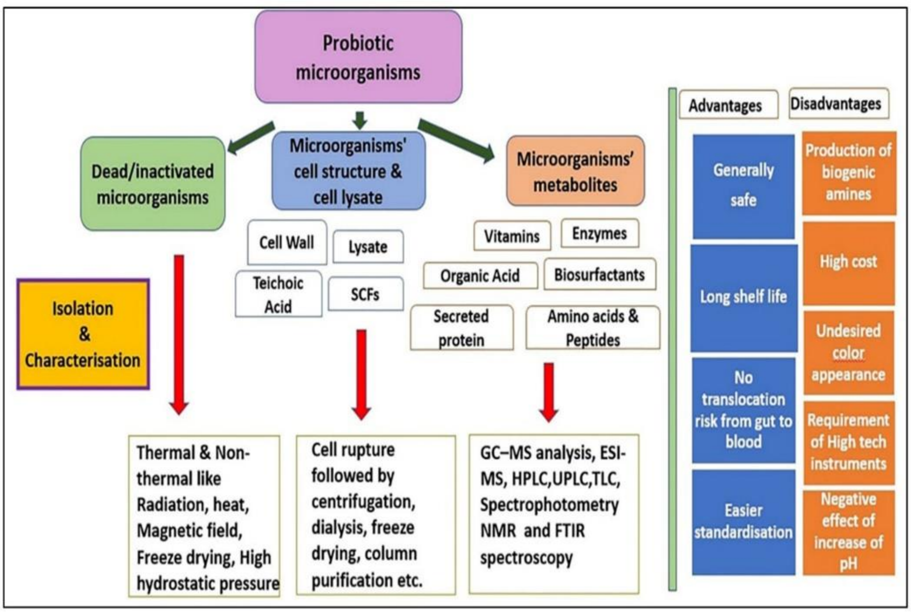

Figure 9. Postbiotic components: production and characterization (İçier et al., 2022)

The reasons are underlying the positive effects of postbiotics on host health: essential compounds; lipids (eg butyrate, propionate, dimethyl acetyl derivative plasmalogen), proteins (eg lactocepin p40 molecule), carbohydrates (eg galactose-rich polysaccharides and teichoic acids), vitamins/cofactors (eg B-group vitamins), organic acids [for example, propionic and 3-phenyllactic acid (PLA)] and peptidoglycan-derived muropeptides are expressed as lipoteichoic acid (Konstantinov et al., 2013; Aguilar-Toalá et al., 2018). Exopolysaccharides (EPS) are postbiotic components synthesized extracellularly by lactic acid bacteria, bifidobacteria and propionibacterium (Laws et al., 2001). EPS has gut-health-promoting and disease-preventing, cholesterol-lowering, antiulcer, anticarcinogenic and immune-modulating effects on health (Salazar et al., 2016). SCFAs perform central metabolic functions to maintain the intestinal mucosal barrier through transport from the intestinal lumen into the bloodstream. When SCFAs in the bloodstream act, they act as signal molecules and are absorbed by the organs. This effect provides positive contributions to lipid metabolism, glucose and insulin homeostasis, and they are beneficial in regulating genetic metabolic deficiencies (Canfora et al., 2015). Biotechnologically, it is known as the main source of the fermentation process of postbiotics. The increase in B group vitamin content in cereals can be given as a good example for postprobiotic fermentation. These B group vitamins contained in cereals are lost in some processes such as grinding and sieving. In addition, losses may occur in this group, which is affected by heat treatment. Fermentation of cereals, as well as pretreatment with lactic acid bacteria (LAB), promotes bacterial synthesis by increasing the content of vitamins B1, B2, B3, B9, B11 and B12. Potentially, postbiotics are considered a good alternative to increase vitamin B content in cereal-based products (Tomasik and Tomasik, 2020). SCFAs, one of the postbiotic varieties, protects the morphological and functional integrity of the intestinal epithelium by increasing mineral absorption, blood circulation and motility, and prevents the formation of colitis that may lead to cancer (Lupton, 2000). Equol is by far the most studied phenolic derivative postbiotic in humans. Although the main source of equol in the human diet is soy and its products. Some *Lactobacillus* sp. bacteria are also known to produce equol. To date, major evidence suggests that equol supplementation may have beneficial effects in protecting against the extremely painful symptoms of menopause. The molecular mechanisms of these meats are still being elucidated, and animal studies show that equol has an effect especially on its estrogenic activity (Di Cagno et al., 2010; Nuraida, 2015; Cortés-Martín et al., 2020). In fact, when bacterial cell walls are examined, most of the components are immunogenic and show a specific immune response. Lipoteichoic acid, a component of gram-positive bacterial cell wall, can also be released out of the cell and have the effect of inducing the production of cytokines (Żółkiewicz et al., 2020).

Figure 10 provides information summarized with the advantages of the increasing approach to postbiotics in recent years. In short;

(i) They are considered to be extremely safe,

(ii) Tolerability rates are very good and tend to decrease risk levels in special group categories of individuals (pregnant women, premature children, older adults, persons with suppressed or impaired immune function or intestinal barrier) (Taverniti and Guglielmetti, 2011; Tsilingiri and Rescigno, 2013; Toscano et al., 2017; Wang et al., 2020),

(iii) They do not carry the risk of transferring genes that are resistant to antibiotics to pathogenic bacteria (Żółkiewicz et al., 2020),

(iv) Their mechanism of action independent of cell viability causes them to remain stable for a longer shelf life (Salminen et al., 2021),

(v) They offer ease of use to industrial processes (Nataraj et al., 2020),

(vi) It is used as stabilizer in the food industry (rheological properties of exopolysaccharides; Patel and Prajapat, 2013; Nataraj et al., 2020) and bioprotective effects of LAB bacteriocins (Zacharof and Lovitt, 2012; Cabello-Olmo et al., 2021). It has been reported that postbiotics produce bacteriocins that compete with pathogenic bacteria by showing bacteriostatic or bactericidal effects, thus contributing to intestinal homeostasis.

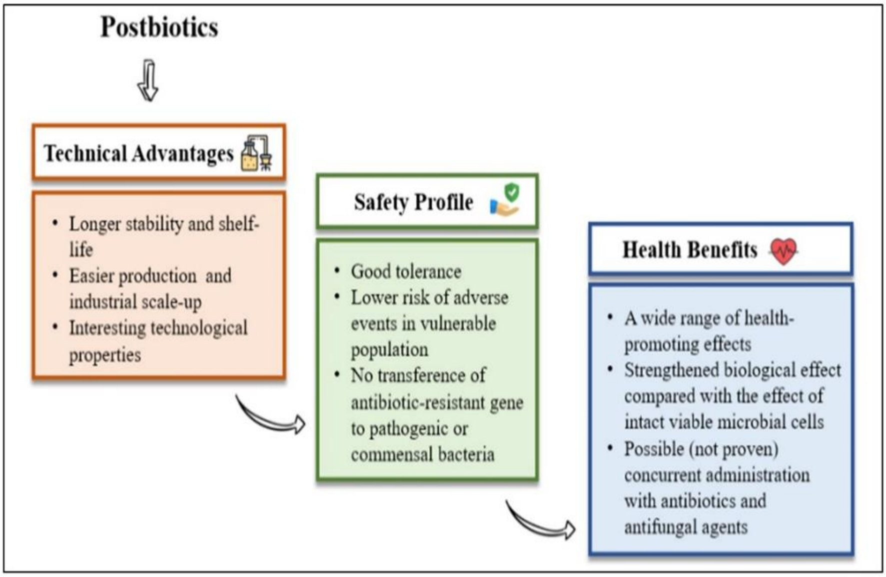

Figure 10. General characteristics of postbiotics (Mosca et al., 2019)

Although the mechanisms related to the health-promoting effects of postbiotics are not fully known, it positively affects the microbiota homeostasis and/or signal pathways in the host, making it antimicrobial, anti-inflammatory, immunomodulatory, anti-obesogenic, antihypertensive, anti-cancer (anti-proliferation effect that can cause cancer), antioxidant and hypocholesterolemic and other potential effects (Verma and Shukla, 2015; Tomasik and Tomasik, 2020; Sak and Soykut, 2021). Postbiotics are especially important in pediatric applications, mainly because they do not pose a risk of intestinal translocation or local inflammation (Nataraj et al., 2020; Morniroli et al., 2021; Dışhan et al., 2022). The purpose of functional nutrients such as postbiotics and probiotics is to increase the endogenous defense capacity of cells. The use of probiotic foods can restore colonic balance and help control the negative effects of antibiotic therapy (Zubilaga et al., 2001). Regulation of intestinal flora: Probiotics can maintain a healthy intestinal flora balance. It is suggested that supplementation with probiotics can be increased by examining stool samples. In healthy adults, the number of specific bacterial strains, the total number of probiotics, and the composition of the intestinal flora can also cause changes in microflora diversity (Khalesi et al., 2019). Depending on the contribution of probiotics with known specific physiological effects, it is suggested that intestinal health can be improved with the protection of healthy intestinal flora and a healthy immune system can be established (Chen et al., 2019; Lu et al., 2021). Local and systemic effects of postbiotics on the host that best explains this information Figure 11. As seen in Figure 11, SCFAs are metabolic products formed as a result of the fermentation of dietary carbohydrates by bacteria in the gastrointestinal tract. Thanks to these features, they show postbiotic properties (Rautiola, 2013).

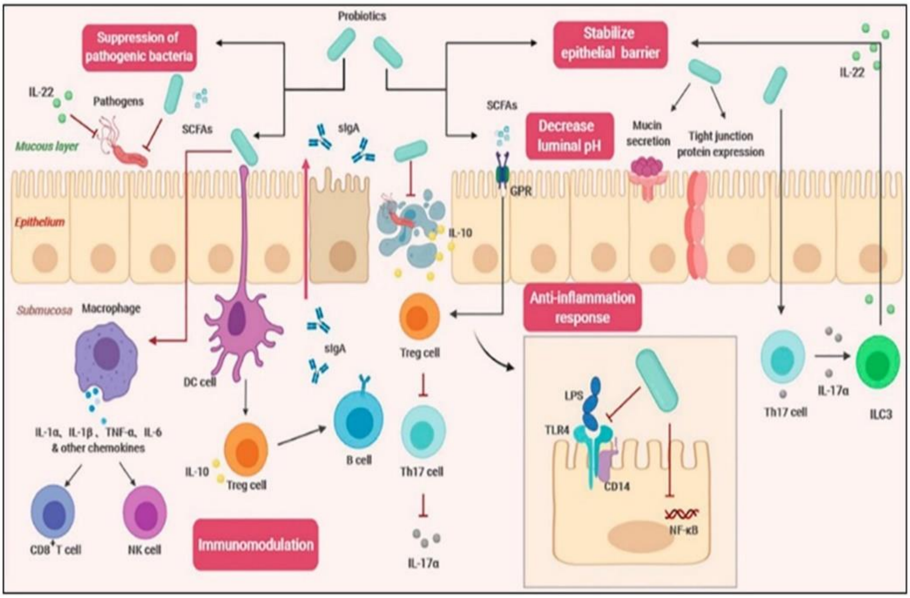

Figure 11. Local and systemic effects of postbiotics on the host (Açar and Kaya, 2021; Sak and Soykut, 2021)

Postbiotic production often involves cell lysis techniques such as heat and enzymatic treatments, solvent extraction and sonication. Additional extraction and post-production processes such as centrifugation, dialysis, freeze-drying and column purification are then used to help achieve production procedures (Aguilar-Toalá et al., 2018).

The application in food of probiotics

The use of postbiotics in the food industry is a new approach, there are current applications such as the removal of biofilms, antimicrobial effect, antioxidant effect, biodegradation of chemical contaminants in food, inhibition of foodborne pathogens and their use in edible coatings

(Moradi et al., 2021). Postbiotics are superior to probiotics due to their unique properties such as long shelf life of up to five years, non-toxic effects, easy transportation, low cost, known chemical composition, safe use and ease of storage, stability in a wide pH and temperature range, and broad-spectrum antimicrobial activity in the food industry. It is considered to be antimicrobial and is a valuable antimicrobial compound that prevents food spoilage (Abbasi et al., 2021). These effects are mainly due to bacteriocins, organic acids, enzymes, alcohols and low molecular weight molecules most postprobiotic metabolites responsible for the antimicrobial effects of lactic acid bacteria (Moradi et al., 2020). There are many studies on the use of postbiotics as natural antimicrobial agents in food packaging. In a study in which lyophilized *L. sakei* concentrated culture supernatants were added to packaging films and fresh steak cubes inoculated with *E. coli* and *L. monocytogenes* were covered with this film, it was determined that the film had an inhibitory effect against pathogens (del Carmen Beristain-Bauza et al., 2017). Exopolysaccharides (EPSs) produced by lactic acid bacteria and bifidobacteria is one of the postbiotic varieties frequently used in the food industry. It is used as an emulsifier, stabilizer and thickener in the dairy industry. It has been reported that yogurt and cheese positively affect product yield by increasing their viscosity and water-holding capacity (Lluis-Arroyo et al., 2014; Han et al., 2016). Many studies have shown that postbiotics can also be used as food additives. Three different *Lactobacillus* spp. A comparison was made between *L. salivarius* cell-free supernatant and it was stated that it could be an effective natural preservative for the control of bacterial pathogens (*Listeria monocytogenes*) in meat and milk (Moradi et al., 2019). In a study on the addition of lyophilized postbiotics in active food coatings, ground beef contaminated with *L. monocytogenes* was covered with a bacterial nanocellulose film containing *L. plantarum* lyophilized supernatant. It has been determined that this produced postbiotic-containing nano paper controls the growth of pathogens and doubles the overall shelf life without causing undesirable changes in the sensory properties of minced meat (Yordshahi et al., 2020). In a study to extend the shelf life of raw strip fish, culture supernatants of *L. plantarum* SKD4 and *Pediococcus stilesii* SKD11 were used and showed that postbiotics extended the shelf life by reducing microbial growth without affecting the physicochemical properties and food quality of the fish (Jo et al., 2021).

In a study conducted with sardine fillets, it was shown that *Enterococcus faecalis* A-48-32 bacteriocins have antimicrobial effects against *Staphylococci* species and reduce the formation of biogenic amines, thus prolonging the shelf life of the fillets (Ananou et al., 2014). In a study in which bacteriocins obtained from *Lactobacillus sakei* subsp. *sakei* 2a were added directly or encapsulated in nanovesicles to UHT goat milk, it was shown that the antimicrobial effect of encapsulated bacteriocin was higher (Malheiros et al., 2016). In another study, culture supernatants of *Lactobacillus* RM1 strain were lyophilized, then concentrated 10 times and used on wheat grains, and it was shown to have antifungal effects (Shehata et al., 2019). In a study conducted on different food groups, strawberries, mushrooms, corn and tomatoes were used as fruit and vegetable models. In this study, which was carried out with the aim of extending the shelf life, the culture supernatants isolated from *Pediococcus* spp. showed antimicrobial effects against

Escherichia coli and *Shigella sonnei* pathogens and extended the shelf life of these products (Skariyachan and Govindarajan, 2019). In a study on low-fat Cheddar cheese, purified EPSs of *L. plantarum* JLK0142 were added to cheese and it was shown that cheeses with EPS added at the end of storage had better moisture, proteolysis and sensory ripening characteristics. In addition, it was determined that the antioxidant and ACE inhibitor bioactivities of cheeses with EPS added were better (Wang et al., 2019). EPSs play an important role in the production of low-calorie bakery products and diet products. *L. delbrueckii* subsp. *bulgaricus*, *Streptococcus thermophilus* strains were added to the cakes as a fat-reducing component, and their properties such as firmness, volume, texture, chewiness and elasticity were compared with standard oil cake. As a result, it was observed that EPSs obtained from lactic acid bacteria improved product properties in low-fat cakes (Doğan et al., 2012). In order to improve the sensory properties of sucuk, in EPS producing *Lactobacillus plantarum* and *Leuconostoc mesenteroides* strains were selected and it was reported that the textural properties of the sucuk samples improved under suitable fermentation conditions and harder and less sticky sucuk products were obtained (Dertli et al., 2016).

The addition of postbiotics to foods can be done directly as a liquid culture supernatant or by adding concentrated culture supernatant as a solution. However, studies show that lyophilized or encapsulated postbiotics give better results (Malheiros et al., 2016; Kuley et al., 2021; İçier et al., 2022). It is necessary to characterize the detailed chemical composition of postbiotics for food and drug applications (Uğur et al., 2021). Postbiotics consist of complex molecules with different degrees of polymerization and bonds. It is recommended to perform complex analyzes for the identification and characterization of postbiotics for their qualitative and quantitative analysis. In order to achieve this, a lot of instrumental methods and innovative approaches should be applied. The appropriate method is generally chosen and applied depending on the analytical objectives and the type of characterization pursued (Barros et al., 2020).

PARAPROBIOTICS

Taverniti and Guglielmetti were the first scientists to propose the term paraprobiotic in 2011. The Food and Agriculture Organization/World Health Organization (FAO/WHO, 2002) conceptualized paraprobiotics as 'inactive (non-living) microbial cells or cell fractions that, when consumed in adequate amounts (Martín and Langella, 2019), provide benefits to consumers', similar to the definition of probiotic microorganisms. Paraprobiotics, which are probiotic or non-probiotic inactivated microbial cells, have a positive effect on consumer health when consumed (de Almada et al., 2016). In one of the different definitions of paraprobiotics, they are named as ghost, non-living or inactivated probiotics and are made as whole or fragmented non-viable microbial cells that can provide benefits to the consumer when used orally or topically in sufficient amounts (Taverniti and Guglielmetti, 2011; Tsilingiri and Rescigno, 2013; Barros et al., 2020; Vallejo-Cordoba et al., 2020). With regard to the use of cell components and bioactive metabolites of probiotics, the terms 'paraprobiotics', 'ghost probiotics', 'inactivated probiotics', 'cell fragments', 'non-living microbial cells', 'metabiotics', 'biogenics' have been proposed (Taverniti and Guglielmetti, 2011; Tsilingiri and Rescigno, 2013; Fesseha et al., 2022).

Literature reviews have shown that paraprobiotics are as effective as living microorganisms in improving the immune system and providing resistance to the host against diseases (Irianto and Austin, 2002; Salinas et al., 2008; Dash et al., 2015; Dawood et al., 2015; Choudhury and Kamilya, 2019). It has also been stated that paraprobiotic administration significantly improves glucose intolerance as a result of increased insulin resistance rate and decreased insulin response to glucose, and that lipid accumulation in the liver is reduced in the prevention of fatty liver. In addition, it has been reported that yeast-derived postbiotics and paraprobiotics have protective effects in vivo animal models. According to Generoso et al. (2011) reported that this compound prevents intestinal permeability in the paraprobiotic *Saccharomyces boulardii* process and reduces bacterial translocation that causes intestinal obstruction in their experiments on mice.

Paraprobiotics are better than probiotics in some clinical situations (Cuevas-González et al., 2020; Martyniak et al., 2021). In recent years, it has been understood that non-living microorganisms and their components have a health effect just like probiotics. The term 'paraprobiotic' can show similarities and differences to the classical definition of probiotics with the prefix 'para' translated from Ancient Greek as 'side by side' or 'atypical'. Technologies used to obtain paraprobiotics focus on reducing the loss of viability in the microorganism completely or substantially. In this context, heat treatment, high pressure, sonication, etc. applications are among the technologies commonly used for these purposes (Cuevas-González et al., 2020). de Almada et al. (2016) reported that the heat treatment applied to the cell did not interfere with the increase in the production of immune-supporting cytokinins in macrophages in inactivations with a heat applied to obtain paraprobiotics so the paraprobiotic positively affected immunity. However, although information about the effect of heat on probiotic microorganisms is still reported to be no problem; however, uncertainties regarding the mechanism of action still remain. It is generally accepted that heat plays a role in cell inactivation by causing damage to different cell structures of microorganisms such as cell membranes, DNA, RNA, ribosomes and certain enzymes (Nguyen et al., 2016). It has been reported that heat-resistant bacteria are more pressure-resistant than other bacteria and that bacteria are generally more sensitive to pressure application at the beginning of their developmental stages (Moerman, 2005). Therefore, several analytical techniques (Figure 12) have been proposed for postbiotic and paraprobiotic identification.

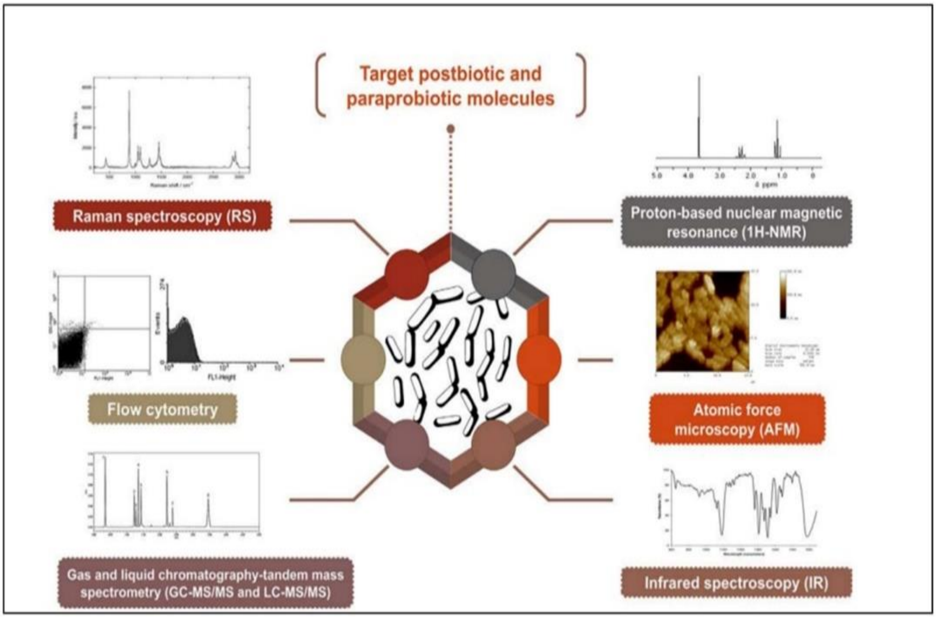

Figure 12. Use of analytical techniques for postbiotic and paraprobiotic characterization (Collado et al., 2019)

The sound waves produced in the ultrasonication process cause cavitation and damage the cell walls of microorganisms. Larger microbial cells, bacilli, anaerobic microorganisms, vegetative cells and gram-negative microorganisms are more sensitive to ultrasonic treatments (Zeuthen and Bøgh-Sørensen, 2003). Microorganism cells have specific mechanisms to destroy these reactive species, prevent damage and repair damaged structures; however, cell viability is compromised when the required capacity for this mechanism is exceeded (Marcén et al., 2017). Newly developed UV light-emitting diodes (UV-LEDs) stand out in applications as they do not show the disadvantages of mercury vapor UV lamps in the above-mentioned aspects (Lawal et al., 2018). Generally, pressure values between 100-400 MPa are used for the inactivation of probiotic microorganisms (Tsevdou and Taoukis, 2011).

PSYCHOBIOTICS

The definition of "psychobiotic", which is a new concept, was first defined by psychiatrist Ted Dinan in 2013 as a subgroup of probiotics that offers alternative treatment opportunities in the treatment of psychiatric diseases. Psychobiotics are defined as a group of probiotic microorganisms that, when taken in adequate amounts, have effects on the central nervous system through metabolic pathways such as the immune system and nervous system, and systems that form the brain-intestinal axis, provide benefits in psychiatric diseases and have antidepressant and anxiety-relieving properties (Dinan et al., 2013, Cheng et al., 2019; Özyürek and Özcan, 2020). In addition, in a different definition, psychobiotics are defined as live (probiotics) microorganisms that provide beneficial effects on health in people with psychiatric illnesses through interactions with commensal gut bacteria when consumed in sufficient quantities (Koçak and Tek, 2019). Compounds such as butyrate, acetate and propionate, which are formed as a result of the symbiotic effect of psychobiotics/probiotics with prebiotics, cause neuroinflammation effects in the brain and reduce the formation of amyloid plaques by improving the intestinal microbiota ecosystem balance, content and functional properties (Blacher et al., 2017). Psychobiotics reduce the level of cortisol, also known as the “stress hormone”, and increase the level of the hormone oxytocin, which is known to be closely related to positive physical and psychological effects in humans (Cheng et al., 2019). Studies have shown that some intestinal microorganisms such as *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Escherichia*, *Bacillus*, *Saccharomyces*, *Candida*, *Streptococcus* and *Enterococcus* can produce serotonin, gammaaminobituric acid and that these microorganisms can produce psychobiotic *Lactobacillus odontolyticus* and *Lactobacillus plantarum* (Roshchina, 2016; Düdükçü and Öğüt, 2022).

It covers conditions such as anxiety disorder, post-traumatic stress, panic and social anxiety disorders, which are stated to affect one out of every ten people in the world (Dean and Campbell, 2020). The use of probiotics as an adjunct in the treatment of depression was first suggested by Logan and Katzman (2005). However, studies on the subject were mainly conducted by Dinan et al. (2013) with the definition of psychobiotic. There are many clinical studies conducted on whether probiotic microorganisms have psychobiotic properties.

A neuroactive substance that psychobiotics can produce, serotonin (5-HT), also known as the "happiness hormone", is a metabolite of the amino acid tryptophan and plays an important role in regulating many body functions, including mood (Dinan et al., 2013). Changing the microbial composition of the gastrointestinal tract leads to a change in the plasma concentration of tryptophan (precursor of serotonin). In this way, it plays an important role in the production and regulation of neuroactive substances such as serotonin, tyrosine, GABA, and glycine. Due to this role of microbiota, it has been reported that it can directly affect brain activity and indirectly affect the behavior of the individual (Clarke et al., 2014). Specific bacteria have a positive effect on mental health, such as increasing our resistance to stress, reducing anxiety and brightening our mood (Mörkl et al., 2020). By increasing the anti-inflammatory cytokine interleukin-10 level, decreasing the proinflammatory cytokine level and suppressing hypothalamic-pituitary-adrenal (HPA) activity, psychobiotics suppress stress conditions and improve intestinal barrier functions (Tuğlu and Kara 2003, Dinan et al., 2013, Foster et al., 2017). It is known that psychobiotics, which control and regulate the neuroimmune and brain-intestinal axis, are effective in neurological disorders with their key roles on mood disorders and immune system (Bermúdez-Humarán et al., 2019; Cohen Kadosh et al., 2021).

Psychobiotics, which produce hormones, immune factors and metabolites, play an important role in cognitive development as well as brain functions. This application, which is very valuable information today, also provides science that the treatment of brain diseases can be started by regulating the intestinal microbiota (Ling et al., 2020). Various evidence from animal and human studies have shown that the gut microbiota can alter the activities of the autonomic nervous system and alter gut function, serotonin biosynthesis and mental health status. The live microorganisms used for these treatments are called “psychobiotics” (Sampson and Mazmanian, 2015; Obata and Pachnis, 2016).

Psychobiotics, which are probiotic microorganisms that affect the central nervous system and neurological functions of the host, can improve the quality of life of individuals with psychological problems by balancing the gastrointestinal system. Adjusting the intestinal microorganism balance has been found to be effective on most psychiatric diseases, including "Anxiety and Depression", "Alzheimer's disease", "Parkinson's disease", "Autism Spectrum Disorder" and "Tourette syndrome". It is also reported that thanks to the consumption of foods containing probiotic products, a response can be obtained against the treatments of these diseases (Magalhães-Guedes, 2020). Most clinical studies involving patients with Parkinson's involving probiotics have focused on gastrointestinal function. In the severity of pulmonary hypertension (PH), an increase in oxidative stress and inflammation has developed. Studies show that psychobiotics will give good results in reducing the symptoms of PH (Taylor et al., 2013). *Lactobacillus fermentum* PS150 TM, *Lactobacillus brevis* SBC8803 and *Lactobacillus helveticus* CM4 are psychobiotics, and they can also provide health to those with psychiatric or neurological diseases, especially in eliminating insomnia problems (Dinan and Cryan, 2017).

In another study investigating the effect on the skin, the skin moisturizing activity of the paraprobiotic in human keratinocytes was evaluated and preliminary data on the use of paraprobiotics as a functional ingredient in moisturizing products were presented (Kim et al., 2020).

Beneficial foods rich in probiotic bacteria that have been shown to have positive effects on the gut microbiome include fermented dairy products such as kefir, and more traditional foods such as raw honey, kimchi, miso, and fermented soy (Tomasi and Webb, 2020). A multi-strain combination of probiotics, and intake of foods such as prebiotics and probiotics (fermented foods) in the diet can be applied as psychobiotic action (Mörkl et al., 2020). In a study of athletes under physical and mental stress, they consumed specially prepared beverages containing inactivated *Lb. gasseri* CP2305 ($1x10^{10}$ CFU/box) for 12 weeks. As a result of the study, it was reported that the fatigue of the participants decreased significantly and their anxiety and depressive moods were relieved (Sawada et al., 2019).

SYNBIOTICS

The concept of "synbiotic" was coined by Gibson and Roberfroid in 1995 as a result of the synergistic effects of probiotics and prebiotic combination (Gibson and Roberfroid, 1995). Symbiotic foods contain approximately 10^4-10^9 CFU/g of live probiotic bacteria during their shelf life (Özden, 2013; Rezac et al., 2018). Synbiotics are combinations developed to facilitate the life of probiotic microorganisms in the gastrointestinal tract (Fernandez and Marette, 2017; Markowiak and Śliżewska, 2017). Foods within this scope show many positive effects by balancing immunity, protecting against cancer, preventing obesity, regulating glucose metabolism, correcting intestinal digestive problems (such as diarrhea, and constipation), protecting mental health, lowering LDL-cholesterol and hypertension, and preventing atherosclerosis (Özden, 2008; Murooka and Yamshita, 2008; Usinger et al., 2009; Tamang, 2010; Özden, 2013; Karaçıl and Acar Tek, 2013; Çeltik et al., 2022).

It is thought that synbiotics selectively enable the development and/or activation of the physiological gut microbiota and thus have beneficial effects on the health of the host. The first issue to be considered when creating a synbiotic product should be the selection of an appropriate probiotic and prebiotic. When used separately, probiotics and prebiotics, which have positive effects on the health of the host, should be combined. Among the most commonly used probiotic and prebiotic combinations (Markowiak and Śliżewska, 2017):

- *Lactobacillus* spp. + inulin,
- *Lactobacillus*, *Streptococcus* and *Bifidobacterium* genera + FOS,
- *Lactobacillus*, *Bifidobacterium*, *Enterococcus* genera + FOS
- *Lactobacillus* and *Bifidobacterium* genera + oligofructose
- *Lactobacillus* and *Bifidobacterium* genera + inulin.

A synbiotic product can lead to modulation of intestinal metabolic activities by improving intestinal biostructure. Synbiotics affect health by increasing the amount of short-chain fatty acids, ketones, carbon disulfide and methyl acetates (Vitali et al., 2010). In addition, synbiotics have shown beneficial effects in the control of lipid profile by reducing serum leptin levels, serum total cholesterol and LDL cholesterol levels (Sekhon and Jairath, 2010; Safavi et al., 2013; Ipar et al., 2015). In addition, although methods such as lactose-free or lactose-reduced milk and dairy products consumption and external enzyme intake (Szilagyi and Ishayek, 2018) have been applied to eliminate lactose intolerance, the effect of synbiotic consumption on lactose intolerance has been focused on in recent years (Akal and Yetişmeyen, 2020). Louzada and Ribeiro (2020) examined the effect of synbiotics formed by the combined use of probiotics and prebiotics on depression in a study they conducted on healthy-looking elderly individuals and found that synbiotics had weak effects on depression symptoms. Despite the potential role of synbiotics in weight regulation, only a few animal studies have evaluated their effects on food intake and hunger-satiety hormones (Lesniewska et al., 2006; Tulk et al., 2013).

Since probiotics provide the nutrients they need from prebiotics, probiotic bacteria in synbiotic products maintain their viability longer (Hu et al., 2006, Mohanty et al., 2018, de Paulo Farias et al., 2019). In a different study by Gallaher and Khil (1999) reported that people would benefit if synbiotics were added to their daily consumption. Since foods containing probiotics also contain prebiotics, they generally show symbiotic properties and can be called by this name. Among the symbiotic foods, the most important nutrients are breast milk, honey and fermented products (Özden, 2013; Karaçıl and Acar Tek, 2013).

Synbiotic compositions are enriched with more than one LAB and prebiotic to achieve a stronger effect. The aim here is to gather together the different effects of varied strains. Hundreds of strains have been isolated and tested for their bioavailability for synbiotic preparations. Today, the preparation called Sinbiotic-2000 FORTE (produced by Medipharm, Kågeröd Sweden and Des Moines, Iowa, USA); consists of four different strains and prebiotics; (probiotics; 1010 pieces each: *Pediococcus pentoseceus* 5- 33:3, *Leuconostoc mesenteroides* 32-77:1, *L. paracasei* ssp *paracasei* 19 and *L. plantarum* 2362, as well as 2.5 g inulin, oat bran, pectin and resistant starch). *Lb paracasei* one of the components of Sinbiotic-2000 FORTE, has been isolated from humans and the other three strains are of rye origin (İlkgül, 2005).

PREBIOTICS

The term prebiotic is defined by Gibson and Roberfroid as “an indigestible food substance that has a beneficial effect by affecting the growth and/or activity of one or a small part of colon bacteria” and is also called “functional food” or “nutracotics” (Gibson and Roberfroid, 1995; Schrezenmeir and de Vrese, 2001; Koçak et al., 2016). Prebiotics, which act as an energy source for the intestinal microbiota, are nutritional components that affect the protection and continuity of the individual's health by regulating the activities of the numbers of gastrointestinal microorganisms (World Gastroenterology Organization, 2017). The mechanism of action of prebiotics is generally on the activities of *Lactobacillus* and *Bifidobacterium* (Notay et al., 2017). ISAPP has defined prebiotics as substrate compounds that provide health benefits and are selectively used by host microorganisms (Gibson et al., 2017). It is believed that for an ingredient to be considered a prebiotic, it must have three key properties:

(i) prebiotics must be able to resist degradation by host enzymes by gastrointestinal absorption,
(ii) prebiotic fermentation must be done by intestinal microorganisms,
(iii) the individual should be selective according to both the development and activity of the intestinal bacteria necessary for the continuity and protection of his health.

In many different foods (asparagus, sugar beets, garlic, chicory, onions, *Jerusalem artichokes*, wheat, honey, bananas, barley, tomatoes, rye, soybeans, human and cow's milk, peas, beans, seaweed and microalgae, etc.) naturally contains prebiotics (Varzakas et al., 2018). Among the most important food components with prebiotic properties are fructooligosaccharides, inulin, glucooligosaccharides, galactooligosaccharides, xylooligosaccharides, isomaltooligosaccharides, gentiooligosaccharides, lactulose, lactosucrose, polydextrose, pyrodextrose, pyrodextrose, pyrodekstrin

(Gibson and Roberfroid, 1995; Ziemer and Gibson, 1998; Holzapfel and Schillinger, 2002; Can and Özçelik, 2003; Yıldırım et al., 2003; Şener et al., 2008). Most prebiotics is either isolated or synthesized from the depolymerization of plant and algal polysaccharides such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), isomaltooligosaccharides (IMO), and xylooligosaccharides (XOS). Basic oligosaccharides such as soy oligosaccharides (SOS), galactooligosaccharides (GOS), and xylooligosaccharides (XOS) are sold in markets in Japan (Gibson and Rastall, 2006; Saad et al., 2013; Al-Sherajia et al., 2013; Özyurt and Ötleş, 2014; Table 2).

Table 2. Prebiotic oligosaccharides

Prebiotic types	Resources
Fructooligosaccharides	Asparagus, sugarcane, garlic, chicory, onion, ground beef, wheat, honey, banana, tomato, rye, barley
Isomaltulose	Honey, cane sugar syrup
Galactooligosaccharides	Human and cow's milk
Raffinose oligosaccharides	Lentil, pea, bean grains
Xylooligosaccharides	Bamboo roots, fruits, vegetables, milk, honey and wheat bran
Cyclodextrins	Water-soluble glucans
Soyoligosaccharides	Soy
Lactulose	Lactose (milk)
Lactosucrose	Lactose
Isomaltulose	Sucrose
Palatinosis	Sucrose

Maltooligosaccharides	Starch
Isomaltooligosaccharides	Starch
Arabinoxylooliosaccharides	Wheat bran
Enzyme resistant dextrin	Potato starch

The purpose of using oligosaccharides in the diet is due to their prebiotic effects. The ability to bind to fimbriae, which allows pathogenic microorganisms to attach to the intestinal surface, prevents the colonization of pathogenic microorganisms and also causes the excretion of these wastes through feces (Spring, 1998). Another important feature of prebiotics is that they are powerful antioxidants. Thanks to these properties, pectin and resistant starch (amylose maize) have a protective effect on the mucosa. It has been reported that this mucosal protective effect provides an effect in the treatment of peptic ulcers in humans and in an experimental colitis model in rats (Best et al., 1984; Hills and Kirwood, 1989; İlkgül, 2005).

In order for a nutrient to be considered a prebiotic, it must have the following characteristics:

(i) It should not be hydrolyzed or adsorbed in the stomach and small intestine,
(ii) It should be selective for beneficial microorganisms in the colon microflora and be able to stimulate their proliferation,
(iii) It should change the flora to form a healthy composition and have beneficial local and systemic effects on the host (Gibson and Roberfroid, 1995; Schrezenmeir and de Vrese, 2001; Gibson, 2004; Yılmaz, 2004).

Various methods used in the preparation of prebiotics are given in Table 3 (Ötleş, 2014; Özyurt and Ötleş, 2014).

Table 3. Prebiotic sources and production methods

Carbohydrates	Natural Resources	Chemical nature	Production method
Inulin	Fruits and vegetables (onions, bananas, garlic, etc.)	B(2-1)-Fructans	Extraction from chicory root and *Agave tequilana*
Fructooligosaccharides	Fruits and vegetables (onions, bananas, garlic, etc.)	B(2-1)-Fructans	Hydrolysis of chicory inulins or transfructosylation from sucrose
Galactooligosaccharides	Human milk	Galactose oligomers and some glucose/lactose/ galactose oz units	Production from lactose by β-galactosidase
Soyoligosaccharides	Soybean	Mixture of starch and raffinose	Extracted from soybeans
Xylooligosaccharides	Bamboo shoots, fruits, vegetables, milk and honey	B(1-4) bound xylose	Enzymatic hydrolysis of xylan by enzymatic treatments from natural lignocellulosic materials, hydrolytic degradation of xylan with diluted solutions of mineral acids, water or steam.
Isomaltooligosaccharides	Starch (wheat, barley, corn, rice, potato, etc.)	α(1-4) glucose and α(1-6) branched glucose	Microbial or enzymatic transgalactosylation of maltose, enzymatic synthesis from sucrose
Pyrodextrins	Starch (lentils, sorghum seeds, sago roots, etc.)	Glucose-containing oligosaccharide mixture	Pyrolysis of corn or potato starch

Prebiotics affect the release of gastrointestinal hormones, especially affecting energy intake and expenditure, and increase satiety by changing the secretion of neuropeptides, gastric motility and insulin sensitivity, and reduce food consumption (Torres-Fuentes et al., 2017). When multiple sclerosis (MS) and the gut microbiome are examined, the effects of probiotics on the modulation of gut microbiota offer new opportunities to treat MS. The immunomodulatory properties of some probiotics, prebiotics and bacteria-associated molecules are used to develop adjuvant therapies that complement the treatment options available for MS patients (Calvo-Barreiro et al., 2018). Dietary fibers and probiotics, as well as the use of newly encountered paraprobiotics and postprobiotics in recent years, have changed the intestinal microbiota, and it is also known that especially nuline and fructo-oligosaccharides or resistant starch-based dietary fibers make serious contributions to the bifidobacterial numbers in the colon. Accordingly, the possibility of effective prevention of Alzheimer's disease with probiotics and prebiotics (containing no chemical agents, but commensal bacteria or herbal products that can regenerate and restore intestinal microbial flora) is considered an important advance in the field (Cuervo et al., 2014). The consumption of prebiotics is also seen to be beneficial in the treatment of constipation. It has been observed that especially the decrease in constipation complaints is with the addition of bifidobacterium to the diet (Türkay and Saka, 2016). The theory for the use of probiotics in nutritional therapy to prevent migraine is that the combination of peptides and probiotics improves nutrient assimilation in most patients (Sensenig et al., 2001).

Prebiotics also show properties such as increasing the absorption of important minerals such as calcium and magnesium, improving plasma lipids as well as providing an effect on blood sugar. Their general characteristics are that they support individual health and have a wide range of uses in different areas of food production. Prebiotic mechanisms of action are due to fermented carbohydrates, which support the growth of probiotic bacteria such as bifidobacteria/lactic acid bacteria and thereby regulating the gastrointestinal and immune systems (Al-Sheraji et al., 2013). Despite the wide range of recommended intake levels for prebiotics, a daily intake of 2-20 g of prebiotics is generally recommended (de Souza Oliveira et al., 2011; Binns, 2013).

The intestinal system provides an area for a wide range of ecology microbes, which is the most important for health, thus the complex mechanism of action of prebiotics can be better understood. Despite all this, the beneficial possibilities of prebiotics on health arise from their mechanisms. These mechanisms of action are shown in Figure 13 and also discussed. It has been prepared with data from studies conducted in vitro or using animal subjects to identify all of these predicted mechanisms. However, in some cases, it can be difficult to determine that they actually occur in the human gut microbiota (Sanders et al., 2019). The premise is that the prebiotics reach the intestine and are used here with a selective effect. At this stage, microorganisms of a certain genus or species can continue to grow and develop specific to the prebiotic. The use of prebiotics by microorganisms is also considered as positive developments for health as a result. Improved intestinal environment with the increase in stool volume is one of the important factors in microbial growth. Immune regulation can be affected by increased biomass of bacteria and cell wall components.

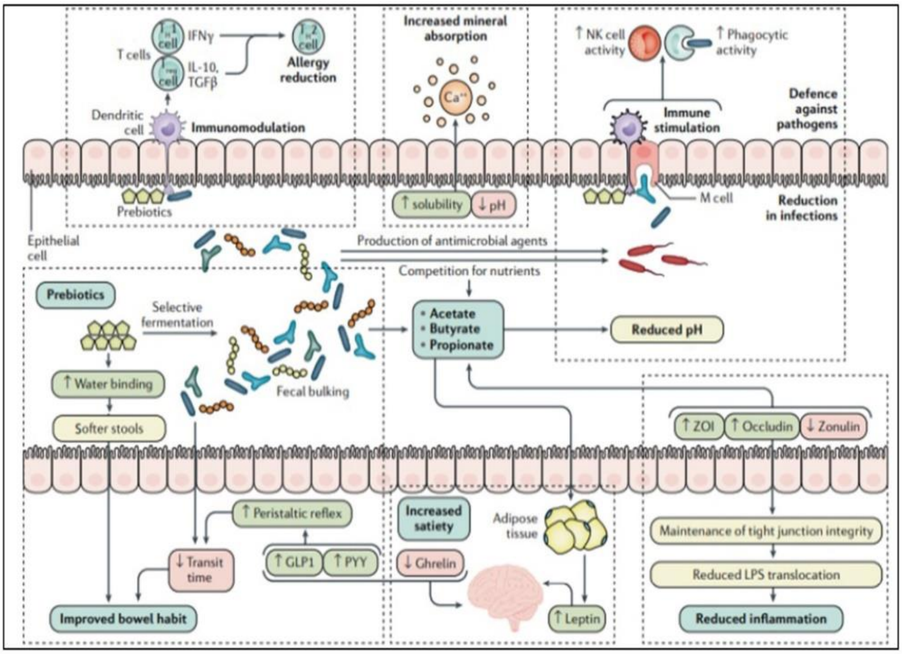

Figure 13. Mechanisms of action of prebiotics defined (Sanders et al., 2019)

Metabolic products show effects on decreasing the pH of the intestinal environment, on pathogens, and at the same time as mineral substance absorption. These products also have an effect on hormonal regulation along with epithelial integrity. Bacteria consuming prebiotics can compete with pathogens in the environment, such as the activation of antimicrobial agents, and thus they can affect microbiota diversity. As a result, it is reported that it decreases the number of bacteria containing lipopolysaccharide (LPS) together with infectious diseases. GLP1, glucagon-like peptide 1; M cell, microfold cell; NK cell, natural killer cell; PYY, peptide YY; TGFβ, transforming growth factor-β; TH 1 cell, type 1 T helper cell; TH2 cell, type 2 T helper cell; Treg cell, regulatory T cell; ZO1, zonula occluded 1 (Sanders et al., 2019).

The main source of the increasing demand for prebiotics is the scientific evidence of their many different positive effects on health. Among them, in the host; it has important health effects such as reducing constipation, increasing mineral absorption, reducing intestinal pH, restoring intestinal bacterial balance, and having an anticarcinogenic effect (Ashwini et al., 2019). When the economic size of prebiotics is analyzed, in 2015 alone, the global prebiotic market was worth 2.90 billion USD and this value is predicted to be 8.5 billion USD or 10.55 billion USD by 2025, according to two different studies (de Paulo Farias et al., 2019; Quigley, 2019).

CONCLUSIONS

Microbiota is the expression of the dynamic system formed by the complete microorganisms present in the digestive system, nervous system, urogenital system and respiratory system. Probiotics, prebiotics and synbiotics are also components that affect the composition of the microbiota. The concepts of postbiotic and paraprobiotic are new concepts compared to these components, and the number of studies on intestinal microbiota and postbiotic/paraprobiotics has been increasing in recent years. Consumers have shown great interest in functional nutrition and subsequently probiotic products in the last two decades. Studies with paraprobiotics and postbiotics have generally shown positive effects on health and similar effects with probiotics. These effects are seen in studies that intracellular components, cell wall compounds, obtained cell extracts and metabolites increase the adhesion to intestinal cells by accelerating the immune system. However, in terms of food safety, more detailed studies are needed to purify and determine the chemical structures of postbiotics. In addition, it is seen that optimization studies are needed to determine the factors affecting the production of postbiotic compounds with different activities during fermentation and also to determine the postbiotic dose that should be applied to the food. At this point, there is a greater need for metabolomic studies with placebo-controlled human and clinical intervention trials planned in order to make sense of the contributions of paraprobiotic/postbiotic supplements on health and to determine the most appropriate therapeutic dose. It is predicted that the production and consumption of postbiotics may increase with the support of increasing scientific studies over time.

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