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ROLE OF MICROBIOTA IN MAINTAINING THE HOMEOSTASIS IN THE HUMAN BODY

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Abstract: The human body is believed to be occupied by around 4×10^{13} microorganism cells, which is 10 times the number of cells of the human body. Multidisciplinary studies conducted worldwide by microbiologists and physicians suggest that the microorganisms which colonize the human body can more actively influence the state of health than previously thought. The most important role in the regulation of the homeostasis is played by ontocenoses of the intestine. Imbalanced taxonomic composition and number of intestinal microbiota may contribute to the development of numerous infectious (HIV), metabolic (diabetes, obesity) and immunological (allergy, asthma, rheumatoid arthritis) diseases, as well as conditions associated with various organs (kidneys, liver, heart, inflammatory bowel disease, Crohn's disease), cancer (colon) and the nervous system (autism, sleeping problems, stress, chronic fatigue syndrome, schizophrenia, Alzheimer's disease). The composition of the intestinal microbiota can be modified by applying a specific type of diet.

1. Introduction. 2. Microbiota in the disorders of the immune system. 3. Microbiota in metabolic diseases. 4. Microbiota in cardiovascular diseases. 5. Microbiota in the disorders of the gastrointestinal tract. 6. Microbiota in renal diseases. 7. Microbiota in central nervous system disorders. 8. Regulation of microbiota through functional foods. 9. Conclusion

Udział mikrobioty w utrzymaniu homeostazy organizmu człowieka

Streszczenie: Ciało człowieka zasiedla około 4×10^{13} komórek mikroorganizmów, czyli 10 razy więcej niż liczba komórek ludzkiego organizmu. Wielodyscyplinarne badania prowadzone na całym świecie przez mikrobiologów i lekarzy sugerują, że mikroorganizmy, które kolonizują organizm człowieka, mogą bardziej aktywnie wpływać na stan zdrowia niż wcześniej sądzono. Najważniejszą rolę w regulowaniu homeostazy odgrywa ontocenoza jelita. Zaburzenia struktury taksonomicznej oraz liczby bakterii jelitowych mogą przyczyniać się do rozwoju licznych chorób zakaźnych (HIV), metabolicznych (cukrzycy, otyłości) i immunologicznych (alergii, astmy, reumatoidalnego zapalenia stawów), a także zaburzeń związanych z różnymi narządami (nerek, wątroby, serca, zapalenia jelit, choroby Crohna), raka (okrężnicy) oraz zaburzeń układu nerwowego (autyzmu, problemów ze snem, stresu, zespołu przewlekłego zmęczenia, schizofrenii, choroby Alzheimera). Skład mikroorganizmów jelitowych można regulować stosując konkretny rodzaj diety.

1. Wstęp. 2. Mikrobiota w zaburzeniach układu immunologicznego. 3. Mikrobiota w chorobach metabolicznych. 4. Mikrobiota w chorobach układu krążenia. 5. Mikrobiota w chorobach przewodu pokarmowego. 6. Mikrobiota w chorobach nerek. 7. Mikrobiota w zaburzeniach układu nerwowego. 8. Regulacja mikrobioty poprzez żywność funkcjonalną. 9. Wnioski

Key words: human health, natural microbiota
Słowa kluczowe: zdrowie człowieka, naturalna mikrobiota

1. Introduction

Multidisciplinary studies conducted worldwide by microbiologists and physicians suggest that the microorganisms that colonize the human body can more actively influence the state of health than previously thought. The human body is believed to be occupied by around 4×10^{13} microorganism cells, which is 10 times the number of cells of the human body. Depending on the location, between 10^4 and 10^{11} cells are found per 1 ml of content of digestive tract, while about 10^7 are found per 1 cm^2 on the skin [52]. Under correct homeostasis mechanisms, microorganisms form multi-species biological membranes composed of cells and extracellular matrix, known as biofilms. Commensal organisms are to a large extent responsible for controlling potentially pathogenic species by competition. Their presence stimulates the immune system by producing invasin and impedin, stimulates the production of interleukins IL17, IL22 and IL23 by leukocytes, and regulates the maturation of Th lymphocytes. They can also actively limit the growth of pathogens by producing bacteriocins and hydrogen peroxide, and by adjusting the pH of the internal environment of macroorganism [37, 42]. The gut microbiota plays an important role in the digestion of polysaccharides, proteins and fatty acids, allows the synthesis of group B vitamins and vitamin K, and promotes the absorption of minerals. The bacteria stimulate epithelial cell proliferation in the intestines, regulate gut motility, and degrade toxins and mutagens contained in foods [37, 42].

The studies performed as part of the Microbiome Human Project indicate that the microorganisms present in the human body have at least a million genes

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whose products may affect the expression of human genes [22, 23]. Scientific reports suggest that the most important role in the regulation of the homeostasis is played by *ontocenoses* of the intestine, which can be defined as collections of organisms inhabiting the different sites of organism [29]. Disorders of the taxonomic structure and the number of intestinal microbiota may contribute to the development of numerous infectious (HIV), metabolic (diabetes, obesity) and immunological (allergy, asthma, rheumatoid arthritis) diseases, as well as conditions associated with the various organs (kidney, liver, heart, inflammatory bowel disease, Crohn's disease), cancer (colon) and the nervous system (autism, sleeping problems, stress, chronic fatigue syndrome, schizophrenia, Alzheimer's disease).

2. Microbiota in disorders of the immune system

Around 70–80% of the cells of the immune system are formed within the lymphoid tissue of the gastrointestinal tract [50]. Interactions between intraepithelial lymphocytes and gut microbiota occur via Toll-like receptors [13]. Intestinal bacteria increase the tightness of the intestinal barrier by regulating the expression of the structural proteins of the connections between the enterocytes and induction of the syntheses of immunoglobulin A [50]. The presence of the microbiota is important during the development of the lymphatic tissue of the intestine, as it stimulates the differentiation of intraepithelial lymphocytes and regulatory T-cells. Polysaccharide A produced by *Bacteroides fragilis* induces CD4 lymphocyte activity. The microbiota participates in maintaining homeostasis by regulating the number of helper and regulatory T lymphocytes. Studies on gnotobiotic mice found a decreased number of dendritic cells and CD4 lymphocytes in the gut and reduced intraepithelial lymphocyte activity compared to animals with normal microbiota [13]. However, lower numbers of the lactic acid bacteria *Bacteroidetes* and *Bifidobacterium*, but an increased amount of the coliform bacilli *Clostridium* and *Enterococcus* were seen in the intestine of people with allergic sensitisation. Studies in children have shown that contact in the first year of life with a wide diversity of bacteria in the environment and animal allergens correlated with a lower risk of allergic respiratory diseases [21].

Infants delivered by Caesarean section who possess a decreased number of *Bacteroides* and reduced diversity of *Bacteroidetes* in the gastrointestinal tract have been found to have an increased risk of developing various allergies [54]. Greater numbers of coliform and *Staphylococcus aureus* were found in the faeces of children presenting with food allergies associated with milk proteins and ovalbumin. In addition, children with eczema demonstrate less *Enterococcus* and *Bifidobacterium*, and more *Clostridium*. It has been shown that colonization of the neonate during the first week of life by lactic acid bacteria reduces the risk of allergic diseases in pre-school age [28].

In the early stages of rheumatoid arthritis, some patients showed a decreased number of intestinal *Bifidobacteria* and *B. fragilis* [56]. However, a significant increase in the prevalence of *Prevotella copri* was observed in patients in the early stages of the disease, which suggests that this species could play a role in inducing this disorder [28].

3. Microbiota in metabolic diseases

A disturbance of the natural balance of intestinal microbiota may be a predisposing factor to obesity. A reduced number of bacteria of the genus *Bacteroides*, and greater numbers of *Firmicutes* type (including *Lactobacillus*, *Enterococcus* and *Peptostreptococcus*) and the *Proteobacteria* family have been reported in patients with obesity compared to people of normal body mass [31]. Species more numerous in obese people are responsible for the increased fermentation of indigestible polysaccharides into bioavailable forms, the absorption of monosaccharides and short chain fatty acids from the gastrointestinal tract. The weight of the mother during childbirth has no effect on the composition of the intestinal microbiota in infants: it has been proven that the children of obese mothers have a similar microbiota to those of slim mothers. In contrast, the occurrence of dysbiosis and the development of obesity depends on eating habits and lifestyle [31]. In a study by Ley *et al.* [33], intestinal microbiota of obese and normal weight individuals were transplanted to gnotobiotic mice. All animals were then fed a low-calories, high-fiber diet. It was found that within two weeks, the mice that had received a transplant from an obese subject had an greater amount of body fat than those whose blots had come from an individual of normal weight. Cannabinoid receptors are also involved in the regulation of energy balance and the development of obesity. Cluny *et al.* [12] demonstrated that the administration of tetrahydrocannabinol (THC) to obese mice resulted in reduced energy demand and thus lower consumption of calories, and prevented increases in body weight induced by a high-fat diet. In animals with normal weight, the administration of THC did not change energy needs. In domestic chickens, infections with adenovirus Ad31, Ad36 and Ad37 were much more frequently diagnosed in obese birds, and non-obese individuals were more likely to have adenovirus Ad5 [46]. Almagren *et al.* [3] found a correlation between adenovirus Ad36 infection and prevalence of obesity in children in Sweden.

Significant differences in the composition and abundance of commensal microorganisms were observed in diabetes. Children with type 1 diabetes were found to have reduced numbers of bacteria of the genera *Lactobacillus*, *Bifidobacterium*, *Prevotella* and the species *Eubacterium rectale*, and increased numbers of *Clostridium*, *Bacteroides* and *Veillonella* bacteria than healthy children [40]. In adults with type 2 diabetes, fewer *Clostridium* and *Firmicutes* bacteria and more *β-Proteobacteria* were observed [30]. Remely *et al.* [48] found significantly lower species diversity in people with diabetes compared to healthy subjects. Due to the greater abundance of *Enterobacteria*, including *Escherichia coli*, patients with diabetes are three to fifteen times more prone to infections caused by these bacteria. The introduction the genus *Bifidobacterium* to the diet of animals was associated with improved glucose tolerance, insulin secretion and normalized inflammatory tone and decreased endotoxemia [7].

4. Microbiota in cardiovascular diseases

Patients with an increased risk of cardiovascular disease were found to have a reduced number of *Alloprevotella* and *Catenibacterium* bacteria, and an increased number of *Prevotella* and *Tyzzerella* [26]. Many diseases of the circulatory system are caused by the deposition of atherosclerotic plaque, which is formed as a result of elevated levels of trimethylamine (TMA) and trimethylamine N-oxide (TMAO) in the blood serum. TMA is produced by gut bacteria from choline and short-chain fatty acids, and thereafter metabolized in the liver to TMAO. The pro-atherosclerotic effect of TMAO is associated with overactive platelets, increased macrophage foam cell information and reverse cholesterol transport. High levels of TMAO are associated with increased numbers of *Clostridiaceae* and *Peptostreptococcaceae* bacteria [55]. Emoto *et al.* [14] observed an increased number of bacteria from the phylum *Firmicutes* (*Lactobacillus*, *Streptococcus* and *Enterococcus*), and reduced prevalence of phylum *Bacteroidetes* (*Bacteroides* and *Prevotella*) in patients with coronary artery disease. More opportunistic *Enterobacter*, *Megasphaera*, *Oscillibacter* and *Desulfovibro* and less commensal *Bacteroides*, *Prevotella* and *Faecalibacterium* are found in patients with myocardial infarction [24, 57]. Yin *et al.* [57] found that the exacerbation of myocardial infarction is associated with the progression of dysbiosis of gut microbiota. The administration of probiotics consisting of *Lactobacillus plantarum* and *L. curvatus* decreased triglyceride levels, increased the levels of apolipoprotein A-V and low-density lipoprotein cholesterol particle size in the blood serum [2].

5. Microbiota in the disorders of the gastrointestinal tract

Two types of inflammatory bowel disease can be distinguished: Crohn's disease and ulcerative colitis. The microbiota of Crohn's disease sufferers is poorer in *Bacteroides* and *Bifidobacteria*, and richer in *Enterobacteriaceae* [51], and a similar composition of intestinal microbiota which differs from that of healthy subjects can be seen between patients with Crohn's disease and their asymptomatic relatives. These results suggest the presence of sub-clinical inflammation in the relatives of patients with Crohn's disease. Ulcerative colitis is characterized by lower numbers of bacteria of the families *Lachnospiraceae* and *Ruminococcaceae*, and genus *Lactobacillus*, and an increased number of *E. coli*, which can serve as a biomarker of inflammation [34, 58]. Between 20 and 37% of patients with ulcerative colitis have also demonstrated co-invasion with *Candida* sp. By stimulating the production of proinflammatory cytokines IL-1β and TNF-α, the fungi delay the healing process and hinder treatment. The use of probiotics, and antifungal therapy in the course of ulcerative colitis, shortens the treatment time [59].

Patients with colorectal cancer present a reduced number of agents of the genera *Prevotella* and *Ruminococcus*, and the species *Pseudobutyrivibrio ruminis*. Bacteria of the genera *Acidaminobacter* and *Phascolarctobacterium*, and species *Citrobacter farmer* and *Akkermansia muciniphila* are more prevalent in intestinal ontocenoses [58]. The tumors of these patients were found to harbour the genetic material of *Fusobacterium nucleatum*: a species typical of the oral cavity which is responsible for the formation of dental plaque. Around 50% of the human population are infected with *Helicobacter pylori*, which in 1994 was officially recognized by the WHO as an etiological agent of cancer of the stomach and duodenum. In addition, *H. pylori* is responsible for 80% of gastric ulcer and 90% of duodenal ulcer cases [16].

The components of natural intestinal microbiota can produce substances with activity inhibiting the proliferation of tumor cells. Some of these compounds are colicin produced by *E. coli*, azurin by *Pseudomonas aeruginosa*, and LSL003, LSL 0510 and LSL 0554 by *Lactobacillus salivarius* [25, 41, 53].

6. Microbiota in renal diseases

There is a link between gut microbiota and chronic kidney diseases. Uremia alters the metabolism of intestinal bacteria, while the p-cresyl sulphate and indoxyl sulphate produced by the bacteria are involved in the development of renal diseases [9]. Greater numbers of

bacteria from 190 taxa, mainly from the family *Pseudomonaceae*, have been found in patients in the terminal stage of kidney disease, together with significant decreases in the numbers of *Lactobacillaceae* and *Bacteroidaceae* [15].

7. Microbiota in central nervous system disorders

Mental disturbances in patients have been associated with changes in the intestinal mucosa. This suggests a relationship between the CNS and the intestine, known as the microbiota-brain-gut axis. Of patients with schizophrenia, 92% present colitis, 88% inflammation of the small intestine, and 50% gastritis [50].

One of the main neurotransmitters responsible for mood, concentration, learning ability and the regulation of appetite and sleep is serotonin. Around 80–90% of serotonin is produced by the enterochromaffin cells of the intestine, whose activity is stimulated by more than 20 species of spore bacteria. Epidemiological data indicates that the serotonin level of children who died of sudden infant death syndrome (SIDS) was about 26% lower than in controls [4].

Changes in the levels of neurotransmitters associated with intestinal dysbiosis are more clearly visible in males. In studies of gnotobiotic animals, Clarke *et al.* [11] observed elevated levels of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in the hippocampus and precursors of serotonin in the blood serum of males, resulting in greater anxiety, which regressed after normalizing microbiota. Reductions in the numbers of bacteria of the genera *Lactobacillus* and *Bifidobacterium* in the intestine is observed in cases of sudden emotional stress. Literature data suggests that the genus *Bifidobacterium* is more sensitive to stress conditions and the physical activity of the host [50]. Rao *et al.* [47] note that patients with chronic fatigue syndrome who received *Lactobacillus casei* (*L. Casei Shitora*) demonstrated greater clinical improvements in neurological stage and increased number of lactic acid bacteria in the feaces compared to the control group. Freestone *et al.* [18] showed an increase in the numbers of non-pathogenic and pathogenic (0157: H7) strains of *E. coli* as a result of the interaction of stress hormones with host catecholamine.

Stress is associated with an elevation of corticotropin level, produced by *inter alia* intestinal enterochromaffin cells, and occludins, proteins which increase the permeability of the intestinal barrier by influencing the connections between enterocytes [35]. Permeability disturbances promote the translocation of bacteria and its products from the intestinal lumen and increased inflammation. Pro-inflammatory cytokines such as TNF-α, IFN-α and IFN-γ activate the enzyme 2,3-dioxygenase indoleamine in the kynurenine pathway, reduce the concentration of serotonin and increase the concentration of tryptophan metabolites [35]. While elevated levels of corticotropin and corticosterone were observed in gnotobiotic mice subjected to stress in another study, no such changes were observed in animals lacking certain microorganisms: administration of *Bifidobacterium infantis* to both groups of mice resulted in partial regression of symptoms of stress in the gnotobiotic animals and total regression in the other group [5].

γ-Aminobutyric acid (GABA) is responsible for inhibition of the inflammatory response and reduction of pain in the CNS, and any disturbances in the activity of GABA receptors can cause depression and anxiety attacks. The administration of probiotic *Lactobacillus rhamnosus* bacteria activates GABA receptors and limits the symptoms of depression or anxiety. Animals with an experimentally damaged vagus nerve did not respond to the probiotic, which indicates that a link exists between the brain and gut microbiota via the vagus nerve [6].

As early as in 1910, Phillips observed positive results of treatment of depression and other psychiatric disorders associated with the use of lactic acid bacteria, while in 1923, Julianelle and Ebaugh recommended the use of *Bacillus acidophillus* in cases of psychosis [50].

Several drugs used in neurological and psychiatric disorders have a negative effect on the gut microbiota, resulting in increased inflammation of the mucous membrane, and can promote weight gain. Conversely, it was found that intestinal bacteria can inhibit the metabolism of psychotropic drugs such as benzodiazepine, clonazepam, risperidone and levodopa [49].

Numerous neurological symptoms, such as psychosis, anxiety attacks and depression, are common in people addicted to alcohol, most of whom also display a number of gastric disorders. Leclercq *et al.* [32] report significant intestinal barrier permeability (HIP) in 43% of alcoholics, and low intestinal barrier permeability (LIP) in 57%. Studies of the intestinal microbiota of HIP patients based on 16S rRNA found increased numbers of *Dorea*, *Blautia* and *Megasphaera* bacteria and reduced numbers of *Clostridium*, *Ruminococcus*, *Subdoligranulum*, *Oscillibacter*, *Anaerofilum*, *Bifidobacterium*, *Lactobacillus* and *Faecalibacterium* bacteria, especially the anti-inflammatory species *F. prausnitzii*, whose presence is negatively correlated to the amount of inflammatory interleukin IL8. However, LIP patients demonstrated similar numbers of bacteria of these genera to those observed in the control group. After detoxification, reduced intestinal permeability and the regression of psychiatric symptoms were found in LIP patients, but not the HIP patients. The authors suggest that the HIP patients are more likely to return to addiction [32].

The structure of the intestinal microbiota of children with autism is significantly different from that of healthy children. Significant reductions in number are observed in the genera *Bifidobacterium*, *Enterococcus*, *Klebsiella*, *Streptococcus* (including hemolytic strains), *Citrobacter*, *Enterobacter* and *Escherichia*; increased numbers was recorded in the bacterial genera *Lactobacillus*, *Bacillus* and *Desulfovibrio* and the fungal genus *Candida*, especially *Candida albicans*, and dysbiotic yeast. The severity of symptoms are correlated with the severity of dysbiosis [1, 39, 45]. Grossi *et al.* [19] describe the case of 12-year-old autistic boy with gastrointestinal disorders, who for several years had unsuccessfully been treated for celiac disease. Further diagnosis suggested irritable bowel syndrome, and the child's diet was duly supplemented with a probiotic preparation containing *Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, *L. bulgaricus*, *L. delbrueckii*, *Streptococcus thermophilus* and *S. salivarius*. Within a few weeks, the gastric disorders had disappeared; however, surprisingly, a simultaneous decrease of autism symptoms and a significant improvement in social affects were also observed [19]. Similar results were observed after the introduction of *Bacteroides fragillis* into the diet of mice with experimentally-induced autism with an increased intestinal permeability and abnormal cytokine profile [20].

Another study reported differences between patients with multiple sclerosis and healthy subjects with regard to the size and structure of microbiota. The population sizes were found to be different in as many as 21 species, 19 of which, mostly belonging to *Bacteroidetes* and *Clostridium*, demonstrated a significant decrease in number [38] Elsewhere, patients with multiple sclerosis were found to possess a reduced number of *Faecalibacterium* and vitamin D deficiency, which may be related to the content of short-chain fatty acids in the diet [8].

The most widely known species within the natural intestinal microbiota is *E. coli*, of which, some strains may be the etiological agent of human gastroenteritis. One of the most dangerous is O104: H4 *E. coli* strain, which produces a Shiga-like toxin. Kleimann *et al.* [27] describe an epidemiological outbreak caused by this strain which took place in northern Germany. Together with haemolytic-uraemic syndrome, the patients also presented psychiatric disorders, including attention deficit and memory disorder in 88%, disturbances of affect in 88% (up to 10 panic attacks a day), disorders of the driver and psychomotility in 84.8%, formal disorders of thoughts in 78.2% and organic psychiatric disorders in 58%. Elsewhere, a microarray assay of the *E. coli* proteome by Chen *et al.* [10] found differences in the protein compositions of the antigenic profiles of patients with bipolar disorder and 48 healthy people. The sensitivity of the identification of bipolar disorder patients was 75% and specificity approximately 80%. Accordingly, the authors suggest that the molecular profiles of certain bacterial species can be used as a sensitive assay for identifying neurological disorders.

8. Regulation of microbiota through functional foods

Recent years have seen increased interest in functional foods, which may be defined as products with generally-recognized nutritional value exerting a beneficial effect on one or more functions of the body. According to the International Life Sciences Institute, such food should strengthen the function of the body, improve well-being and reduce the risk of diseases, especially civilization diseases. Functional foods include, among others, probiotic bacteria, prebiotic oligosaccharides, bioactive peptides, natural antioxidants, vitamins, fiber, choline, lecithin and omega-3 fatty acids, but do not include any form of pills, tablets, syrups or drops, regardless of their beneficial effects on health [17]. The most popular group of functional foods are preparations such as yogurt or kefir which contain probiotics.

Recently, great interest has arisen in the bacteria *Mycobacterium vaccae*. *M. vaccae* is an aerobic bacterium commonly occurring in soil, and as a transient biota in animals. Mathews & Jenks [36] examined the effect of *M. vaccae* on the ability to think in studies in mice. Bacterial inoculate was administered to animals in food consisting of white bread and peanut butter, and the animals were placed in a maze. Experiments showed that mice fed with *M. vaccae* needed half of the time to go through the maze and committed fewer errors compared to mice on a normal diet. In addition the experimental mice showed lower levels of anxiety, the effect being maintained even after the administration of bacteria was completed. O'Brien *et al.* [43], in a clinical trial among patients in the terminal stage of lung cancer, observed improvements in emotional and cognitive function after administration of attenuated *M. vaccae*.

The composition of the intestinal microbiota can be adjusted by applying a specific type of diet. A diet rich in protein is associated with an increased number of *Alistipes*, *Bilofila* and *Bacteroides*, and reduced levels of the *Firmicutes* (*E. rectale*, *Ruminococcus bromii*). Physical activity is essential in this diet to avoid weight gain. A high-fat diet is associated with a higher level of *Firmicutes* and a lower level of *Bacteroidetes*. High fat content increases the permeability of the intestinal mucosa and increases its capacity for energy harvest and storage. The consumption of products containing a large amount of plant fiber is associated with higher levels of *Bifidobacteria* and lower levels of *Bacteroides*

and *Clostridium histolyticum*, and is associated with a lower risk of kidney cancer. Long-term observations suggest that variations in colon microbiota depend on the diet. The Western diet, based on eating large amounts of fat, is considered to be the least favourable for the balance of the intestinal microbiota; the Mediterranean diet on the other hand, is regarded as one of the most optimal diets with demonstrated beneficial effects in the treatment of Crohn's disease [44].

9. Conclusion

The analysis of available world literature indicates the very important role of natural microbiota in the proper functioning of the human body. Any kind of internal imbalance within individual ontocenoses, variations in the proportion of different groups of microorganisms and the occurrence of dysbiosis can result in health disorders. These disorders may be conducive to not only infectious diseases, but also metabolic, autoimmune, psychiatric, etc. Unfortunately, all the possible effects of microbiota changes are still unknown. On the other hand, many years of research indicate the possibility of regulating the composition of commensal microorganisms through the use of certain nutrients and supplementing the diet with beneficial bacteria.

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