DOI: 10.20514/2226-6704-2022-12-5-341-351
EDN: EBLUAU
УДК 616.34:579.61]-048.25

Е.Г. Малаева*, И.О. Стома

Гомельский государственный медицинский университет,
Гомель, Республика Беларусь

ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ МОДИФИКАЦИИ КИШЕЧНОГО МИКРОБИОМА

E.G. Malaeva*, I.O. Stoma

Gomel State Medical University, Gomel, Republic of Belarus

Possibilities and Prospects of Modification of the Intestinal Microbiome

Резюме

Микробиом кишечника является вариабельной системой, которая не только адаптируется к сигналам и информации, поступающей от человека, но и влияет на своего хозяина за счет сложной системы взаимодействий живых микроорганизмов, фагов, вирусов, плазмид, мобильных генетических элементов, молекул, синтезируемых микроорганизмами, в том числе их структурных элементов (нуклеиновых кислот, белков, липидов, полисахаридов), метаболитов (сигнальных молекул, токсинов, органических и неорганических молекул) и молекул, синтезируемых организмом человека. Модификация или модулирование микробиома путем коррекции рациона питания, характера физической активности, назначения компонентов персонализированных продуктов (пребиотиков, пробиотиков, парапробиотиков, постбиотиков, аутопробиотиков) может приводить к изменению видового разнообразия, метаболического профиля микробиома кишечника и регуляции обменных процессов, локального и системного ответа на инфекционные заболевания, метаболизма лекарственных средств, деятельности многих органов и систем за счет наличия физиологических осей «микробиом кишечника–центральная нервная система», «микробиом кишечника–печень», «микробиом кишечника–почки» и некоторых других. Изучаются новые, таргетные направления модификации микробиома кишечника, которые заключаются в целенаправленном воздействии на патогенные микроорганизмы, в том числе внутриклеточные и устойчивые к антибактериальным лекарственным средствам.

Динамический характер кишечного микробиома, способность изменяться и адаптироваться под воздействием некоторых изученных факторов открывает новые перспективные направления медицинской профилактики и лечения соматических и психических заболеваний. Несомненно, модификация микробиома с клинической целью направлено на укрепление здоровья человека. Однако, индивидуальные, не всегда предсказуемые, изменения микробиома в ответ на модифицирующие факторы могут быть обусловлены уникальностью видового состава и функционального потенциала микроорганизмов у каждого человека.

Ключевые слова: *микробиота, микробиом, антибиотики, пробиотики, пребиотики, трансплантация фекальной микробиоты*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 23.03.2022 г.
Принята к публикации 21.04.2022 г.

Для цитирования: Малаева Е.Г., Стома И.О. ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ МОДИФИКАЦИИ КИШЕЧНОГО МИКРОБИОМА. Архивъ внутренней медицины. 2022; 12(5): 341-351 DOI: 10.20514/2226-6704-2022-12-5-341-351 EDN: EBLUAU

Abstract

The gut microbiome is a variable system that not only adapts to signals and information coming from humans, but also affects its host due to a complex system of interactions of living microorganisms, phages, viruses, plasmids, mobile genetic elements, molecules synthesized by microorganisms, including their structural elements (nucleic acids, proteins, lipids, polysaccharides), metabolites (signaling molecules, toxins, organic and inorganic

*Контакты: Екатерина Геннадьевна Малаева, e-mail: dr-malaeva@mail.ru
*Contacts: Ekaterina G. Malaeva, e-mail: dr-malaeva@mail.ru
ORCID ID: https://orcid.org/0000-0003-1051-0787

molecules) and molecules synthesized by the human body. Modification or modulation of the microbiome by correcting the diet, the intensity of physical activity, the appointment of components of personalized products (prebiotics, probiotics, paraprobiotics, postbiotics, autoprobiotics) can lead to changes in species diversity, the metabolic profile of the intestinal microbiome and the regulation of metabolic processes, local and systemic response to infectious diseases, drug metabolism, the activity of many organs and systems due to the presence of physiological axes "gut microbiome–central nervous system", "gut microbiome–liver", "gut microbiome–kidneys" and some others. New, targeted directions of modification of the intestinal microbiome are being studied, which consist in targeted exposure to pathogenic microorganisms, including intracellular and resistant to antibacterial drugs.

The dynamic nature of the intestinal microbiome, the ability to change and adapt under the influence of some of the studied factors opens up new promising areas of medical prevention and treatment of somatic and mental diseases. Undoubtedly, the modification of the microbiome for clinical purposes is aimed at improving human health. However, individual, not always predictable, changes in the microbiome in response to modifying factors may be due to the uniqueness of the species composition and functional potential of microorganisms in each person.

Key words: *microbiota, microbiome, antibiotics, probiotics, prebiotics, fecal microbiota transplantation*

For citation: Malaeva E.G., Stoma I.O. Possibilities and Prospects of Modification of the Intestinal Microbiome. The Russian Archives of Internal Medicine. 2022; 12(5): 341-351 DOI: 10.20514/2226-6704-2022-12-5-341-351 EDN: EBLUAU

FMT — fecal microbiota transplantation, SCFAs — short-chain fatty acids

Introduction

Human gut microbiome is a comprehensive and complex ecosystem thickly populated by species of microorganisms that interact with each other and with the human body [1, 2].

The composition of microbiota varies between individuals and depends on the host genotype host and environmental factors, including nutrition, physical activity, and the use of antibacterial agents [1–5]. It is known that the large intestine contains more microorganisms than the other GIT sections; the predominant types are *Firmicutes and Bacteroides* [1–4]. Gut microbiota synthesizes metabolites (short-chain fatty acids (SCFAs), secondary bile acids, neurotransmitters, etc.) that play an essential role in the regulation of the dynamic balance of the internal environment and the stability of basic physiological functions of human body, as well as in the pathogenesis of some diseases [2, 6]. The role of clinically significant bacterial metabolites is to maintain intestinal barrier function, to regulate food intake and energy expenditure (SCFAs), immune response (SCFAs, indole derivatives), risk of cardiovascular diseases (trimethylamine N-oxide), hepatic diseases (phenylacetate, acetaldehyde), diseases of central nervous system (4-ethylphenyl sulfate) [7].

Modification or modulation of microbiome implies the impact of any intervention aimed at successful and beneficial changes in disturbed or depleted microbiota for the benefit of human health. The objective of microbiome modification is as follows: to increase the quantitative composition of microbiota, to change the relative distribution of bacterial species or strains, their metabolic activity, virulence, bacterial antigens, ability to form biofilms, etc. However, it should be noted that it is a complex and dynamic individual ecosystem that is not fully understood yet. Simplified ideas about the potential effect of prebiotics, probiotics and other components on gut microbiome do not reflect the real matter of the issue and can have unpredictable effects [5].

Microbial interactions and axes of interactions between gut microbiota and other biotopes

The stability of gut microbiome and its tolerance by host organism is provided by several mechanisms, in particular, the spatial separation of microorganisms from the mucous membrane itself by a layer of mucus, as well as the synthesis of antimicrobial peptides, secretory immunoglobulins A, that contribute to removal of microorganisms from intestinal epithelial surface [3]. A stable microbial community can resist the invasion of foreign bacteria and the spread of opportunistic microorganisms using the mechanisms of colonization resistance. One of the ways is the formation of gut biofilms that results in the protection of bacteria from aggressive factors and the improvement of exchange of nutrients between bacteria and the host organism. The formation of gut biofilms by beneficial bacteria is being studied, however, the development of biofilms in pathological conditions, for example, *Bacteroides fragilis* in inflammatory bowel diseases, is deemed proven [1, 3].

The interaction between microorganisms can be positive (mutualism, synergism, commensalism), negative (amensalism: predation, parasitism, antagonism, competition), and neutral [3]. A special type of interaction between gut microbes is known as cross feeding, or syntrophy, when microorganisms create highly efficient cooperative metabolic pathways and exchange nutrients or other compounds. Gut microorganisms can use each other's complementary abilities to break down nutrients and produce vitamins that support the production of metabolites for mutual exchange. For example, *Akkermansia muciniphila* degrades glycans to oligosaccharides (galactose, fructose, mannose) and SCFAs (acetate, propionate, 1,2-propanediol) that are used by other bacteria (*Faecalibacterium prausnitzii, Anaerostipes caccae, Eubacterium halii)* for the synthesis of vitamin B_{12} and SCFAs (acetate, propionate, butyrate) [8]. Bifidobacteria populations can also interact with each other, as well as

with other representatives of gut microbiota, through cross-feeding when they collectively use their saccharolytic properties to metabolize carbohydrates. Interspecies hydrogen transfer is another example of a mutually beneficial process in the gut when one microorganism decomposes organic compounds such as polysaccharides and releases reducing equivalents in the form of hydrogen that are used by other microorganism as an electron donor [3]. Amensalism is expressed in the competition for nutrients, as well as the synthesis of bacteriocins and toxic metabolites. For example, microcins synthesized in the gut by *Escherichia coli*, reduce the activity of other reperesentatives of *Enterobacteriaceae* family [9]. Bacteria can use signaling molecules that function as a communication system to inform about cell density, diffusion conditions and species composition of the environment allowing microorganisms to collectively change their behavior in response to changes [10]. Such communication within and between different types of microorganisms can impact the network of interactions in the ecosystem and, therefore, change the composition of microbiota [1–3].

The importance of gut microbiota in the development of pathological conditions of many organs and systems became apparent after the discovery of the following communication axes: "gut — brain", "gut — liver"", "gut — respiratory system", "gut — urogenital tract"; so, the gut became the main organ responsible for human health. Results of studies of the interconnection between gut microbiota and the microbiota of other biotopes can affect the strategy of managing patients with chronic diseases and expand the possibilities for their prevention and treatment [3, 11]. For example, in the study performed by Dubourg G. et al. (2020), it was found that 64 % of bacterial species in urine samples coincide with the identified species in gut microbiota [12]. Moreover, the reduced incidence of recurrent urinary tract infections after fecal microbiota transplantation may support the hypothesis of the interconnection between gut microbiota and urobiota [11, 13]. Modification of gut microbiota can possibly result in a change in the quantitative and qualitative composition of the microbiota of urinary tract, vagina and other localizations.

Modification of gut microbiome

Bacteria can be described as a highly flexible and adaptive system. Lifestyle modifications and clinical interventions can alter gut microbiome (Figure 1). It should be considered that the measures aimed at one or several types of bacteria (prescription of antibacterial agents, probiotics, synbiotics) can indirectly affect other types of microorganisms due to the close relationship between them [2, 3].

When modulating the microbiome, special attention should be paid to potential negative consequences, such as the increase in the proportion of pathogenic microorganisms, transfer of antibiotic resistance, or induction of pathological host reactions.

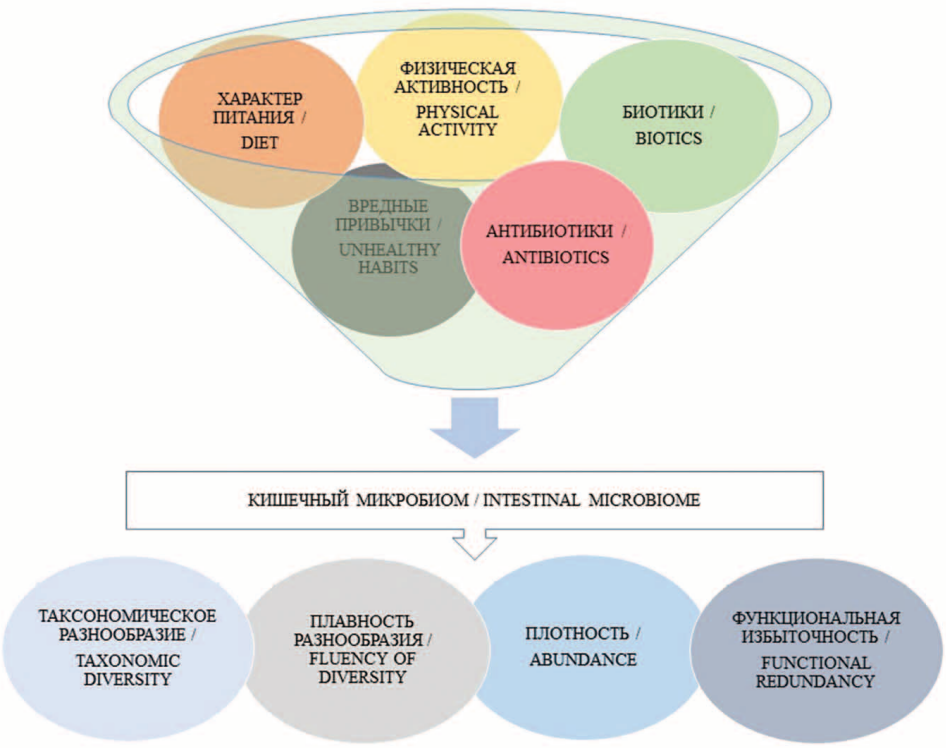

Figure 1. *The main factors and parameters of modification of the intestinal microbiome*

Lifestyle modification

The results of many studies demonstrate the relationship between nutrition, physical activity, presence of pernicious habits (smoking, alcohol consumption, drug abuse) and gut microbiome, as well as other biotopes (of skin, oral cavity, urogenital tract, etc.) [14–32].

Nutrition

The interconnection between nutrition, microbiota and human health is undeniable. Diet is one of the key determinants of microbiome variability; it can be an important link between nutrition and human health. Long-term diets are associated with dynamic changes in the composition and metabolic activity of gut microbiome, while short-term diets are not enough to cause serious changes in the ecosystem [14].

General diet, intake and ratio of macro- and micronutrients affect the species diversity and metabolic profile of gut microbiome. Alongside with the macronutrients fermentation products (SCFAs, branched chain fatty acids, phenolic metabolites, etc.), there are numerous metabolites developed as a result of the bioconversion of food substrates, minor components of food, and trace elements that can potentially impact on human health [2, 3, 14].

The effect of carbohydrates, consumed with food, on microbiome is due to their characteristics and the features of human digestion. Indigestible dietary fibers, by definition, are not digested by human saccharolytic enzymes; accordingly, they subject to fermentation in large gut, and if resistant to fermentation, will be excreted with feces. Dietary fibers affect the species composition and metabolic profile of gut microbiome. Individuals with high intake of plant fiber demonstrate a predominance of phylum bacteria *Prevotella* over *Bacteroides*, high content of *Bifidobacterium spp*. and *Lactobacillus spp.* compared to those with low-fiber diets or placebo [14, 15]. When the amount of indigestible dietary fiber is reduced, bacteria can switch to alternative energy sources from the diet or can degrade host glycans in the intestinal mucus layer contributing to the development of inflammatory conditions associated with allergic, infectious and autoimmune diseases [16].

Resistant starch that is not digested in small gut can provide as much carbohydrate substrate for microbiota as dietary fiber. The changes in gut microbiome in response to the consumption of different types of resistant starch (granular, modified, etc.) may depend on the original human microbiome profile. Similarly, natural non-absorbable sugar alcohols that are added to food as low calorie sweeteners provide a substrate for intestinal fermentation. The increased amount of *Bifidobacterium spp*. is observed after the consumption of isomaltose, maltitol, lactitol, and xylitol [17]. High carbohydrate diets promote the growth of *Clostridium cluster XVIII*, *Lachnospiraceae* and *Ruminococcaceae* [5].

In individuals with high fat intake (69.5% fat as the energy source), the composition of gut microbiota is altered due to the increase in bile-resistant bacteria including *Alistipes, Bilophia, Bacteroides* and the decrease in the number of bacteria with carbohydrate substrate — *Roseburia, Eubacterium, Ruminococcus* [18]. A low-fat diet (20% fat as energy source) increases the alpha diversity of gut microbiota and the relative amount of *Blautia* and *Faecalibacterium* [14, 19].

The quantity and quality of proteins consumed (red meat protein, white meat protein, non-meat protein sources) can modulate gut microbiome. For example, high-protein diet with limited calorie intake in overweight patients results in a decreased amount of *Eubacterium rectale* and *Collinsella aerofaciens* [14]. However, the changes in the microbiome of these patients can hardly be associated with protein intake only, since other factors, in particular, decreased energy intake, could affect microbial diversity.

Despite the small number of studies on the modifying function of vitamins and minerals on gut microbiome, there is no doubt that they are important for the symbiotic relationship between the host and microorganisms, and play a certain role in the development of gut microbial composition. Vitamin K and B vitamins are usually found in the diet, however, they can be synthesized by intestinal bacteria and then distributed between species via cross-interaction [1]. Competition for minerals that are essential cofactors for a number of human and microbial metabolic processes can also determine the species that can grow and survive in gut ecosystem. For example, a high level of iron in the gut is associated with the increased growth of pathogenic microorganisms [20].

Reducing the risk of chronic disease is associated with healthy diets, such as the Mediterranean diet, and plant-based diets [21, 22].

The Western diet is characterized by high intake of meat, saturated fats, sugars, processed grains, and a low consumption of fibers. The Western diet in men living in communities is associated with a higher amount of microorganisms such as *Alistipes, Anaerotruncus, Collinsella, Coprobacillus, Desulfovibrio, Dorea, Eubacterium* and *Ruminococcus* [14, 23]. At the same time *Prevotella copri* that is aimed at the digestion of carbohydrates is much less common in the Western population individuals [24].

The Mediterranean diet is characterized by a high consumption of vegetable products such as fruits, vegetables, whole grains and legumes, moderate consumption of fish, poultry and wine, olive oil as the main source of fat, and dairy products in small amounts. The Mediterranean diet in overweight and obese people results in the increase in *Faecalibacterium prausnitzii* (taking part in the synthesis of a SCFA — butyrate) and a decrease in *Ruminococcus gnavus* (possibly producing a pro-inflammatory effect) [14, 25].

Vegetarian diets are characterized by high consumption of plant-based foods, and, correspondingly, fiber. Vegan diets are free from any animal products. Pregnant

women practicing a vegetarian diet demonstrate the increase in *Roseburia* genus *Lachnospiraceae* family bacteria and the decrease in the number of *Collinsella* and *Holdemania* [26]. Vegans and vegetarians have a higher diversity of microbial genes and proteins involved in the hydrolysis of polysaccharides, proteins and the synthesis of vitamins [14, 27].

Very low-carbohydrate ketogenic diets are characterized by high intake of fat, moderate intake of protein, and very low intake of carbohydrates that results in the development of ketosis. A ketogenic diet in children with drug-resistant epilepsy can result in modification of gut microbiome, i.e. a decrease in the number of bacteria of *Firmicutes* type, *Bifidobacterium*, *Eubacterium rectale, Dialister* families and an increase in *Bacteroides* bacteria [14, 28]. Elite athletes after ketogenic diets develop an increase in *Bacteroides* and *Dorea* bacteria of and a decrease in *Faecalibacterium* [29].

The modified Mediterranean ketogenic diet increases the amount of *Enterobacteriaceae* family bacteria, *Akkermansia, Slackia, Christensenellaceae* and *Erysipelotriaceae* genera, and results in the decreased number of *Bifidobacterium* and *Lachnobacterium* families bacteria. Interestingly, that this type of diet is associated with a decrease in Alzheimer's biomarkers in cerebrospinal fluid [14].

The Paleolithic diet is characterized by the consumption of grass-fed meat, fish, seafood, fresh fruits and vegetables, eggs, nuts and seeds, and vegetable oils. In the Paleolithic diet followers, there is an increase in the number of bile-resistant bacteria — similarly to the individuals with high fat intake [14, 18].

Thus, the type of human nutrition undoubtedly affects the species diversity and metabolic potential of intestinal microbiome. Healthy diet with much plant foods maintains favorable microbiome profiles with a higher content of species capable of fermenting carbohydrates. However, due to the high level of interindividual variability of human microbiome, no well-defined microbiome profiles that correspond to specific diets or nutrient intake have yet been established. A promising area of research is the study of the role of diets in the modification of microbiota, metabolome, aimed at the treatment and prevention of chronic diseases. To develop clinically relevant dietary recommendations for enhancing the gut microbiome stability, microbiome studies should integrate population epidemiology with narrow but in-depth clinical studies of personalized nutrition, including approaches that help in understanding the mechanisms of individual response to modulating interventions. Moreover, the future studies should go beyond the single nutrient approach and focus on the effects of the entire diet on gut microbiome [1, 14].

Physical activity

Physical activity is one of the main factors that has an independent impact on the composition and metabolic activity of gut microbial communities what results in the overall increase in biodiversity, the increase in the number of bacteria that synthesize SCFAs or utilize lactate, alongside with simultaneous reducing potential pathobionts. Some of these changes are persistent and do not depend on age, weight, or food consumption [5, 30, 31].

The potential mechanisms underlying the modification of gut microbiome during physical activity are diverse: the increased gut motility, intestinal nervous system activity, mucus secretion, immunity of intestinal mucosa, integrity of the mucous barrier, availability of nutrients, changes in blood circulation, intestinal pH, enterohepatic circulation of bile acids, ability to produce biofilms [30, 32].

Clinical interventions

Clinical interventions can produce diverse changes in gut microbiome. On the one hand, the prescription of antibacterial agents results in collateral and often negative changes in gut microbiome and the development of antibiotic-resistant strains. On the other hand, the revealed protective effect of beneficial microflora and its bioactive metabolites has resulted in the emergence of various functional biotics, such as probiotics, prebiotics, synbiotics, postbiotics, next-generation probiotics, psychobiotics, oncobiotics, pharmabiotics, smart probiotics and metabiotics that are aimed at human health benefits and found wide application in the clinical practice.

Antibacterial agents

Antibiotic therapy causes one of the most serious disorders of intestinal microbiome affecting not only on the pathogens it is deigned against, but other microbiota representatives as well. For example, antibiotics with significant anti-anaerobic effect cause a long-term decrease in the relative amount of *Bifidobacterium* (ciprofloxacin, clindamycin) and *Bacteroides* (clindamycin) [33]. β-lactams and fluoroquinolones result in the increase in the ratio of *Bacteroides/Firmicutes* phylums and the decrease in microbial diversity due to the reduction of basic phylogenetic microbiota from 29 to 12 microbial taxa [34]. As a result, microbial diversity and functional potential of gut microbiota is decreased [1–4].

Oral administration of antibacterial agents directly affects the growth of microorganisms in the gut and results in the decreased thickness of parietal mucus, changes in intestinal pH, decreased synthesis of antimicrobial peptides, SCFA (butyrate), and immune tolerance [3]. For example, ampicillin is associated with a decrease in the number of acid-producing bacteria and changes in intestinal pH from slightly acidic to neutral; oral administration of vancomycin results in the decrease in the relative amount of *Coprococcus eutactus* and *Faecalibacterium prausnitzii* — butyrate producers [35]. The protective role of SCFAs and the acidic environment of

intestine is to maintain homeostasis by counteracting the massive reproduction of such dangerous bacteria as *Klebsiella* [3].

The consequence of changes in gut microbiota after the use of antibiotics may be decreased resistance to colonization by pathogens what increases the susceptibility to infections [36]. An example is the antibiotic-associated diarrhea caused by a nosocomial pathogen *Clostridioides difficile* [1]. Another problem may be the emergence of antibiotic-resistant microorganisms that can persist in the microbial community for a long time after the end of antibiotic therapy and cause difficulties in the management of bacterial infections [3, 37].

The studies of duration and nature of changes in gut microbiome after antibacterial treatment are ongoing. According to Kriss M. et al. (2018), the bacterial diversity decreases withing a week following the antibiotic therapy, after that the restoration starts, however, it does not return to its baseline state [38]. Long-term (over several years and decades) study of the species composition of gut microbiota and antibiotic resistance of bacteria in humans after administration of antibacterial agents is of interest.

The grade of damage to the representatives of gut microbiota depends on the chemical nature, the target spectrum of action, pharmacokinetic and pharmacodynamic properties, dose and duration, route of administration and excretion of a drug, microbial diversity, functional redundancy, metabolic flexibility of gut microbiome before treatment, immunological tolerance, mucus thickness, the degree of blood supply and oxygen saturation, the level of intestinal motility, and some other factors. In this regard, the degree and direction of changes in response to the treatment with antibacterial agents are highly individual [35].

Reasonable prescription of antibacterial agents and early de-escalation of antibacterial therapy can reduce the adverse effects of antibiotics on human microbiome. Moreover, alternative methods of antimicrobial therapy are currently being developed; they are aimed at the selective destruction of infectious agents with no damage to other microbiome representatives.

Prebiotics

Prebiotics are the substances that cause specific changes in the composition and/or function of microbiota to benefit human health. The most important groups of prebiotics include fructooligosaccharides and galactooligosaccharides, that, when taken orally, are selectively fermented by intestinal microorganisms to SCFAs, mainly acetate, propionate and butyrate; these substances interact with free fatty acid receptors and thus modulate the metabolic activity of intestinal colonocytes and enterocytes, reinforce the integrity of gut epithelium, maintain intestinal homeostasis, affect the immune system, and change the epigenetic signature of the host [3, 6, 39].

Probiotics

Probiotics are the preparations of live microorganisms that are aimed at benefiting the health of human body when used in appropriate amount [3, 39, 40].

The wholesome functions of probiotics include: maintaining colonization resistance, improving metabolism and utilization of end products of energy substrates breakdown, producing substances necessary for human body, regulating local immunity, restoring the intestinal barrier, improving the metabolism of drugs and xenobiotics, regulating the metabolism of bile acids, restoring native microbiota. Antagonistic activity of probiotics against a wide range of pathogenic microorganisms can be mediated by the synthesis of antimicrobial compounds such as organic acids, hydrogen peroxide, SCFAs, carbon dioxide, diacetyl, reuterin, acetaldehyde, phenyl lactic acid, bacteriocins and bacteriocin-like inhibiting compounds, biosurfactants, and other low molecular compounds [6].

The adhesion of probiotics that was previously considered an important beneficial property of a bacterium is now considered as a negative feature of strain, since many adhesins are considered to be pathogenic factors, and the adhesion of probiotic bacteria to gut epithelium can be carried out only in the absence of mucous layer what is typical for pathology.

Commonly used probiotics include *Lactobacillus spp., Bifidobacterium spp., Streptococcus spp., Bacillus spp.* bacteria , individual strains *Escherichia Coli* and *Saccharomyces* fungi. Probiotics have a broad spectrum of action; they can be monocomponent or multicomponent. Zendeboodi F. et al. (2020) proposed a new concept of true probiotics and pseudoprobiotics based on their metabolic activity. It lies in the fact that true probiotics include viable microorganisms that can synthesize biochemical metabolites, and pseudoprobiotics consist of spores and bacteria that have undergone any type of exposure (temperature, pH, lack of nutrients, osmotic pressure, etc.) that results in metabolic rest [39, 41].

The results of clinical trials revealed the effectiveness of the use of certain probiotic strains in most patients with irritable bowel syndrome and inflammatory bowel diseases [6, 42]. However, depending on the individual characteristics of human body and comorbidities, probiotics can, in rare cases, produce negative effect on human body, alongside with positive or neutral effects [3, 6, 42]. In this regard, the prescription of probiotics should be justified and individual-based, including the monitoring of adverse reactions.

Synbiotics

The concept of synbiotics is based on a combination of prebiotics (substances) and probiotics (microorganisms) that increases the viability, survival and successful implantation or colonization of probiotic bacteria in gut. For example, the combination of bifidobacteria or

lactobacilli with fructooligosaccharides, inulin and oligofructose is currently well studied. A synbiotic combination has a synergistic effect inhibiting the growth of pathogens and enhancing the growth of beneficial microorganisms. Prebiotics, in combination with probiotics, improve the absorption of minerals, lower cholesterol levels, normalize metabolic profile and prevent the development of type 2 diabetes, obesity and inflammation. Despite the numerous positive effects of synbiotics, their development require careful selection of probiotics and prebiotics to ensure their maximum beneficial effect on human health [3, 6, 39].

Pharmabiotics

Pharmabiotics are the wholesome commensal microbes, yeasts, bacteriophages, or their derivative biomolecules (vitamins, SCFAs, γ-aminobutyric acid, serotonin, catecholamines, acetylcholine, conjugated linoleic acid, antimicrobial, exopolysaccharides) clinically proven to be effective and safe [6, 39].

Postbiotics (meta-, paraprobiotics)

Postbiotics are non-viable bacterial products or metabolic products of microorganisms that display biological activity in the host body. Postbiotic molecules are a mixture of metabolic products from live probiotic bacteria such as vitamins, SCFAs, extracellular-secreted biosurfactants, secreted proteins or peptides, organic acids, acellular supernatant, amino acids, and released components after bacterial lysis. Ultraviolet rays (5-30 min), heat inactivation (60-121°C /5-60 min), ionization (10 kGy), and sonication are used to obtain various postbiotic components [39].

Paraprobiotics are inactivated/non-viable microbial cells of probiotics containing teichoic acids, mucopeptides derived from peptidoglycans, surface proteins, polysaccharides such as exopolysaccharides, surface-protruding molecules such as pili, fimbriae, flagella, or crude cellular extracts that, when administered in sufficient quantities, provide benefit for human body [6, 39].

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a medical procedure that is based on replacing the host microbiota with the microbiota of a healthy donor [3, 5, 43].

FMT can be considered as an alternative treatment for patients with *Clostridioides difficile*-associated infection, that refers to as recurrent if there were two episodes that required hospitalization, or three or more confirmed episodes of the disease, as severe — in the absence of response to standard treatment, and as fulminant — in cases when surgical interventions are impossible [44, 45].

FMT can be a high-potential method of managing many diseases and disorders associated with changes in gut microbiota, i.e. metabolic diseases, functional and inflammatory bowel diseases, hepatic diseases, autoimmune, hematological, neurodegenerative, allergic diseases, autism, malignant neoplasms, with resistance to antibacterial agents [3, 5, 44, 45]. However, FMT-associated adverse reactions should be taken into consideration (Fig. 2) [3, 6, 45].

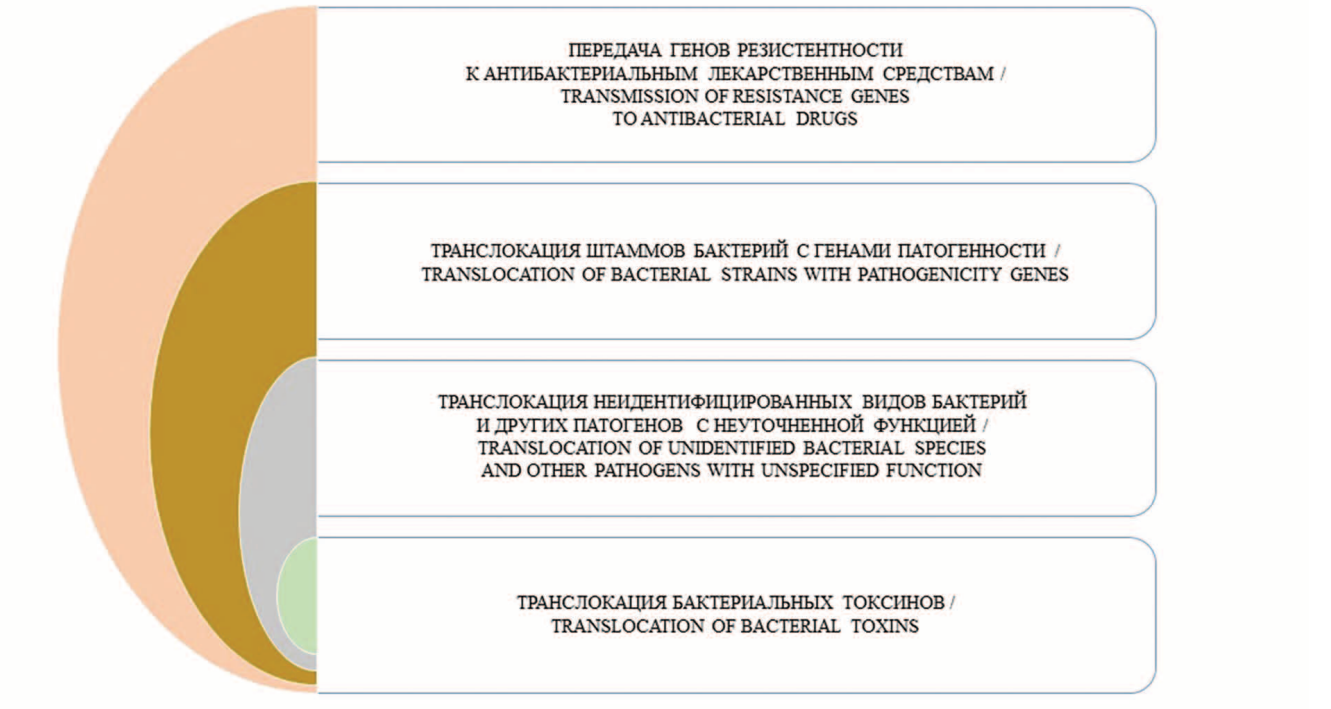

Figure 2. *Potential negative consequences after fecal microbiota transplantation*

Thus, despite its proven effectiveness, FMT remains a complex and expensive procedure that carries risks of adverse collateral effects.

High-potential trends of gut microbiome modulation

The most promising trends of gut microbiome modulation for therapeutic and prophylactic purposes are presented in Table 1 [3, 6, 46].

A promising method to reduce the adverse effects of FMT is the administration of microbial cocktails and autoprobiotics to the patient. The most appropriate microbial cocktails can include microorganisms of *Lachnospiraceae, Ruminococcaceae, Bacteroides* families [3]. Other types of microorganisms can be used depending on the final purpose. For example, the use of a microbial cocktail of three bacterial strains of fecal microbiota (genera *Escherichia, Bacillus, Enterobacter)* that metabolize urea and creatinine into amino acids, significantly decreases the concentration of urea and creatinine in the blood of animals and causes no side effects [47]. The effectiveness and safety of microbial cocktails in athletes and patients with various diseases is a promising trend to study [5, 48].

The wide use of antibacterial agents has resulted in the development of infections associated with the colonization of patients with antibiotic-resistant pathogens, for example, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, and extremely resistant enterobacteria. In connection with the high damaging potential of common antibacterial agents, alternative methods of targeted measures on pathogenic microorganisms are considered, i.e. targeted antibacterial therapy, small molecules, bacteriophages, CRISPR-CAS9 methods of genetic engineering [3].

Practical importance of modifying gut microbiome

Rapid development of scientific knowledge and the large number of studies in the field of human microbiome, its characteristics, its role in human body, its relationship with the development of diseases will lead to the implementation into clinical practice of recommendations based on the methods of targeted effect on the patients' microbiome, for example, to prevent atherosclerosis , non-alcoholic fatty liver disease, to control the course of diabetes mellitus, to optimize the response to the treatment of cancer, to increase endurance and to accelerate recovery of athletes after exercises (Fig. 3) [3-5, 29-31].

The basic methods of affecting human microbiome will be lifestyle modification, specialized diets, administration of beneficial microbial communities, and personalized antibacterial treatment.

Conclusion

Accumulation of new scientific knowledge has provided understanding of the role of gut microbiome as an organ that maintains and regulates the homeostasis in the human body, and participates in the pathogenesis of pathological conditions and diseases. The results of many studies revealed the relationship between the imbalance of gut microbiome and the development of somatic and mental diseases such as obesity, diabetes mellitus, asthma, allergic diseases, atopic eczema, non-alcoholic fatty liver disease, inflammatory bowel disease, multiple sclerosis, Alzheimer's disease, etc. [1-3, 11]. The role of gut microorganisms in the development of ankylosing spondylitis, systemic lupus erythematosus, psoriasis, bacterial vaginosis, and urinary tract infections is under

Table 1. *Prospects of microbiome-associated interventions*

Type of the intervention	The principle of the intervention	Potential effects of the intervention
Microbial cocktails	administration to the patient of a prepared and purified mixture of beneficial types of the microbiome	- alternative fecal microbiota transplantation - effect on metabolic processes
Personalized symbiotic therapy (autoprobiotics)	isolation of pure cultures of individual types of the microbiota, their genetic analysis, cultivation outside the body and administration back into the human intestine	- alternative fecal microbiota transplantation - prevention and diseases control
Next-generation probiotics	the use of non-traditional intestinal commensal bacteria, such as *Akkermansia muciniphila, Faecalibacterium prausnitzii, Eubaterum hallii, Bacteroides fragilis*, clusters of Clostridium IV, XIVA and XVIII, etc. and their metabolites	expanding the potential of probiotics
Bacterial ligands	administration of microbial ligands — agonists of Toll-like receptors — 4, 5, 7/8	restoration of innate immunity and protection against infection
Small molecules	administration of thiopeptides — lactocillin, ribocil, bacteriocins (turicin CD, avidocin CD)	targeted exposure to pathogenic microorganisms
Targeted antibacterial therapy	administration of the conjugated complex «antibiotic-antibody against pathogen»	targeted exposure to pathogenic microorganisms, including intracellular
CRISPR-CAS9 methods of genetic engineering	CRISPR-CAS9 is a bacterial immune system that can be modified by molecular genetics methods	targeted exposure to pathogenic microorganisms, including those resistant to antibiotics

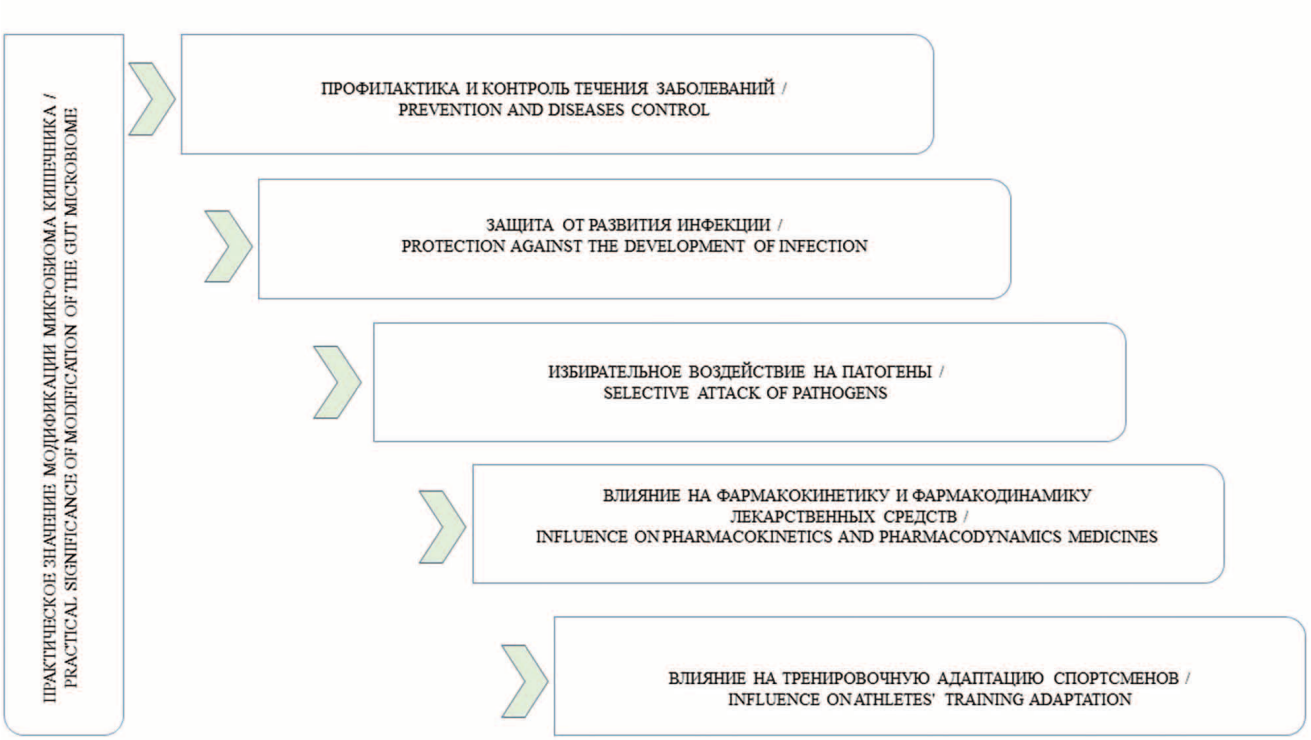

Figure 3. *Potential practice-oriented prospects for modification of the gut microbiome*

discussion [3, 4]. It has been proven that gut microbiota is involved in the biotransformation of medications, increasing or, on the contrary, reducing their effectiveness [3]. Therefore, in the near future, studying the pharmacokinetics or computer modeling of new agents will require considering the characteristics of gut microbiota.

The concept of the parameters that can be used to describe a normal microbiome is currently only being developed. A large number of microorganisms and their role in human body remain unidentified. The measures aimed at modifying gut microbiome are at the core of microbiome-associated medicine that is an actively developing branch of science. However, in real practice, it is not always possible to assess the range of potential interactions between an intervention and the host's diet, genome, immune system, local commensal bacteria which can result in the lack of a proper response to the intervention or to the development of negative effects. In this regard, the unique projects aimed at studying gut microbiome and the possibilities of its programmed modulation in human diseases are the basis for new knowledge about the microbiome that will contribute to the development of personalized medicine.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Малаева Е.Г. (ORCID ID: https://orcid.org/0000-0003-1051-0787): концепция и дизайн статьи, обзор публикаций по теме статьи, написание текста рукописи, взаимодействие с редакцией в процессе подготовки публикации к печати

Стома И.О. (ORCID ID: https://orcid.org/0000-0003-0483-7329): научная консультация, редактирование текста, утверждение финального варианта статьи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Malaeva E.G. (ORCID ID: https://orcid.org/0000-0003-1051-0787): concept and design of the article, review of literature on the topic of the article, writing the text of the manuscript, interaction with the editors in the process of preparing the publication for printing

Stoma I.O. (ORCID ID: https://orcid.org/0000-0003-0483-7329): scientific advising, text editing, approval of the final version of the article

Список литературы/ References:

1. Fassarella M., Blaak E.E., Penders J., et al. Gut microbiome stability and resilience: elucidating the response to perturbations in order to modulate gut health. Gut. 2021; 70(3): 595–605. https://doi.org/10.1136/gutjnl-2020-321747
2. Ситкин С.И., Ткаченко Е.И., Вахитов Т.Я. Метаболический дисбиоз кишечника и его биомаркеры. Экспериментальная и Клиническая Гастроэнтерология. 2015; 124(12): 6–29.
Sitkin S.I., Tkachenko E.I., Vahitov T.Ya. Metabolic intestinal dysbiosis and its biomarkers. Experimental and Clinical Gastroenterology. 2015; 124(12): 6–29 [In Russian].
3. Стома И.О. Микробиом в медицине. Москва, ГЭОТАР-Медиа. 2020; 320 с.

Stoma I.O. Microbiome in medicine. Moscow, GEOTAR-Media. 2020; 320 p. [In Russian].
4. Малаева, Е.Г. Инфекции мочевыводящих путей и микробиота. Проблемы здоровья и экологии. 2021; 18(3): 5–14. https://doi.org/10.51523/2708-6011.2021-18-3-1
Malaeva E.G. Urinary tract infections and microbiota. Health and Ecology Issues. 2021; 18(3): 5–14 [In Russian]. https://doi.org/10.51523/2708-6011.2021-18-3-1
5. Quigley E.M.M., Gajula P. Recent advances in modulating the microbiome. F1000Res. 2020; 27(9). https://doi.org/10.12688/f1000research.20204.1
6. Даниленко В.Н., Ильясов Р.А., Юнес Р.А. и др. Жебраковские чтения X. Минск, Институт генетики и цитологии НАН Беларуси. 2021; 68 с.
Danilenko V.N., Ilyasov R.A., Yunes R.A., et al. Zhebrakov readings X. Minsk, Institute of Genetics and Cytology of the National Academy of Sciences of Belarus. 2021; 68 p. [In Russian].
7. Kolodziejczyk A. A., Zheng D., Elinav E. Diet-microbiota interactions and personalized nutrition. Nature Reviews Microbiology. 2019; 17(12): 742–753. https://doi.org/10.1038/s41579-019-0256-8
8. Belzer C., Chia L.W., Aalvink S., et al. Microbial metabolic networks at the mucus layer lead to diet-independent butyrate and vitamin B12 production by intestinal symbionts. mBio. 2017; 8(5): e00770–00717. https://doi.org/ 10.1128/mBio.00770-17
9. Sassone-Corsi M., Nuccio S.-P., Liu H., et al. Microcins mediate competition among Enterobacteriaceae in the inflamed gut. Nature. 2016; 540: 280–283. https://doi.org/ 10.1038/nature20557
10. Papenfort K., Bassler B.L. Quorum sensing signal-response systems in gram-negative bacteria. Nature Reviews Microbiology. 2016; 14(9): 576–588. https://doi.org/ 10.1038/nrmicro.2016.89
11. Perez-Carrasco V., Soriano-Lerma A., Soriano M., et al. Urinary Microbiome: yin and yang of the urinary tract. Frontiers in Cellular and Infection Microbiology. 2021; 11: 617002. https://doi.org/10.3389/fcimb.2021.617002
12. Dubourg G., Morand A., Mekhalif F., et al. Deciphering the urinary microbiota repertoire by culturomics reveals mostly anaerobic bacteria from the gut. Frontiers in Microbiology. 2020; 11: 513305. https://doi.org/ 10.3389/fmicb.2020.513305
13. Tariq R., Pardi D.S., Tosh P.K., et al. Fecal microbiota transplantation for recurrent Clostridicum difficile infection reduces recurrent urinary tract infection frequency. Clinical Infectious Diseases. 2017; 65 (10): 1745–1747. https://doi.org/ 10.1093/cid/cix618
14. Dahl W.J., Rivero M.D., Lambert J.M. Diet, nutrients and the microbiome. Progress in Molecular Biology and Translational Science. 2020; 171: 237–263. https://doi.org/ 10.1016/bs.pmbts.2020.04.006
15. So D., Whelan K., Rossi M., et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. American Journal of Clinical Nutrition. 2018; 107(6): 965–983. https://doi.org/ 10.1093/ajcn/nqy041
16. Costea P.I., Hildebrand F., Arumugam M., et al. Enterotypes in the landscape of gut microbial community composition. Nature Microbiology. 2018; 3(1): 8–16. https://doi.org/ 10.1038/s41564-017-0072-8
17. Ruiz-Ojeda F. J., Plaza-Diaz J., Saez-Lara M. J., et al. Effects of sweeteners on the gut microbiota: a review of experimental studies and clinical trials. Advances in Nutrition. 2019; 10: s31–s48. https://doi.org/ 10.1093/advances/nmy037
18. David L.A., Maurice C.F., Carmody R.N., et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014; 505: 559–563. https://doi.org/ 10.1038/nature12820
19. Wan Y., Wang F., Yuan J., et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomized controlled-feeding trial. Gut. 2019; 68(8): 1417–1429. https://doi.org/ 10.1136/gutjnl-2018-317609
20. Palleja A., Mikkelsen K.H., Forslund S.K., et al. Recovery of gut microbiota of healthy adults following antibiotic exposure. Nature Microbiology. 2018; 3: 1255–1265. https://doi.org/ 10.1038/s41564-018-0257-9
21. Tosti V., Bertozzi B., Fontana L. Health benefits of the mediterranean diet: metabolic and molecular mechanisms. The Journals of Gerontology Series A Biological Sciences and Medical Sciences. 2018; 73(3): 318–326. https://doi.org/ 10.1093/gerona/glx227
22. Kahleova H., Levin S., Barnard N. Cardio-metabolic benefits of plant-based diets. Nutrients. 2017; 9(8): 848. https://doi.org/10.3390/nu9080848
23. Shikany J.M., Demmer R.T., Johnson A.J., et al. Association of dietary patterns with the gut microbiota in older, community-dwelling men. American Journal of Clinical Nutrition. 2019; 110(4): 1003–1014. https://doi.org/ 10.1093/ajcn/nqz174
24. Tett A., Huang K.D., Asnicar F., et al. The Prevotella copri complex comprises four distinct clades underrepresented in Westernized populations. Cell Host Microbe. 2019; 26(5): 666–679. https://doi.org/ 10.1016/j.chom.2019.08.018
25. Meslier V., Laiola M., Roager H.M., et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. Gut. 2020; 69(7): 1258–1268. https://doi.org/ 10.1136/gutjnl-2019-320438
26. Barrett H.L., Gomez-Arango L.F., Wilkinson S.A., et al. A vegetarian diet is a major determinant of gut microbiota composition in early pregnancy. Nutrients. 2018; 10(7): 890. https://doi.org/ 10.3390/nu10070890
27. De Angelis M., Ferrocino I., Calabrese F.M., et al. Diet influences the functions of the human intestinal microbiome. Scientific Reports. 2020; 10(1): 4247. https://doi.org/ 10.1038/s41598-020-61192-y
28. Zhang Y., Zhou S., Zhou Y., et al. Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet. Epilepsy research. 2018; 145: 163–168. https://doi.org/ 10.1016/j.eplepsyres.2018.06.015
29. Murtaza N., Burke L.M., Vlahovich N., et al. The effects of dietary pattern during intensified training on stool microbiota of elite race walkers. Nutrients. 2019; 11(2): 261. https://doi.org/ 10.3390/nu11020261
30. Pedersini P., Turroni S., Villafañe J.H. Gut microbiota and physical activity: is there an evidence-based link? Science of the Total Environment. 2020; 727: 138648. https://doi.org/ 10.1016/j.scitotenv.2020.138648
31. Mailing L.J., Allen J.M., Buford T.W., et al. Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health. Exercise and sport sciences reviews. 2019; 47(2): 75–85. https://doi.org/ 10.1249/JES.0000000000000183

32. de Sire A., de Sire R., Petito V., et al. Gut-joint Axis: the role of physical exercise on gut microbiota modulation in older people with osteoarthritis. Nutrients. 2020; 12(2): 574. https://doi.org/ 10.3390/nu12020574
33. Rashid M.-U., Weintraub A., Nord C.E. Development of antimicrobial resistance in the normal anaerobic microbiota during one year after administration of clindamycin or ciprofloxacin. Anaerobe. 2015; 31: 72–77. https://doi.org/ 10.1016/j.anaerobe.2014.10.004
34. Panda S., El khader I., Casellas F., et al. Short-term effect of antibiotics on human gut microbiota. PLoS One. 2014; 9(4): e95476. https://doi.org/ 10.1371/journal.pone.0095476
35. Reijnders D., Goossens G.H., Hermes G.D., et al. Effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: a randomized double-blind placebo-controlled trial. Cell metabolism. 2016; 24: 63–74. https://doi.org/ 10.1016/j.cmet.2016.06.016
36. Kim S., Covington A., Pamer E.G. The intestinal microbiota: antibiotics, colonization resistance, and enteric pathogens. Immunological reviews. 2017; 279: 90–105. https://doi.org/ 10.1111/imr.12563
37. Willmann M., Vehreschild M.JGT., Biehl L.M., et al. Distinct impact of antibiotics on the gut microbiome and resistome: a longitudinal multicenter cohort study. BMC biology. 2019; 17: 76. https://doi.org/ 10.1186/s12915-019-0692-y
38. Kriss M., Hazleton K.Z., Nusbacher N.M., et al. Low diversity gut microbiota dysbiosis: drivers, functional implications and recovery. Current Opinion in Microbiology. 2018; 44: 34–40. https://doi.org/ 10.1016/j.mib.2018.07.003
39. Nataraj B.H., Shivanna S.K., Rao P., et al. Evolutionary concepts in the functional biotics arena: a mini-review. Food Science and Biotechnology. 2020; 16(30): 487–496. https://doi.org/ 10.1007/s10068-020-00818-3
40. Reid G., Gadir A.A., Dhir R. Probiotics: reiterating what they are and what they are not. Frontiers in microbiology. 2019; 12(10): P. 424. https://doi.org/ 10.3389/fmicb.2019.00424
41. Zendeboodi F., Khorshidian N., Mortazavian A.M., et al. Probiotic: conceptualization from a new approach. Current Opinion in Food Science. 2020; 32: 103–123. https://doi.org/ 10.1016/j.cofs.2020.03.009
42. Farup P.G., Jacobsen M., Ligaarden S.C., et al. Probiotics, symptoms, and gut microbiota: what are the relations? A randomized controlled trial in subjects with irritable bowel syndrome. Gastroenterology Research and Practice. 2012: 214102. https://doi.org/ 10.1155/2012/214102
43. Wang J.W., Kuo C.H., Kuo F.C., et al. Fecal microbiota transplantation: review and update. Journal of the Formosan Medical Association. 2019; 118: S23–S31. https://doi.org/ 10.1016/j.jfma.2018.08.011
44. Cammarota G., Ianiro G., Tilg H., et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017; 66(4): 569–580. https://doi.org/ 10.1136/gutjnl-2016-313017
45. Якупова А.А., Абдулхаков С.Р., Сафин А.Г. и др. Трансплантация фекальной микробиоты: критерии выбора донора, подготовки и хранения биоматериала (обзор современных рекомендаций). Терапевтический архив. 2021; 93(2): 215–221. https://doi.org/10.26442/00403660.2021.02.200615
Yakupova A.A., Abdulhakov S.R., Safin A.G., et al. Fecal microbiota transplantation: criteria for donor selection, preparation and storage of biomaterial (review of current recommendations). Therapeutic Archive. 2021; 93(2): 215–221 [In Russian]. https://doi.org/10.26442/00403660.2021.02.200615
46. Suvorov A., Karaseva A., Kotyleva M., et al. Autoprobiotics as an approach for restoration of personalised microbiota. Frontiers in Microbiology. 2018; 9: 1869. https://doi.org/ 10.3389/fmicb.2018.01869
47. Zheng D.W., Pan P., Chen K.W., et al. An orally delivered microbial cocktail for the removal of nitrogenous metabolic waste in animal models of kidney failure. Nature Biomedical Engineering. 2020; 4(9): 853–862. https://doi.org/ 10.1038/s41551-020-0582-1
48. Scheiman J., Luber J.M., Chavkin T.A., et al. Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. Nature Medicine. 2019; 25(7): 1104–1109. https://doi.org/10.1038/s41591-019-0485-4