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Antidysbiotic prophylaxis and therapy of non-infectious colitis

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Abstract

The increasing incidence of dysbiosis and its pathogenic consequences naturally raises questions about the search for treatment and prevention.

It is established that in the pathogenesis of non-infectious colitis the decisive role is played by dysbiosis, that is, the reduction of the level of probiotic bacteria and the increase in the number of conditionally pathogenic species, especially their virulent strains. Under the conditions of functioning of the normal microbial composition of the microbiome, the probiotic bacteria exert a suppressive effect on the conditionally pathogenic microflora.

It is important that even with the development of dysbiosis only the ratio of the two groups of microorganisms changes, and, for example, the biotic bacteria do not completely disappear, which makes it possible to restore them.

The results of many years of experimental studies carried out in the laboratory of Professor AP Levitsky showed the antidysbiotic property of polyphenolic compounds, in particular bioflavonoids. It is known that bioflavonoids belong to plant substances and have a very wide range of biological effects: antioxidant, anti-enzyme, membrane-protecting, hepatoprotective, anti-dysbiotic, anti-inflammatory and therefore used for the treatment of many diseases, in the first place.

Key words: dysbiosis; colitis; probiotics; prevention

The increasing incidence of dysbiosis and its pathogenic consequences naturally raises questions about the search for treatment and prevention.

It is established that the pathogenesis of non-infectious colitis plays a decisive role in dysbiosis, that is, the reduction of the level of probiotic bacteria and the increase in the number of conditionally pathogenic species, especially their virulent strains. Under conditions of normal microbial composition of the microbiome, the probiotic bacteria exert a suppressive effect on the conditionally pathogenic microflora [1-3].

The endogenous microflora of a healthy person is represented by probiotic bacteria that interact with the macroorganism under conditions of mutualism (mutual aid). Disruption of the species and quantitative composition of endogenous microbes (dysbacteriosis) is characterized, as a rule, by the violation of the balance between the number of probiotic bacteria and conditionally pathogenic. In a healthy person, this balance is 100: 1, whereas in the case of dysbiosis it can be 60:40 or even less (20:80) [4].

It is important that even with the development of dysbiosis changes only the ratio of the two groups of microorganisms, and, for example, about biotic bacteria do not completely disappear, which makes it possible to restore them.

In this case, the number of microbial toxins that penetrate into the system v increases significantly (by tens of times). porta and enter the liver. Therefore, in all cases of intestinal dysbiosis, the liver takes on a powerful toxic and infectious stroke, which leads to the activation of Kupffer cells, which begin to secrete proinflammatory cytokines, which cause inflammation in the liver parenchyma and are accompanied in turn by excretion of hepatocytes in the blood. also leads to the development of systemic inflammation, and these protective factors (C-reactive protein, ceruloplasmin, etc.) are involved in protecting the body and systemically combating inflammation [5].

Therefore, the treatment of dysbiosis (Table 1) can be carried out by increasing the content of probiotic bacteria by introducing exogenous probiotic bacteria in the composition of probiotics.

Table 1. Classification of antidysbiotic agents (ADA) [7]

Classes	Subclasses	Specific examples
Alimentary	1.1 Proteins, carbohydrates, fats, vitamins, minerals 1.2. Prebiotics	Collagen, elastin, starch Inulin, raffinose, lactulose
Probiotics	2.1 Monobiotics 2.2 Symbiotics (muatibiotics) 2.3 Synbiotics	Lactobacterin, Symbiter Bactulin
Immunomodulators	3.1 Factors of nonspecific immunity 3.2 Factors of specific immunity	Lysozyme, peroxidase Immunoglobulin
Antimicrobial	4.1. Selective antibiotics 4.2. Bacteriocins 4.3. Inhibitors of microbial enzymes	 Antioxidants, polyphenols, heparin

A number of these drugs contain some one type of probiotic bacteria (bifidumbacteria, lactobacilli, or probiotic streptococci). These are the so-called monobiotics, which include bifidumbacterin, lactobacterin, colibacterin and others. [6].

It is shown that the combination of different types of probiotic bacteria (so-called symbiotics) in one preparation significantly increases their effectiveness in the treatment of dysbiosis. Symbiotics include such drugs as Bifiform, Symbiter, symbiotic "Harmony of Life", Linex, Atsilak, Bifilong [8-10].

The use of probiotics is carried out not only in the form of pharmaceuticals, but also in the composition of foods (yoghurts, jellies, cereals, jelly beans, etc.), which increases the possibilities, especially for the prevention of dysbiosis. [11-13].

Medicinal products containing live cultures of bacteria include not only probiotics but also preparations containing conditionally pathogenic bacteria, mainly of the genus Bacillus [14].

It is shown that B. subtilis and B. licheniformis31, which are part of the drug "Biosporine", in the used doses are not toxic, whereas B. cereus (drug "Baktisubtil") and B. subtiliso and B. licheniformis09 (drug "Irylis") exhibit some toxicity.

Although a number of authors have called preparations of live bacteria of the genus bacilli a probiotic, however, they cannot be considered as probiotics by the mechanisms of their antidysbiotic action. In bacillary bacteria, the therapeutic effect on endogenous microbiocenosis is realized through the secretion of bacteriocins, which in turn cause stimulation of both non-specific and specific immunity, which increases mucosal resistance to dysbiosis. [15, 16].

Recently, antidisbiotic agents have appeared that contain not living probiotic bacteria, but their secrets, which include a large number of biologically active substances and which simultaneously exert their influence on both the microbiota and the functional state of the intestinal mucosa, ie confirm the above and emphasize that dysbiosis depends on both the action of the pathogenic microflora and its interaction with the intestinal mucosa [17, 18].

Thus, the effect of the drugs used on the microbiota was further studied. In the authors determined the rate of microbiota recovery in the feces of white mice over a period of 14 days on the background of antibiotic-associated diarrhea when using native culture or its components. The relevant data are presented in Table 2, which shows that the greatest stimulating effect on microbiota recovery is exerted by the culture supernatant, which exceeds the activity of living bacteria by almost 9,000 times by this indicator, again confirming that the positive effects of the culture used are first and foremost due to secondary effects.

These data indicate that the therapeutic effect of probiotic drugs depends not only on their ability to replace endogenous probiotic bacteria, but also to a greater extent on the stimulatory action of the metabolites synthesized by these drugs.

Table 2 - Effect of native culture of bifidobacteria on the rate of microbiota (MB) recovery in conventional white mice with antibiotic-associated diarrhea [19]

Oral culture its components	MB Reduction Rate	
	CFU, g-1 / ____	Multiplicity to control
Control (liquid nutrient medium)	$1,0x10^4$	1
Native culture of bifidobacteria (whole complex)	$6,8x10^5$	61,8
Native living bacteria	$7,2x10^3$	0,7
Inactivated bacteria	$3,6x10^2$	0,03
Culture supernatant	$6,9x10^7$	6273

The effect of drugs can be varied, so in children with intestinal infections against the background of allergic reactivity the use of a probiotic drug containing Lactobacillus casei Defensae from the first day of the disease contributes to reducing the main symptoms of the disease, improving the composition of microbiota (elimination of dysbacteriosis) enhancement of mucosal immune protection [20].

The use of probiotic preparations "Bifiform" or "Biosporine" in patients with influenza with dysbacteriosis of the colon reduces the content of conditionally pathogenic bacteria and significantly increases the content of probiotic microflora. The use of probiotic drug "Bifidumbacterin forte" in children with acute intestinal infections after 2 - 3 days of treatment has both detoxification and anti-diarrheal effects, which is accompanied by a rapid decrease in pathogenic bacteria (shigella, salmonella) [21].

Unfortunately, not all researchers confirm the positive effect of probiotic drugs on the condition of patients with dysbiotic phenomena. It should be noted that the negative or little clear positive results of probiotic therapy can be explained by the fact that exogenous probiotic bacteria are very quickly eliminated from the macroorganism, in addition, a much larger number (almost 95 - 98%) is usually inactivated by gastric juice and, as shown in the paper, the main acting factor is no longer the bacteria themselves, but the products and exometabolism, which are usually not used in pharmaceuticals and are not formed after inactivation of biotic bacteria.

In 1995, Dutch researchers proposed a new concept of "prebiotic". They called this term all positive substances (mainly oligo- and polysaccharides) that are not absorbed in the small intestine of humans and animals due to the lack of appropriate enzymes for their hydrolysis. These are carbohydrates with β-glycosidic, β-fructoside, or α-galactoside bonds. However, these substances are easily hydrolyzed in the large intestine under the action of microbial hydrolases, which produce mainly probiotic bacteria. Prebiotics also include polyfructoside inulin, which accumulates in the roots of chicory, Jerusalem artichoke, dahlias and many other plants that are quite widely used in nutrition as food and as nutritional supplements to improve nutritional quality. [22, 23].

Prebiotic properties also have α-galactosaccharides from soybeans, namely raffinose and stachiosis [24, 25].

Among the prebiotics are pectins that inhibit the growth of germs such as staphylococci, E. coli, proteas, pseudomonads and inhibit enterotoxin synthesis.

Inulin and fructo-oligosaccharides have been shown to selectively stimulate the growth of bifidobacteria in the colon, while providing effective treatment for constipation in patients. Simultaneously, it has been shown that inulin and fructo-oligosaccharides have immunomodulatory and carcinoprophylactic activity, which partially explain the mechanisms of therapeutic and prophylactic action of these substances.

Synthetic prebiotic is also known today - lactulose (a disaccharide consisting of galactose and fructose), a glycosidic bond that does not hydrolyze human and animal digestive enzymes, but is easily cleaved by enzymes of probiotic bacteria. It is known that lactulose is widely used for the treatment of constipation in children, in pregnant women, in adults. In general, lactulose is effective in treating non-infectious colitis, which is associated with its positive effect on the microbiota [26-29].

The largest modern functional classification of prebiotics is presented in the paper.

The results of many years of experimental studies carried out in the laboratory of Professor A. P. Levitsky showed the antidysbiotic property of polyphenolic compounds, in particular bioflavonoids. It is known that bioflavonoids belong to plant substances and have a very wide spectrum of biological action: antioxidant, anti-enzyme, membrane-protective, hepatoprotective, anti-dysbiotic, anti-inflammatory and therefore used for the treatment of many diseases, especially in the furnace.

Depending on the chemical structure, all the bioflavonoids that are derivatives of the flavan tricycle (Fig. 1), on the basis of which a whole group of substances, numbering over 5 thousand natural compounds and which are divided into 8 major groups, originated [30].

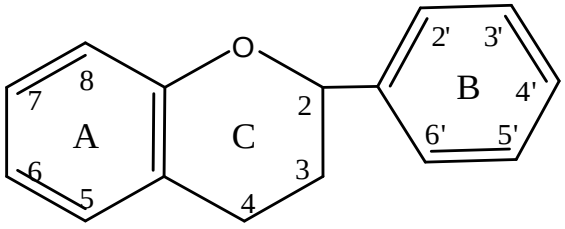

Figure 1 - Flavan

The largest number of bioflavonoids belongs to the class of flavones, which provided the common name for all derivatives of flavones [31].

Bioflavonoids are synthesized and accumulated only in plants. The most abundant sources of bioflavonoids are citrus fruits, grapes, black currant, blueberries, raspberries, flowers and fruits of Sophora, onion, bell pepper, leaves of almost all plants. Because of their angioprotective (capillary-strengthening) properties, they were called vitamin P. With vitamin P, skin hemorrhages (patechiae) appear on the skin and bleeding from the gums increases.

It should be noted that most of the bioflavanoids are in the surface structures of fruits and berries, and therefore, a considerable part of them is lost during processing. That is, the food of modern man is depleted of this group of substances.

As shown, the molecular mechanisms of biological action of bioflavonoids consist of their antioxidant, anti-enzymatic and neuro-endocrine activities. Of all bioflavonoids studied, quercetin, which is widely and long used in therapeutic practice, has the strongest antioxidant property [32, 33].

Due to the antioxidant activity of the bioflavonoids, the membrane protector function, protecting the membrane phospholipids from destruction under the action of free radicals, that is, they effectively block the leading biochemical mechanism of damage in the pathology of different genesis.

Many representatives of bioflavonoids have the inherent property of inhibiting also the activity of a large number of so-called destructive enzymes: phospholipase A2, lipoxygenase, hyaluronidase, protease, NADP (H) -oxidase, and thus affect the course in the first place.

Some bioflavonoids have a similarity to hormones. For example, soybean genistein has estrogenic activity. A number of bioflavonoids are similar to benzdiazepam and therefore may interact with the appropriate neuroreceptors, which should be considered in nutrition and used especially for prophylactic purposes.

Such a wide range of biochemical activities of bioflavonoids determines a significant range of their biological and therapeutic and prophylactic properties: anti-inflammatory, immunomodulatory, estrogen-like, cardioprotective, angioprotective, antidiabetic, osteoprotective4, 27 anti-diabetic, 27 This list indicates the prospects of using bioflavanoids.

Considering such a wide range of biological action of bioflavonoids, especially quercetin, as the most active of them, in the laboratory of prof. A. P. Levitsky developed the multifunctional antidysbiotic agent "Quertulin". Quercetin includes quercetin, prebiotic inulin and calcium citrate, which made it possible to combine the biological action of bioflavanoids and probiotics (inulin). This drug is anti-dysbiotic, hepatoprotective, anti-inflammatory and is widely used for the prevention of hepatitis, gastritis and gastroduodenitis, dental diseases [34].

The hepatoprotective properties of quercetin have been shown in experimental CCI4-toxic hepatitis. Due to its hepatoprotective activity, quercetin was not inferior to the prebiotic of inulin, and the combination of these two agents significantly increased the antidisbiotic, antioxidant and

hepatoprotective efficacy. On this basis, a complex hepatoprotective agent with a broad spectrum of biological action was developed, which was called "Kvertulin", which developed regulatory and technical documentation (TU, TI) and obtained permission from the Ministry of Health of Ukraine for use as a preventive agent.

In the future, the hepatoprotective properties of querculin have been shown in rats with systemic endotoxinemia, experimental non-alcoholic steatohepatitis, with experimental metabolic syndrome, that is, primarily in diseases underlying inflammation.

Hepatoprotective efficacy of querculin has been investigated in patients with hepatobiliary pathology (hepatitis, cholecystitis, cirrhosis).

Thus, the analysis of literary sources leads to the conclusion about the important physiological role of the microbiome in the life of the body, especially the gastrointestinal tract. The role of the microbiome is especially important in the final stage of digestion, that is, in the colon. This, on the one hand, changes our view of the functional significance of this organ for the human body. Moreover, it focuses our attention, first of all, not on the composition of the microflora and its functional role, but which allowed us to consider the microbiome, in essence, as a separate organ, which is the largest among all parenchymatous cells, which is also significant in the number of cells (10 times) exceeds the sum of all somatic cells. Therefore, the more we become aware of the biological essence of the coexistence of the human body with the microbe ohm, the deeper our attention becomes regarding its physiological role. But at the same time, it becomes clear how purely this interaction of the macro-organism and the micro-organism is a violation and what consequences it can lead to.

The deepening of our understanding of dysbiosis as a major consequence of impaired interaction of the human body with the microbiome has raised a number of questions, without which many medical problems cannot be solved. First, it is necessary to study all the possible causes of such a pathology. Secondly, to determine its main mechanisms both from the microbiome and the human body. Only then will we be able to influence the interaction of the body with the microbiome, which in medicine is defined as the prevention of possible disorders and, finally, to correct them in the event of pathology, that is, effective treatment. Undoubtedly, the very task of clinical medicine is a priority in solving the problem of dysbiosis.

However, it should be noted that although clinical observations are the initial stage of knowledge of the problem, but if it concerns the problem of dysbiosis, it can be solved only in experimental studies, because if the phenomenon of dysbiosis can be recorded and studied in the clinic, then the opportunities to study the pathogenesis of dysbiosis are available mainly in an experiment where there are opportunities to study disorders of the initial link of dysbiosis - the mucous membrane. It is the first object in which pathological changes in dysbiosis occur, which are then transformed into the whole macroorganism.

Given the above, we set out to study the main etiological factors that cause dysbiosis in the experiment and the main initial pathological mechanisms in order to develop pathogenetically justified therapeutic and prophylactic agents.

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