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Evaluating the environmental and therapeutic impacts of dietary supplement (Case study: The supplement Oyox for prevention of environment damages, treatment and disorders in the hepatobilliary system)

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ABSTRACT

Globally recommended diets are a powerful method for raising the public's awareness of dietary choices. Although dietary choices drive both health and environmental outcomes, these diets make almost no reference to environmental impacts. Besides, Encephalic damage and disorders of the hepatobiliary system occur against the background of metabolic disorders. Metabolic processes largely depend on the activity and the qualitative and quantitative characteristics of sirtuin-type proteins. Protein deficiency can be filled by artificially introducing them into the body through dietary supplements. The study aimed to analyze the possibilities of using the dietary supplement OYOX to prevent environmental harm as well as treating encephalic damage and disorders of the hepatobiliary system. We used theoretical and practical research methods. In particular, the methods of analysis of literature sources, statistical data, results of clinical and preclinical studies were used. The method of generalization, analysis, systematization, classification of the obtained data was used. The results were evaluated 3 and 6 months after taking the dietary supplement. In the group of people taking OYOX, a statistically significant decrease was observed in the percentage of short telomeres ($p = 0.029$); a decrease in the percentage of senescent cytotoxic (CD8+ / CD28-) T cells (by 1.5%; 4.4%; 8.6% and 7.5% after 3 and 6 months respectively); improvement in lipid and carbohydrate metabolism glycosylated hemoglobin (HbA, 1%) by 4.9% ($p = 0.01$), total cholesterol 5.7 mmol L^{-1} ($p = 0.003$), low density lipoprotein (LCL-C): 3.82 mmol L^{-1} ($p = 0.0021$), homocysteine: 3.4 mmol L^{-1} ($p = 0.001$). In conclusions, dietary supplement OYOX is effectively used to eliminate the deficiency of sirtuin-type proteins SIR1, SIR3, SIR6.

Keywords: Encephalic damage, Environmental damage, Nutrigenomic preparation, Orthomolecular composition, OYOX, Sirtuin-type Proteins.

INTRODUCTION

Undoubtedly, the food choices we make on a daily basis hold a considerable impact on the environment. The great news is that even small alterations in what we purchase and eat can contribute to actual environmental advantages, such as fewer toxic chemicals, reduced global warming emissions, and preservation of our ocean resources. Encephalic damage and disorders of the hepatobiliary system are very numerous and are characterized by a fairly high prevalence, especially in countries with a Western lifestyle (Europe, North America, Russia). These diseases are recorded with a frequency of 10-20%. Dietary habits explain such a high frequency and the important contribution of genetic factors with the use of large amounts of simple carbohydrates. In Africa, Asia, and Japan, these pathologic prevalence is lower: 3.5-5% (Chen & Zhou 2015).

The ratio of incidence among men and women is 1: 3. In recent decades, there has been an increase in the hepatobiliary system incidence in children and adolescents. An increase in the encephalic system's diseases is

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observed mainly in old and senile age. Among the various causal factors that contribute to the development of encephalic damage and violations of the hepatobiliary system in childhood, nutritional disorders are of great importance (Abdellatif 2012). The risk of calculus formation in the biliary tract, even with relatively minor nutritional disorders, increases significantly already at an early age. It is no coincidence that balanced nutrition, including breastfeeding, is the cornerstone for preventing disorders of the hepatobiliary system in childhood. Neurodegenerative disorders and various encephalic damage often occur against the background of metabolic disorders (Brian & Verdin 2014).

Research problem

Disorders of metabolic processes largely depend on the activity and the qualitative and quantitative characteristics of sirtuin-type proteins (Kelly 2010). The deficiency of sirtuin-type proteins is a common cause of metabolic disorders, resulting in severe damage to the brain and hepatobiliary tract. Nevertheless, the deficiency of proteins can be compensated by artificially introducing them into the body through dietary supplements. The aim of the study is to analyze the possibilities of using the dietary supplement OYOX for the treatment and prevention of encephalic as well as environmental damages and disorders in the hepatobiliary system.

Research objectives

1. To analyze the role of sirtuin-type proteins in environmental harm and the development of metabolic disorders leading to the hepatobiliary system encephalic damage and disorders.
2. To consider the possibilities of activating and replenishing the deficiency of sirtuin-type proteins by means of a dietary supplement OYOX.
3. To analyze the effectiveness of the use of a dietary supplement, OYOX for the treatment and prevention of encephalic damage and disorders of the hepatobiliary system, considering its environmental consequences.

MATERIALS AND METHODS

We used theoretical and practical research methods. In particular, the methods of analysis of literature sources, statistical data, results of clinical and preclinical studies were used. The method of generalization, analysis, systematization, classification of the obtained data was used. In the practical part of the research, we used laboratory, molecular genetics, and clinical diagnostic research. From molecular genetic methods, the method of measuring telomere length was used. Biochemical methods were used to assess CRP, cholesterol, HDL, LDL, glycated hemoglobin, creatine, bilirubin, ALS, AST. To process the data obtained, mathematical and statistical research methods were used.

Statistical analyses

For statistical analyzing, the SPSS22 software was used, which is an efficient software in the field of statistical analysis. The ANOVA test (X^2) was used to compare between groups at the significant level of 0.05 ($p \leq 0.05$; MacFarland & Yates 2016).

RESULTS AND DISCUSSION

The role of sirtuins in maintaining metabolic processes

Both genetic and environmental factors influence epigenetic processes controlling gene expression. Humans are exposed to many compounds that act as modulators of epigenetic processes on a daily basis through their diet and environment (Kim *et al.* 2011).

Sirtuins (silencer information regulator) are a family of proteins that have received much attention in the last decade due to their central regulatory role in metabolic homeostasis in lower organisms and mammals. Proteins SIRT1-4 were first discovered in yeast as NAD^+-dependent deacetylases, which, through suppression of gene expression, contributed to an increase in cell lifespan (Lan *et al.* 2018).

The subsequent discovery of homologous SIRTUIN (SIRT), a family of proteins in mammalian systems, soon led to the realization that these molecules have a regulatory effect on metabolism, aging, and the pathogenesis of diseases associated with aging (Lan *et al.* 2018). There are 7 representatives of the sirtuin classes in the human genome. SIRT-1, 6, 7 show their functions mainly by directly affecting the nuclear transcription of genes involved in metabolism, although a certain amount of SIRT1 is found in the cytosol. SIRT3–5 are found exclusively in

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mitochondria and regulate enzymes involved in the cycles of tricarboxylic acids, urea, oxidative phosphorylation, as well as in the production of reactive oxygen species (Nogalska & Pankiewicz 2016).

SIRT2 is cytoplasmic, although in certain situations, it can also be found in the nucleus. The ability of sirtuins to influence metabolism and potentially life span is related to the ability of members of the SIRTUIN family to function as protein deacetylases. In addition to this function, SIRT4 can perform ADP-ribosylation of target proteins (Simonsen *et al.* 2018). Unlike other protein deacetylases, sirtuins require NAD^+ as a cofactor in the deacetylation reaction (Tao *et al.* 2011). The relationship between NAD^+, NADH, and the biological effects of sirtuins has led to the opinion that this family of proteins acts as sensors of energy status.

In the deacetylation reaction carried out by sirtuins, 3 stages can be distinguished:

- hydrolysis of NAD^+ to ADP-ribose and nicotinamide;
- cleavage of the acetyl group from the lysine residue in the protein and the formation of deacetylated protein;

Transferring the acetyl group to ADP-ribose with the formation of 2'-O-acetyl-ADP-ribose (Wolfson & Budovsky 2019). SIRTUIN1 (SIRT1) plays a central role in the regulation of metabolic processes in mammals among the sirtuin family, regulating such cellular processes as changes in chromatin structure and gene transcription, DNA repair and cell differentiation, metabolic homeostasis, inflammation, apoptosis, aging, and circadian rhythm (Yoshino *et al*. 2011). The variety of its physiological functions is associated with the variety of its substrates. SIRT1 targets are histones and non-histone proteins (Yoshino *et al.* 2011). The acetylation/deacetylation status of histone proteins determines whether chromatin is available for gene transcription. SIRT1 actively deacetylates a number of histones and facilitates chromatin condensation, regulates the transcription of silent genes (Tao *et al.* 2011). SIRT1 non-histone substrates are molecules or enzymes that control signal transmission, metabolism, or gene transcription. Their diverse properties and cellular localization allow SIRT1 to play a dual regulatory role in different cellular processes or different phases of a particular process (Kennedy *et al.* 2019). For example, SIRT1 deactivates pro-inflammatory gene expression by deacetylation of NFκB / p65. However, it stimulates the anti-inflammatory transcription factors RelB and PGC-1α in acute inflammation (Yoshino *et al*. 2011). SIRT1 inhibits apoptosis by deacetylation of p53 but stimulates the synthesis of fatty acids by deacetylation of Acetyl-CoA synthase 1 (Chahirou *et al.* 2018). Specific binding sites allow SIRT1 inhibitors/activators to regulate the intensity of its deacetylase activity, but the availability of NAD^+ is primary in the activation of SIRT1. The NAD^+ / NADH ratio determines the movement of SIRT1 between cell compartments; an increase in the NAD^+ level leads to the activation of SIRT1. The product of NAD^+ hydrolysis, nicotinamide, inhibits the activity of SIRT1, competing with NAD^+ for binding sites in the active center (Fefelova *et al.* 2016).

SIRT1 activity can be controlled by various environmental signals that can alter the availability of NAD^+ to cells (Kawahara *et al.* 2019). For example, a state of low energy consumption during CR nutrition or physical exertion can increase the cellular level of NAD^+, which stimulates SIRT1 activity (Kelly 2010). At the same time, the state of high energy consumption, caused, for example, by a diet high in fat or the development of acute inflammatory reactions, decreases the cellular level of NAD^+, which, in turn, decreases the activity of SIRT1 (Chen & Zhou 2015). In addition to the cellular NAD^+ level, the content and activity of SIRT1 are under the control of complex regulation, which turns on in response to hormonal and environmental signals (Kendrick *et al.* 2011). This regulation is carried out at different levels and is critical for maintaining an optimal SIRT1 level in response to various environmental stimuli (Fefelova *et al.* 2016).

In the liver and brain, SIRT1 plays an important role in the regulation of fatty acid metabolism. In particular, SIRT1 regulates lipid metabolism by activating the AMPK / LKB1 signaling pathway. AMPK (AMP-activated protein kinase) regulates lipid metabolism, glucose, and cholesterol metabolism in the brain, neuroglia, liver, muscles, and adipose tissue (Chen & Zhou 2015). AMPK is the driver of the expression of nicotinamide phosphoribosyl transferase, which catalyzes the first step of NAD biosynthesis from nicotinamide. SIRT1 deacetylating, activates LKB1 kinase (Serine/threonine kinase 11 or liver kinase B1), which, in turn, activates AMPK (Kelly 2010). The influence of SIRT1 and AMPK can be mutual. SIRT1 activation stimulates fatty acid oxidation and indirectly activates AMPK (Chen & Zhou 2015). In hyperglycemia, SIRT1-mediated AMPK activation prevents lipid accumulation. Liver SIRT plays an important role in the regulation of local and systemic metabolic homeostasis. SIRT is activated during negative energy balance, which occurs during fasting and restriction of the diet energy value. In addition to the effect on gluconeogenesis in the liver, lipid metabolism, cholesterol synthesis, SIRT promotes insulin production in pancreatic β-cells (Kelly 2010). In β-cells of the

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pancreas, SIRT regulates glucose-stimulated insulin secretion by affecting the synthesis of uncoupling protein 2 (UCP2).

UCP2 promotes longevity by enhancing the use of fatty acids as energy sources. SIRT1 inhibits UCP2 transcription by binding to its promoter. It was noted that transgenic mice with excess SIRT1 in pancreatic β-cells are characterized by lower levels of UCP2 and increased insulin secretion. SIRT1 promotes adipogenesis and differentiation inhibition due to its combination with the transcriptional activator PPARγ, which regulates fatty acid metabolism, glucose metabolism, and is considered as one of the main regulators of adipocyte differentiation (Kennedy *et al.* 2019). SIRT1 suppresses PPAR in white adipose tissue, thereby inhibiting the expression of adipose tissue markers such as adipocyte Protein 2, which promotes lipolysis and immobilization of fatty acids in response to caloric restriction. Another way of modulating the lipolytic activity of SIRT1 in adipocytes involves deacetylation of FOXO1 and stimulation of transcription of adipocyte triglyceride lipase (ATGL) genes (Kelly 2010). Genetic elimination of SIRT1 from adipose tissue leads to increased obesity and insulin resistance (Kendrick *et al.* 2011).

Possibilities of activating and replenishing the deficiency of sirtuin-type proteins by means of a dietary supplement OYOX

The deficiency of sirtuin-type proteins negatively affects both the state of individual metabolic processes and the state of the body as a whole. Proteins SIRT1, SIRT3, SIRT6 are closely interconnected, and their mechanism of action is largely intertwined. However, a number of effects associated with the deficiency of each individual type of protein can be distinguished separately.

SIRT1 deficiency significantly reduces the rate of cell division, reduces the rate of epigenetic mechanisms, which is reflected in the slowing down of repair processes, a decrease in the rate of damage healing, and a decrease in tissue regeneration. The body's ability to turn off inactive genes and repair DNA damage is significantly reduced. At the same time, the number of free radicals sharply increases, oxidative stress develops, which leads to premature aging and cell/tissue death. Also, a deficiency of this type of protein can lead to the suppression of the transcriptional activity of the tumor suppressor p53, as a result of which the processes of cell apoptosis are disrupted, and tumor growth occurs. The protein's ability to deacetylate HSF1 decreases, as a result of which the risk of cell death from heat shock increases, the amount of misfolded proteins accumulates.

The number of stress-resistant proteins decreases due to which the cell cycle is suspended, and the amount of reactive oxygen species is significantly reduced. This increases the risk of developing oxidative stress, leading to premature cellular aging. Also, against the background of protein deficiency, glucose concentration in the blood can significantly increase. The risk of developing diabetes mellitus and metabolic disorders increases sharply (Kendrick *et al.* 2011). Deficiency of SIRT3 proteins is associated with disruption of the neural network and weakening of the signaling cascade, disruption of metabolic processes in the neuroglia, which increases the risk of neurodegenerative diseases. The deficiency of this protein is often associated with Alzheimer's disease. Also, the ratio of AMP / ATP in cells is disrupted, as a result of which all processes of oxidative phosphorylation are disrupted, the rate of ATP synthesis decreases. Accordingly, the energy potential of the cell decreases and metabolic processes are disrupted. Against the background of protein deficiency, inhibition of the tricarboxylic acid cycle regulators occurs and oxygen metabolism is impaired (Kennedy *et al.* 2019).

The deficiency of SIRT6 proteins leads to impaired immune response, resulting in an increased risk of developing infectious diseases, an increased risk of malignant cell transformation, an increased likelihood of oxidative stress, which leads to premature aging. In addition, against the background of a deficiency of this type of protein, lipid metabolism is disturbed and also the risk of atherosclerosis and metabolic disorders increases (Kelly 2010). One of the methods for activating sirtuins and replenishing their deficiency in the body is a dietary supplement OYOX. By their function, sirtuins are control proteins that regulate the sequence of synthesis and the activity of other proteins, which provide the cell with the ability to adapt to various kinds of tasks, factors, and stresses. Sirtuins correctly reject molecules, even with insignificant errors, thereby achieving the correct and, more importantly, sequential protein molecules synthesis. The flawless work of cellular processes leads to a balanced work of the whole human body systems at all levels (Zubaidha 2019; Tam 2019; Shafiei 2020; Adhikari 2020; Rehman 2021). OYOX activates sirtuins production, replenishing their deficiency, and prevents the development of various pathologies associated with age-related intracellular disruptions and disorders. Having achieved balance, the human body is capable of producing optimal levels of neurotransmitters, enzymes, hormones. Ready for

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physiologically normal regeneration of tissues, collagen, elastin, and flawless functioning of the body as a whole, characteristic of a young age.

OYOX has undergone repeated testing on laboratory models and clinical studies - in contrast to many dietary supplements. OYOX has been convincingly proven to be highly effective and environmentally-friendly. By creating OYOX, DANDA Pharma united the world's leading R&D centers, modern pharmaceutical and biotechnological production. As a result, the work of scientists was crowned with the invention of a unique method of producing substances, due to which their activity increases. This is how the key element of OYOX was born, the unique molecule "CYC-8", which supports protein synthesis and metabolic rate. In addition, DANDA Pharma has implemented artificial intelligence technologies to further process data from clinical trials to determine the optimal course of OYOX and to analyze long-term use.

The effectiveness of the use of a dietary supplement OYOX for the treatment and prevention of encephalic and environmental damage and disorders of the hepatobiliary system.

A multicenter, open, randomized study of the efficacy and reliability of clinical effects, safety, the immunogenicity of OYOX in humans was carried out according to a voluntary trial protocol. Natural activator SIRT1; SIRT3; SIRT6 as part of a health maintenance program (Kelly 2010). The aim of this study was to evaluate the clinical effects of OYOX. Within the framework of this study, the telomere length was determined. Lymphocytes and granulocytes were used as research material. The FlowFISH method was used. The main attention was paid to the study of biological indicators of aging processes. The subjects underwent a blood test with a detailed study of the leukocyte formula, immunogram. Additionally, the kidneys functional state, liver, endocrine, and cardiovascular systems, bones, and skin were assessed. Among the biochemical indicators, special attention was paid to determining the level of cholesterol and glucose. The study involved 980 people aged 30-87 years, of them, 58% were men and 42% were women. During the study, the participants were divided into two groups: experimental and control. The experimental group took OYOX; the control group took a placebo. The study's comparative results before the start of taking the drug and after 3 and 6 months are presented in Tables 1-2 and in Fig. 1.

Table 1. Results of the OYOX study (before priming and after three months).

Indicator	Drug				Placebo			
	Before taking		After three months		Before taking		After three months	
Sex	m	w	m	w	m	w	m	w
Age	45-67	42-59	45-67	42-59	46-66	43-54	46-66	43-54
Telomere length, kb	4.4	5.4	10.1	9.4	4.8	4.7	4.8	4.5
RTL index	7.3	8.4	12	11.8	7.9	8.2	6.2	7.9
CRB, mg L^{-1}	4.3	4.8	3	2.9	4.4	4.9	4.5	4.8
Total cholesterol. mmol L^{-1}	5.2	5	4.8	4.6	5	4.6	5.3	4.9
LPNV, mmol L^{-1}	2.8	3.1	2	2.2	2	2.4	2	2.3
HDL, mmol L^{-1}	0.7	1	1.5	1.7	0.9	1.9	1	1.9
Glycosylated hemoglobin (HbAlc, %)	5.8	5.7	4.6	5.1	5.9	5.6	5.8	5.8
Creatine µmol L^{-1}	98	96	80	77	98	105	100	101
Total bilirubin, µmol L^{-1}	10.8	12.2	9.6	9.8	11.3	11.9	11.2	11.5
ALT, U L^{-1}	23	26	20	19.2	28	31	28	31
AST, U L^{-1}	29	30	28	20	23	28	24	27

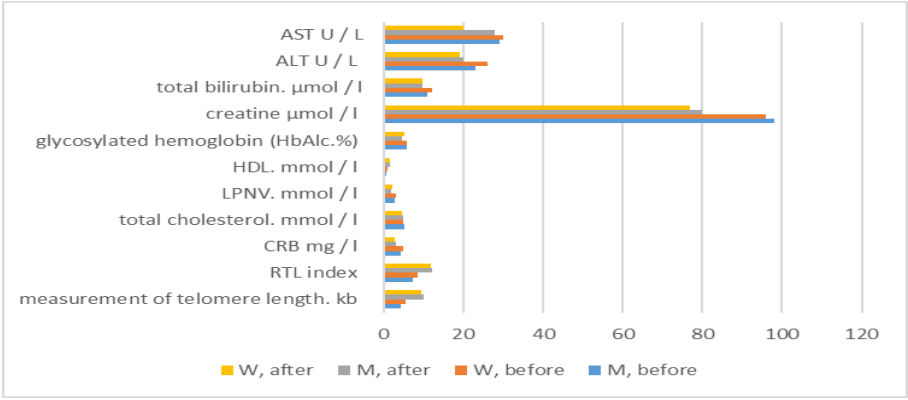

Fig. 1. The effectiveness of treatment using OYOX (before priming and after three months).

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Table 2. Results of the OYOX study (before priming and after six months).

Indicator	Drug				Placebo			
	Before taking		After six months		Before taking		After six months	
Sex	m	w	m	w	m	w	m	w
Age	45-67	42-59	45-67	42-59	46-66	43-54	46-66	43-54
Telomere length, kb	7.9	8.1	12.3	10.4	7.3	7.9	7.5	7.2
RTL index	10.4	11.5	15.4	13.3	8.2	9.4	9	8.3
CRB mg L^{-1}	4.2	4.1	2.5	2.9	4.3	3.8	5.4	2.6
Total cholesterol, mmol L^{-1}	5.4	5.8	4.8	5	5.9	4.9	6	5.4
LPNV, mmol L^{-1}	2.8	2.6	2	1.8	2.8	1.9	3	1.8
HDL. mmol L^{-1}	1.3	1.4	2	1.8	1.5	1.6	1.4	1.3
Glycosylated hemoglobin (HbAlc,%)	5.8	5.6	4.9	5	5.3	5.9	5.5	5.4
Creatine, µmol L^{-1}	100	98	90	85	112	99	111	102
Total bilirubin, µmol L^{-1}	12.8	10.7	10.2	9.4	11.6	10.9	11.8	10.2
ALT, U L^{-1}	25	19	22	16	22	28	23	27
AST, U L^{-1}	22	21	19.5	20	25	26.7	25.2	27.1

The results of the study before treatment and six months after treatment are shown in Fig. 2.

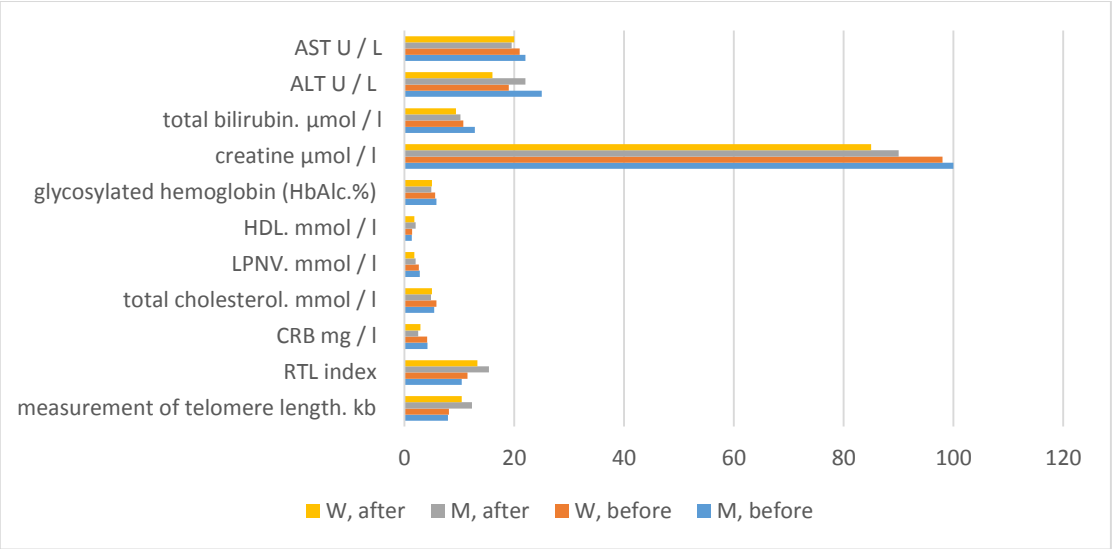

Fig. 2. The effectiveness of treatment before taking the drug and after 6 months.

Thus, in the group of people taking OYOX, it was reliably noted:

- Statistically significant decrease in the percentage of short telomeres ($p = 0.029$);
- Reduction in the percentage of senescent cytotoxic (CD8 + / CD28-) T cells (by 1.5%; 4.4%; 8.6% and 7.5% after 3 and 6 months respectively);
- Improvement of lipid and carbohydrate metabolism indicators glycosylated hemoglobin (HbA 1%) by 4.9% ($p = 0.01$), total cholesterol 5.7 mmol L^{-1} ($p = 0.003$) low density lipoprotein (LCL-C): 3.82 mmol L^{-1} ($p = 0.0021$) homocysteine: 3.4 mmol L^{-1} ($p = 0.001$).

CONCLUSION

Over the last few years, a great effort has been made bring to global attention the impact of human activities on planetary health. Among others, food production is considered a major driver of environmental change. Among the various causal factors that contribute to the development of environmental and encephalic damage and disorders of the hepatobiliary system, nutritional disorders are of no small importance. Neurodegenerative disorders and various encephalic damage often occur against the background of metabolic disorders. Disorders of metabolic processes largely depend on the activity and the qualitative and quantitative characteristics of sirtuin-type proteins. Protein deficiency can be filled by artificially introducing them into the body through dietary supplements. We have analyzed the possibilities of using the dietary supplement OYOX for the prevention of environmental damage, as far as possible, and treatment of encephalic damage and disorders of the hepatobiliary

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system. In the liver and brain, sirtuins play an important role in the regulation of fatty acid metabolism. In particular, they regulate lipid metabolism by activating the AMPK / LKB1 signaling pathway. The deficiency of proteins of the sirtuin- type negatively affects both the state of individual metabolic processes and the state of the body as a whole. Proteins SIRT1, SIRT3, SIRT6 are basic. They are closely interrelated, and their mechanism of action is largely intertwined. One of the methods for activating sirtuins and replenishing their deficiency in the body is a dietary supplement OYOX. The drug activates the production of sirtuins, replenishing their deficiency, prevents the development of various pathologies associated with age-related intracellular disruptions and disorders. A multicenter, open, randomized study of the efficacy and reliability of clinical effects, safety and immunogenicity of OYOX in humans was carried out according to a voluntary trial protocol.

The results were evaluated 3 and 6 months after taking the drug. There was an improvement in lipid and carbohydrate metabolism indicators glycosylated hemoglobin (HbA 1%) by 4.9% ($p = 0.01$), total cholesterol by 5.7 mmol L^{-1} ($p = 0.003$), low density lipoprotein (LCL-C) by 3.82 mmol L^{-1} ($p = 0.0021$) and homocysteine by 3.4 mmol L^{-1} ($p = 0.001$). The decrease in systolic and diastolic blood pressure of the dynamics was 17.1-4.2 mm Hg ($p = 0.006$ and 0.002, respectively).

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