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EFFECT OF ANTIDISBIOTIC DRUGS ON THE LIVER CONDITION IN RATS AFTER ANTI- HELICOBACTER THERAPY

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Abstract

The purpose: in experiment to determine the hepatoprotective effects of phytogels "Kvertulin" and "Kvertulion" during anti-Helicobacter pylori therapy by defining the liver condition by hepatic enzymes indexes and the degree of dysbiosis in rats.

Materials and methods: Two series of experiments were carried out. I series – 30 white rats of the Wistar line (females, 10 months, average weight 300 g). The animals were divided into 3 groups: 1 - control (norm), got a complete bio-feed, animals of the 2nd and 3rd got additionally *per os* mixture of antihelicobacter therapy drugs for 8 days. The 3rd group animals received applications of phytogel "Kvertulin" on the oral mucosa from the first day of the experiment during 11 days. In the II series of experiments, 30 rats with similar characteristics were also used. The animals were divided into 3 equal groups: 1- control (norm), animals of the 2nd and 3rd got additionally *per os* mixture of antihelicobacter therapy drugs for 8 days (omeprasol -1.3 mg/kg; augmentin – 50 mg/kg; clarithromycin -7.5 mg/kg). The 3rd group animals received applications of phytogel "Kvertulidon" on the oral mucosa from the first day of the experiment during 11 days.

Results: The number of leukocyte cells (percentage of neutrophils and lymphocytes) was determined in the blood of rats and the immunodeficiency index (lymphocyte / neutrophil ratio) was calculated. The level of hepatic markers was also determined: the activity of alanine aminotransferase and alkaline phosphatase enzymes, the level of inflammatory markers (malonic dialdehyde content and elastase activity), the activity of protective enzymes (lysozyme and catalase). In the liver homogenate (50 mg / ml 0.05 M Tris-HCl buffer pH 7.5) the content of malonic dialdehyde, the activity of elastase, alkaline phosphatase, catalase, lysozyme and urease (indicator of microbial contamination) was determined. The antioxidant-prooxidant index was calculated from the ratio of catalase activity and malonic dialdehyde content, and from the ratio of relative urease and lysozyme activities the degree of dysbiosis by Levitsky was calculated.

Conclusions: The signs of primary and secondary liver damage due to intestinal dysbiosis were detected. The positive effect of phytogel "Kvertulidon" applications on the oral mucosa at the background of antihelicobacter therapy due to its antioxidant, immunostimulatory and prebiotic properties was determined. The data obtained provide a basis for clinical studies of the therapeutic and

prophylactic effects of oral applications of phytogel "Kvertulidon" in patients who got antihelicobacter therapy in order to prevent or reduce the development of its adverse effects..

Keywords: *phytogel "Kvertulin", phytogel "Kvertulidon", antihelicobacter therapy, liver damage.*

Introduction

The drugs used in the treatment of *Helicobacter pylori* in rats caused liver damages. The results of our clinical studies suggest that antihelicobacter therapy is associated with some complications that may be the result of either direct hepatotoxic effects, or gastrointestinal dysbiosis, which in turn affects liver function, one of which is that of barrier.

The liver absorbs and neutralizes almost 95% of all microbes and toxins that enter the bloodstream through the *vena portae* from the intestine. Therefore, its damage due to antihelicobacter therapy reduces the barrier function and the flow of lipopolysaccharides and other toxins entering into the body from the intestine, increases. Thus, the vicious circle that is formed in chronic *Helicobacter pylori* and its treatment, is closed. At the same time, data on the beneficial therapeutic and prophylactic effect on the liver of bioflavonoid drugs are increasingly mentioned in the literature [3]. The hepatoprotective effect of these compounds is enhanced by the simultaneous introduction of antidisbiotic drugs, especially pro- and prebiotics [10]. The use of such drugs can contribute to the disappearance of the vicious circle due to the impact on two different, although related, pathogenetic links.

"Kvertulin" is a drug which combines bioflavonoids and antidisbiotic, therapeutic and prophylactic properties. It includes bioflavonoid quercetin (from sophora fruits), which has muco- and hepatoprotective properties due to its antioxidant action; prebiotic inulin (from chicory's root and is one of the effective prebiotics), and calcium citrate - the most easily digestible form of calcium with prebiotic, mucoprotective and anti-inflammatory properties [7].

Materials and methods

II series of experiments were performed. Pets of animals, their nutrition and manipulation with them were carried out in accordance with the provisions of the European Convention on the Protection of vertebrate animals used for research and other scientific purposes (Strasbourg, 1986).

In the first study, 30 white Wistar rats (females, 10 months, average live weight 300 g) were used. The animals were divided into 3 groups: the animals of 1st group (control, norm), received a complete feed, the 2nd and 3rd group of experimental animals received an additional *per os* mixture of antihelicobacter therapy drugs: omeprazole (Farmak, Ukraine) at a dose of 1.3 mg / kg, amoxil (Kyivmedpreparat, Ukraine) at a dose of 50 mg / kg and clarithromycin (Kyivmedpreparat, Ukraine) at a dose of 7.5 mg / kg for 8 days. The 3rd group animals from the first day of the experiment received oral cavity applications of phytogel "Kvertulin" (Odessa Biotechnology, Ukraine) at a dose of 0.5 ml per rat for 11 days.

Euthanasia of animals was performed on the 12th day of the study under thiopental anesthesia (20 mg / kg) by total bloodletting from the heart.

The number of leukocytes, the percentage of neutrophils and lymphocytes was determined in the blood [1], and immunodeficiency index was calculated from the lymphocyte / neutrophil ratio. Liver markers (alanine aminotransferase enzymes [12] and alkaline phosphatase [2]) were determined in blood serum, level of inflammatory markers [2] - malonic dialdehyde content and elastase activity, as well as activity of two protective enzymes - lysozyme (nonspecific) [9] and antioxidant enzyme catalase [2] were investigated. In the liver homogenate (50 mg / ml 0.05 M Tris-HCl buffer pH 7.5) the content of malonic dialdehyde, the activity of elastase, alkaline phosphatase, catalase, lysozyme and urease (microbial contamination) [4] were determined. According to the ratio of catalase activity and malonic dialdehyde content the antioxidant-prooxidant index was calculated [2], and according to the ratio of relative activities of urease and lysozyme the degree of dysbiosis was evaluated according to Levitsky [11].

Due to dysbiosis the body's immune defense reduces, including that at the liver level, so **the purpose of this study** was to determine the hepatoprotective properties of a new antidisbiotic drug - mucose-adhesive phytogel "Kvertulidon", which contains quertulin and immunostimulant imudon.

In the 2nd series of experiments 30 white Wistar rats (females, 10 months, 300 ± 12 g) were used. The animals were divided into 3 equal groups: the 1st (control, normal), animals of the 2nd and 3rd groups got antihelicobacter therapy (omeprazole 1.3 mg / kg, augmentin 50 mg / kg and clarithromycin 7.5 mg

/ kg) for 8 days daily *per os*. The 3rd group rats received applications on the oral mucosa of the mucosa - adhesive phytogel "Quertulidone" at a dose of 0.5 mg per rat for 11 days obtained from the first day of the experiment. Euthanasia of rats was performed on the 12th day of the experiment under thiopental anesthesia (20 mg / kg) by total bloodletting from the heart.

The number of leukocytes was determined blood; leukocyte formula and the lymphocyte index which is the ratio of the number of lymphocytes to the number of neutrophils [1] was calculated. In the blood serum the activities of the enzymes alanine aminotransferase [6], alkaline phosphatase [2], urease [4] and lysozyme [9] were determined.

The level of biochemical markers of inflammation was determined in liver homogenates (50 mg / ml 0.05 M Tris-HCl buffer pH 7.5): malonic dialdehyde content and elastase activity, urease activity (microbial contamination index) [4], lysozyme (indicator of nonspecific immunity) by bacteriological method [9], antioxidant enzyme catalase [2] and APh [2]. According to the ratio of relative activities of urease and lysozyme, the degree of dysbiosis was calculated according to the method of Levitsky [11], and the antioxidant-prooxidant index was calculated according to the ratio of catalase activity and malonic dialdehyde content [2].

Statistical processing of the results obtained was carried out according to the recommendations, determining the mean values (M), the error of the mean value (± m) and the significance of differences between the means of the Student's t-test, assuming a reliable value ≤ 0.05.

Results

The results of determining the serum parameters of rats treated with antihelicobacter therapy and applications to the oral mucosa of the phytogel "Kvertulin", the number of leukocytes and the ratio of lymphocytes / neutrophils are presented in Table 1.

The above data show that antihelicobacter therapy has little effect on the total number of leukocytes, but significantly (3 times) increases the ratio of lymphocytes / neutrophils, which indicates the possible activation of specific, rather cellular immunity, i. e. corrects changes caused by antihelicobacter therapy. Phytogel "Kvertulin" significantly increases the number of leukocytes (due to neutrophils) and reduces by 2 times the ratio of lymphocytes / neutrophils.

Table 2 shows the level of markers of inflammation in the liver of rats: malonic dialdehyde and elastase, which confirm the previously substantiated data that the damaged liver is involved in both proteolytic systems and oxidative stress. Both markers of inflammation increase their activity after antihelicobacter therapy, which indicates the possible participation in the pathogenesis of liver pathology oxidative stress and inflammation. At this stage, the application of phytogel "Kvertulin" reduces both indicators, which proves that the drug has a pronounced anti-inflammatory effect, possibly due to the normalization of free radical processes.

Table 3 presents the results of the determination of liver markers in the blood serum of experimental rats specifically, activity of alkaline phosphatase and catalase. After antihelicobacter therapy alkaline phosphatase activity increases significantly, and phytogel "Kvertulin" applications to the oral mucosa of experimental rats normalize its indexes. This indicates the elimination of cholestasis in the liver, i. e. secondary disturbances which appear due to hepatic edema accompanying its inflammation. The latter occurs under the influence of antihelicobacter therapy, but this effect does not depend on the state of antioxidant protection, judging by the indicators of catalase.

Evidence of liver damage raises the question of the possibility of dysbiosis occurrence, which was a justification for subsequent experiments.

Thus, Table 4 shows the results of determining the activity of hepatic urease and lysozyme. From these data it is seen that the conducted antihelicobacter therapy 1.5 times increases the activity of urease, i. e. indicates an increase in microbial contamination of the liver after antihelicobacter therapy. That is, we recorded the phenomenon of dysbiosis in the liver, which indicates its possible pathogenetic role in the development of inflammation. On the other hand, this allows us to assume that liver pathology occurs not only due to the direct toxic effects of drugs and secondary disorders, i. e. due to dysbiosis. Dysbiosis, in turn, leads to a decrease of nonspecific

protection, and this is evidenced by lysozyme's more than twice decrease. The applications to the oral mucosa of phytogel "Kvertulin" reduces the activity of urease (however, p>0.05). On the contrary, after antihelicobacter therapy, lysozyme activity reduces by 2.5 times. However, after applications of "Kvertulin" it increases 1.6 times, although this is not enough to normalize the activity of lysozyme. That is, the use of phytogel "Kvertulin" is therapeutically justified, but its effect is not significant. The liver may not produce sufficiently effective concentrations of the active substances.

*Calculated by the method of Levitsky [11], the degree of dysbiosis (Fig. 1) increases after antihelicobacter therapy by almost 3.9 times, and after "Kvertulin" applications to the oral mucosa decreases twice. That is, "Kvertulin" deminishes the hepatotoxic effect of antihelicobacter therapy by reducing dysbiosis, which are important secondary pathogenetic mechanisms.

Moreover, the antioxidant-prooxidant index (Fig. 2) after antihelicobacter therapy is significantly reduced too, which indicates a violation of the balance of antioxidant-prooxidant systems in favor of the latter. Thus, this therapy contributes to the phenomena of oxidative stress. Applications of 'Kvertulin' to the oral mucosa increase the antioxidant-prooxidant index (however, p> 0.05) due to the prevention of oxidative stress, which confirms the prospects for the use of antioxidant and antidisbiotic drugs in hepatic pathology.

The mechanisms of oxidative stress and proteolysis we have identified are likely to damage the liver, causing inflammation. Indeed, Table 5 shows the results of the determination of "hepatic" markers of hepatocytes and the billiary system damage - alanine aminotransferase and alkaline phosphatase. After antihelicobacter therapy, the level of both markers increases significantly, which may indicate the development of hepatitis with impaired hepatocytes and suppressed bile secretion, and applications to the oral mucosa of "Kvertulin" reduce both alanint transaminase and alkaline phosphatase levels, which may indicate its pronounced hepatoprotective properties.

Table 6 presents the results of determining the blood cytological parameters of rats treated with antihelicobacter therapy and mucosa-adhesive phytogel "Kvertulin". These data show that although the absolute number of leukocytes in the blood of the experimental rats changes little during antihelicobacter therapy and after applications to the oral mucosa "Kvertuline", but they significantly changes the ratio of neutrophils and monocytes. Thus, the percentage of neutrophils decreases twice, while the percentage of lymphocytes increases by 1.5 times. This ultimately leads to lymphocytes index a 3-fold increase and indicates a relative decrease in the activity of nonspecific immunity, which is largely provided by phagocytic cells, while the possibilities of immune protection increase.

Applications of phytogels on the oral mucosa sigificantly increase the percentage of neutrophils and significantly reduce the percentage of lymphocytes and, as a result, the lymphocyte index reduces by 1.4 times. Besides, in the use of oral phytogel "Kvertulidon" normalizes the reduced in antihelicobacter therapy level of monocytes which are important precursors in the formation of immune defense.

The data related to a number of blood indicators turned out to be interesting. Table 7 presents the results of determining the activity of some enzymes in the serum of rats treated with antihelicobacter therapy and applications to the oral mucosa of the phytogel "Kvertulin". From these data it is seen that after antihelicobacter therapy the activity of the enzyme urease increases more than 3 times, which indicates an increase in microbial contamination of the blood, ie the occurrence of bacteremia.

Applications of phytogel "Kvertulin" reduce urease activity more than twice. On the contrary, the activity of serum lysozyme, significantly reduced after antihelicobacter therapy under the action of prebiotic and phyto gel "Kvertulin" returns to normal, i. e. there is a restoration of immune protection. In rats treated with antihelicobacter therapy, the activity of hepatic markers - alanine transaminase and alkaline phosphatase - significantly increases, which may indicate the possible development of hepatitis and cholestasis.

Phytogel "Kvertulidon" reduces the level of "hepatic" markers of inflammation, but only the activity of alanine transaminase is reliable (Table 7), which indicates the hepatoprotective role of the drug. Its effect on the state of the biliary system is much smaller.

In subsequent experiments, we studied the possible biochemical mechanisms of liver damage. Table 8 shows the results of determining a number of biochemical parameters in the liver of rats treated with antihelicobacter therapy and applications to the oral mucosa of phytogel "Kvertulidone". After antihelicobacter therapy, the level of both markers of inflammation - malonic dialdehyde and the activity of the enzyme elastase - increases significantly. It is possible that oxidative stress occurs, which is one of the main pathogenetic mechanisms of inflammation. Applications of phytogel "Kvertulin" reduce the level of the indicators under study, but only the activity of the enzyme elastase is significantly reduced.

In rats treated with antihelicobacter therapy the activity of alkaline phosphatase which indicates the development of cholestasis, also increased significantly in the liver, and the activity of urease increased 1.5 times, which indicates an increase in microbial contamination of the organ. In contrast, the activity of lysozyme in the liver of experimental rats after antihelicobacter therapy reduced by 2.5 times. The use of the phytogel "Kvertulidon" reduces the increased level of alkaline phosphatase and urease activity and has little effect on the activity of lysozyme. As for the activity of the antioxidant enzyme catalase, it does not change either after antihelicobacter therapy or after applications to the oral mucosa of phytogel "Quertulidon" (Table 8), i. e. dysbiosis is more important in the affected liver.

Subsequent experiments fully confirmed the above mentioned. Thus, Fig. 3 - 4 show the results of determining the degree of dysbiosis according to Levitsky, which shows that antihelicobacter therapy significantly (almost 4 times) increases the degree of dysbiosis in both serum and liver. Oral applications of "Kvertulidon" significantly reduce the degree of dysbiosis, but do not return them to norm. It is possible that for the complete normalization of this indicator either a large dosage of the drug, or longer treatment is necessary, although judging by the direction of therapeutic action of the drugs they may be recommended for use in clinical practice.

Dysbiosis registered in the blood could be the result of liver damage. Indeed, in Fig. 5, the identified changes in hepatic antioxidant-prooxidant index which reflects the imbalance of the processes of lipid peroxidation and antioxidant protection with their subsequent normalization shown. It is seen that the use of antihelicobacter therapy leads to a significant decrease in the antioxidant-prooxidant index, and oral applications of phytogel "Kvertulidon" contribute to the tendency to increase this index.

Conclusions

Thus, the studies made showed the presence of pathogenic effects of antihelicobacter therapy on the liver with the development of hepatitis and holestasis as a consequence of gastrointestinal tract dysbiosis development and increased excretion of toxins formed in the intestine in violation of microbiocobacteriosis. This is the result of antihelicobacter therapy side effect with subsequent entry into the liver without excluding the presence of direct hepatotoxic effects of antihelicobacter therapy drugs. Applications to the oral mucosa of phytogel "Kvertulidon" significantly reduces the detection of dysbiotic manifestations and has a hepatoprotective effect. The latter can be explained by the antioxidant effects of quertulin and antidysbiotic effect of inulin, i. e. their effects on both leading pathogenic mechanisms.

Our studies have once again confirmed that the development of complications after antihelicobacter therapy leads to impaired liver function most likely by the mechanism of inflammation development and the development of systemic endotoxinemia. These disorders may be based on changes in the hepatic antimicrobial function [16], which is manifested by the development of dysbiosis in both the liver and blood. One of the reasons for the development of dysbiosis may be immunodeficiency that occurs after antihelicobacter therapy, mainly due to a decrease in the level of nonspecific immunity, as evidenced by a decrease in the percentage of phagocytes and lysozyme activity. The possibility of drug effects on the intestinal microflora should not be ruled out.

That is, there are signs of primary and secondary liver damage due to intestinal dysbiosis. The positive effect of applications on the oral mucosa of phytogel "Kvertulidon" at the background of

antihelicobacter therapy may be based on its antioxidant, immunostimulatory and prebiotic properties.

The data obtained provide a basis for clinical studies of the therapeutic and prophylactic effects of oral applications of phytogel "Kvertulidon" in antihelicobacter therapy patients in order to prevent or reduce the development of its adverse effects.

A variety of drugs that have antioxidant activity enhanced by antidysbiotic properties are promising for use.

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Table 1. The effect of phytogel "Kvertulin" on the level of leukocytes in the serum of rats after antihelicobacter therapy (AGBT) (M ± m, n = 10)

NN	Groups	Leucocytes, g/l	Lymphocytes/ Neutrophils
1	Control(norm)	13.3 ± 0.3	1.07 ± 0.05
2	Antihelicobacter therapy	14.0 ± 0.3 p> 0.05	3.14 ± 0.09 p <0.01
3	Antihelicobacter therapy + " Kvertulin"	17.3 ± 0.4 p <0.01; p_1 <0.01	1.58 ± 0.10 p <0.05; p_1 <0.01

Note: p - in comparison with group 1, p_1 - in comparison with group 2.

Table 2. The effect of phytogel "Kvertulin" on the level of markers of inflammation in the liver of rats after antihelicobacter therapy (AHBT) (M ± m, n = 10)

NN	Groups	Malon dialdehyde, mmol/kg	Elastase,mcat/kg
1	Control (norm)	20.7 ± 3.0	0.25 ± 0.01
2	Antihelicobacter therapy	33.9 ± 3.1 p <0.05	0.31 ± 0.02 p<0.05
3	Antihelicobacter therapy +"Kvertulin"	26.0 ± 3.0 p> 0.1; p_1> 0.05	0.26 ± 0.01 p> 0.3; p_1 <0.05

Note: p - in comparison with group 1, p_1 - in comparison with group 2.

Table 3. The effect of phytogel "Kvertulin" on the activity of alkaline phosphatase and catalase in the liver of rats after antihelicobacter therapy, (M ± m, n = 10)

N	Groups	Alkaline phosphatase, mkat/kg	Catalase, mkat/kg
1	control (norm)	5.16 ± 0.42	6.33 ± 0.08
2	AHBT	6.56 ± 0.50 p <0.05	26 ± 0.06 p> 0.3
3	AHBT+ Kvertulin	5.62 ± 0.50 p> 0.3; p_1> 0.05	6.33 ± 0.36 p = 1.0; p_1> 0.3

Note: p - in comparison with group 1, p_1 - in comparison with group 2.

Table 4. The effect of phytogel "Kvertulin" on the activity of urease and lysozyme in the liver of rats after antihelicobacter therapy, (M ± m, n = 10)

N	Groups	Urease, mkat/kg	Lysozyme, U/kg
1	Control (norm)	0.21 ± 0.02	104 ± 12
2	AHBT	0.32 ± 0.02 p <0.01	41 ± 8 p <0.01
3	AHBT+ Kvertulin	0.26 ± 0.03 p> 0.05; p_1> 0.05	67 ± 8 p <0.05; p_1 <0.05

Note: p - in comparison with group 1, p_1 - in comparison with group 2.

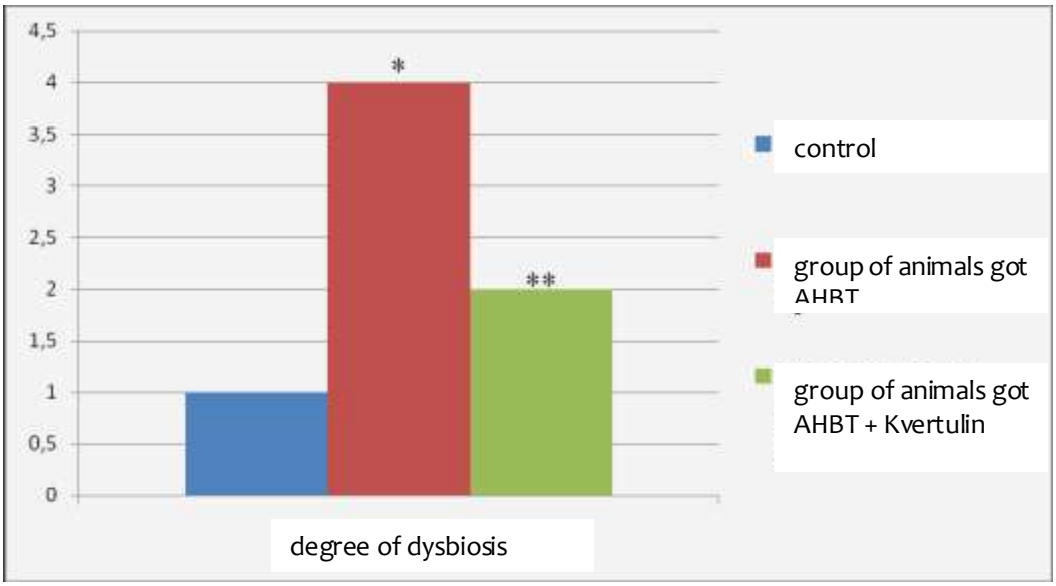

Figure 1. Effect of phytogel Kvertulin on disbiosis degree in the rats' liver after AHBT
* - p <0.05 in comparison with control;
** - p <0.05 in comparison with the animals got AHBT

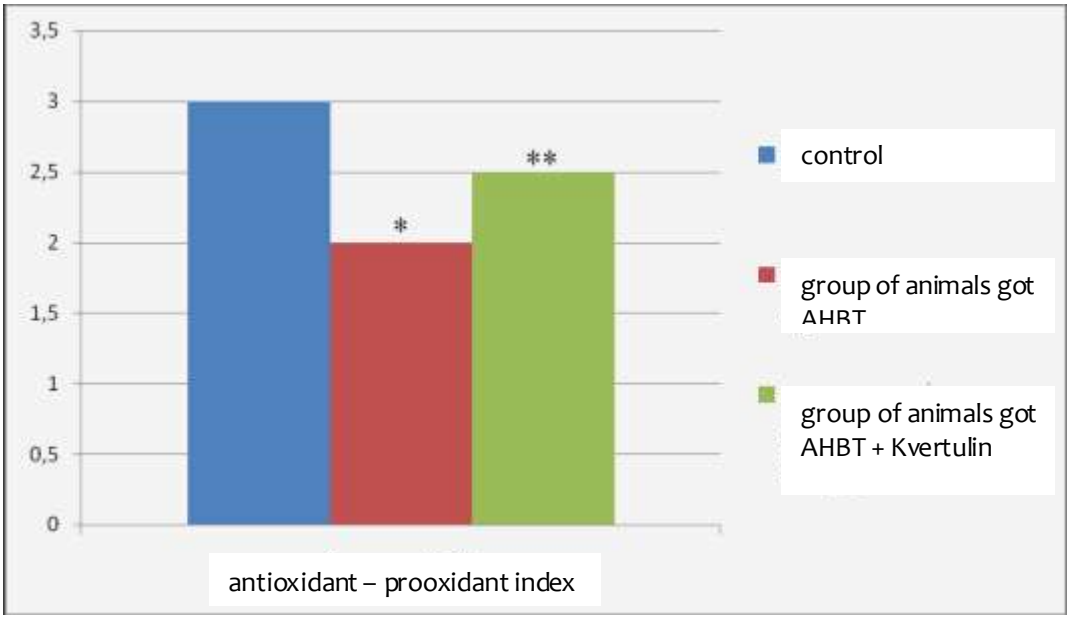

Figure 2. Efect of phytogel Kvertulinon antioxidant – prooxidant index the rats' liver after AHBT
(* - p <0.05 in comparison with control;
** - p <0.05 in comparison with the animals got AHBT).

rat serum after antihelicobacter therapy (AHBT), (M ± m, n = 10)

№	Groups	ALT, mk-kat/l	APh, mk-kat/l
1	Control (norm)	0,38±0,03	0,91±0,08
2	AHBT	0,57±0,04 p<0,05	1,45±0,12 p<0,05
3	AHBT+Kvertulin	0,40±0,02 p>0,3; p_1<0,05	1,24±0,11 p<0,05; p_1>0,05

Note: p – in comparison with group 1, p_1 – in comparison with group 2.

Table 6. Leukocytosis and leukocyte blood count of rats treated with antihelicobacter therapy and Kvertulidon, (M ± m, n = 10)

Indications	groups		
	1. Control	2. AHBT	3. AHBT+ Kvertulidon
Leukocytes, x10^9/l	13,3 ± 0,3	14,0 ± 0,3 p > 0,05	14,9 ± 0,8 p > 0,05 p_1 > 0,05
Neutrophils (H), %	42,4 ± 1,4	21,0 ± 0,9 p < 0,01	25,8 ± 1,9 p < 0,01 p_1 < 0,05
Lymphocytes (Л), %	45,2 ± 1,6	66 ± 2,8 p < 0,01	58,6 ± 1,3 p < 0,01 p_1< 0,05
Monocytes, %	8,8 ± 0,5	6,2 ± 0,9 p < 0,05	7,4 ± 0,9 p > 0,05 p_1 > 0,3
Lymphocyte index (LI)	1,07 ± 0,05	3,14 ± 0,09 p < 0,001	2,27 ± 0,11 p < 0,01 p_1 < 0,01

Note: p – in comparison with group 1; p_1 – in comparison with group 2.

Table 7. The activity of enzymes in the serum of rats treated with antihelicobacter therapy and Kvertulidon, (M ± m, n = 10)

Indications	Groups		
	1. control	2. AHBT	3. AHBT+ Kvertulidon
Ureasa activity, mk-kat/l	0,04 ± 0,01	0,13 ± 0,02 p < 0,01	0,06 ± 0,02 p > 0,05 p_1 < 0,05
Lyzosyme activity лізоциму, U/l	131 ± 8	107 ± 4 p < 0,05	132 ± 5 p > 0,8 p_1 < 0,05
ALT activity, mk-kat/l	0,38 ± 0,03	0,57 ± 0,04 p < 0,05	0,44 ± 0,04 p > 0,1 p_1 < 0,05
APh activity, мk-kat/l	0,91 ± 0,08	1,45 ± 0,12 p < 0,01	1,26 ± 0,10 p < 0,05 p1 > 0,05

Note: p – in comparison with group 1; p_1 – in comparison with group 2.

Table 8. Biochemical parameters of the liver of rats treated with antihelicobacter therapy and Kvertulidone, (M ± m, n = 10)

Indications	groups		
	1. control	2. AHBT	3. AHBT+ Kvertulidon
MDA, mmol/kg	20,7 ± 3,0	33,9 ± 3,1 p < 0,05	30,2 ± 2,9 p < 0,05 p_1 > 0,3
Elastase activity, мkat/kg	0,25 ± 0,01	0,31 ± 0,02 p < 0,05	0,25 ± 0,01 p = 1,0 p_1 < 0,05
APh activity mk-kat/kg	5,16 ± 0,42	6,56 ± 0,50 p < 0,05	5,79 ± 0,44 p > 0,3 p_1 > 0,2
Urease activity, mk - kat/kg	0,21 ± 0,02	0,32 ± 0,02 p < 0,01	0,24 ± 0,02 p > 0,3 p_1 < 0,05
Lyzosyme activity, U/kg	104 ± 12	41 ± 8 p < 0,01	53 ± 9 p < 0,01 p_1 > 0,3
Catalase activity, mkat/kg	6,33 ± 0,08	6,26 ± 0,06 p > 0,3	6,32 ± 0,35 p > 0,9 p_1 > 0,5

Note: p – in comparison with group 1; p_1 – in comparison with group 2.

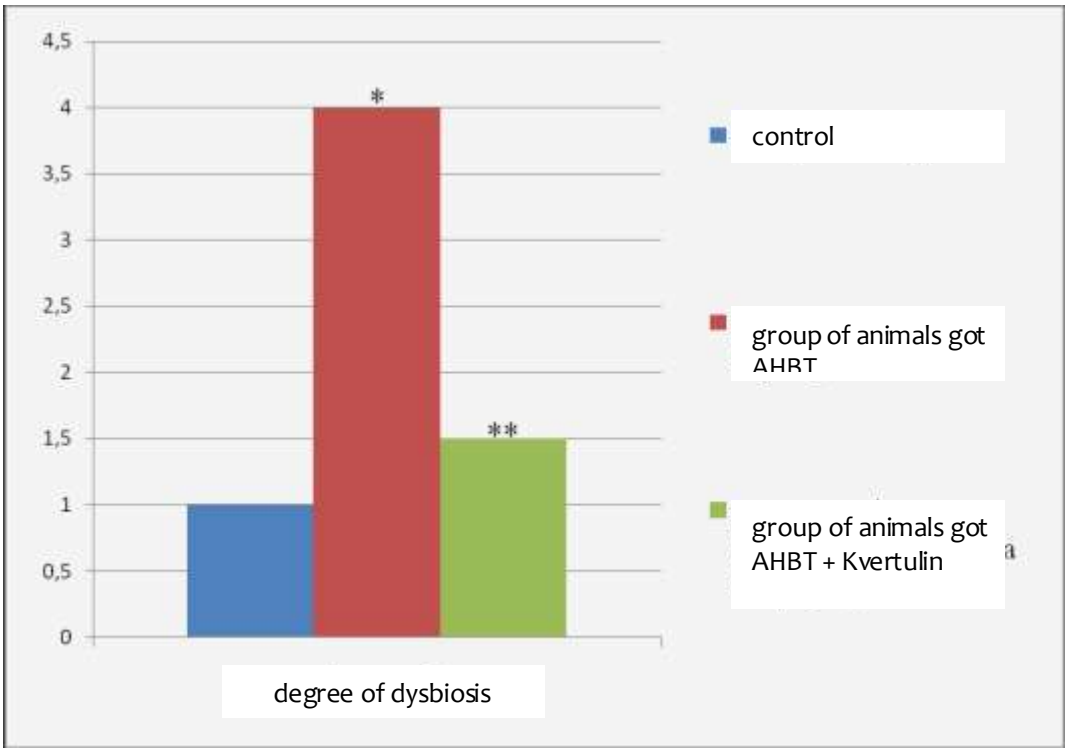

Figure 3. The degree of dysbiosis in rats' serum which got AHBT and Kvertulidone

* - p <0.05 in comparison with the control group;

** - p <0.05 compared with the group of AHBT rats

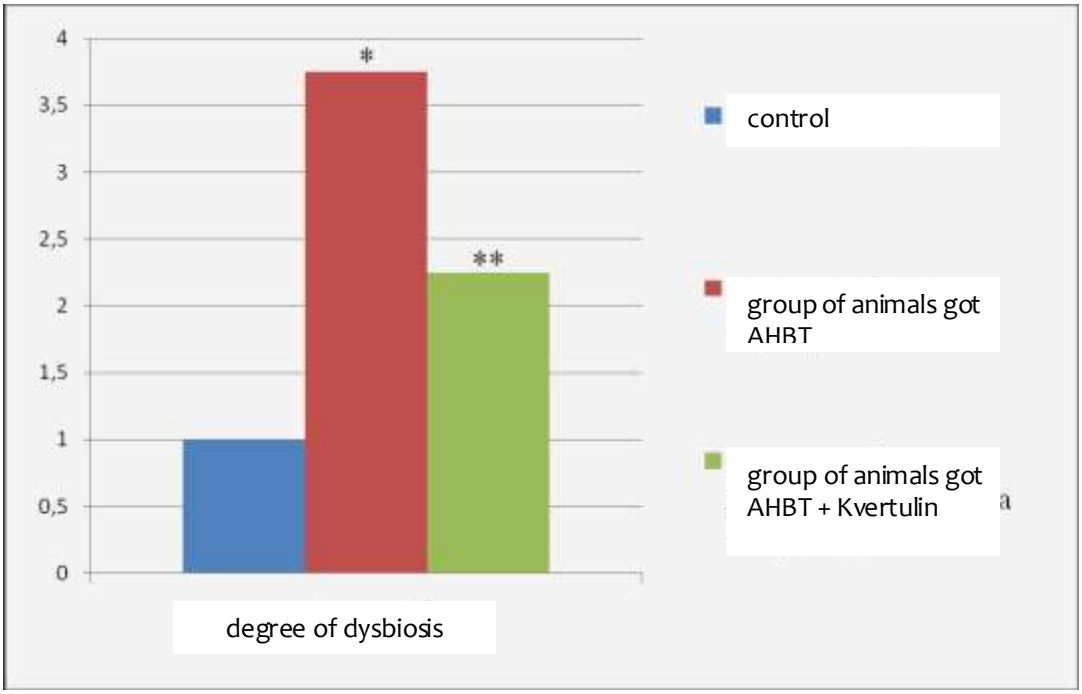

Figure 4. The degree of dysbiosis in the liver of AHBT rats + Kvertulidon
***** - p <0.05 in comparison with the control group;
****** - p <0.05 compared with the group of AHBT rats

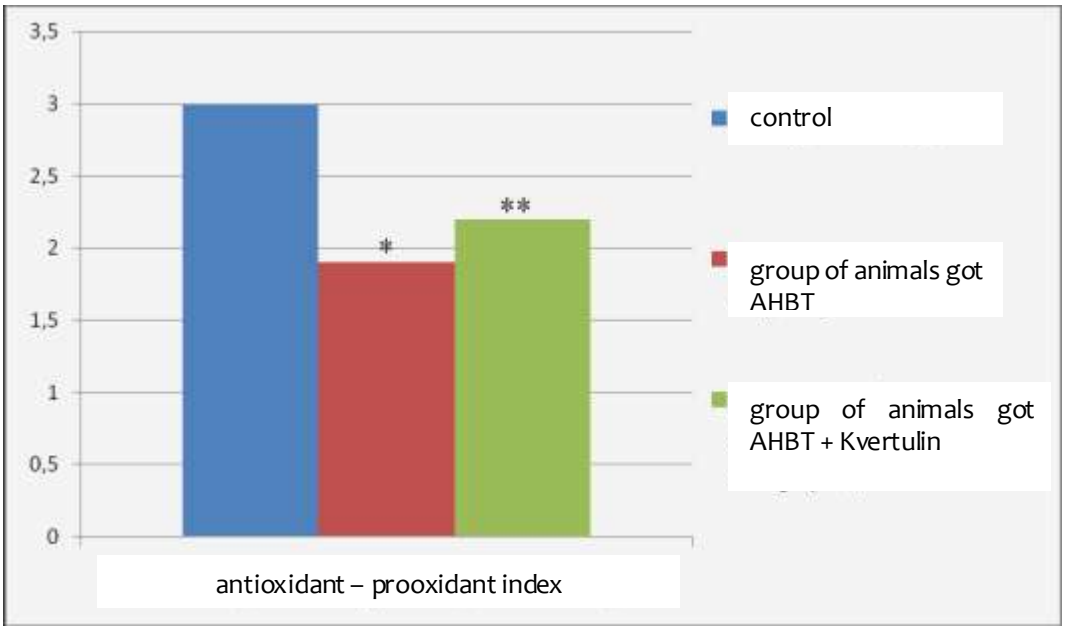

Figure 5. Indications of antioxidant - prooxidant index in the liver of AHBT rats + Kvertulidone,
***** - p <0,05 in comparison with the control group;
****** - p <0.05 compared with the group of AHBT rats