Changes In Biochemical Indexes Of Rats' Blood During Chronic Ethanol Poisoning And Treatment Them With Herbal Preparations

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Abstract. Relevance: Alcoholism worldwide is one of the main causes of premature death of the population. Alcohol is a leading etiological factor in liver damage, this necessitates the search for new, more effective pharmacological drugs with a pathogenetic orientation with antioxidant and metabolic effects. Promising are Geranium saxatile and proanthocyanidins active ingredients ah. **Purpose:** to experimentally substantiate the feasibility of using geranil for the protection of organs and tissues in chronic alcohol intoxication. **Material and methods:** Chronic alcohol intoxication in 50 rats was modeled by intragastric administration of 25% ethanol at a dose of 10 ml / kg for 28 days daily. Experimental pharmacotherapy with geranil (main group) and carsil (comparison drug) was carried out from 21 days of the experiment for 7 days at a dose of 100 mg / kg. The determination of serum biochemical parameters was carried out on a MINDRAYBA-88A biochemistry analyzer (China) using commercial reagent firms from CYPRESS Diagnostics (Belgium). Digital material processed by the method of variation statistics. **Results:** The results of the study showed the development of structural and functional disorders of hepatocytes under the influence of ethanol and its metabolic products, leading to a change in blood biochemical parameters and liver indicators. Experimental pharmacotherapy with carsil, to a greater extent geranyl, reduced hyperenzymes, hyperbilirubinemia, hypercholesterolemia, and the pharmaco-metabolizing function of hepatocytes, due to a decrease in hyperlipoperoxidation. **Conclusion:** Experimental pharmacotherapy with a new drug from the group of proanthacyanidins geranyl and bioflavonoids - Carsil leads to a decrease in lipid peroxidation intensity, causing restoration of the structural and functional parameters of hepatocytes. Geranil turned out to be more effective in this regard.

Index Terms: Geranil, carsil, alcoholic liver damage, biochemical parameters.

1 INTRODUCTION

Chronic alcoholization is a vivid example of the most common long-lasting exogenous chemical effects on the body. According to world health organization statistics, by 2010 more than 180 million people with alcoholism were registered. Among the general mortality of the population, mortality from the effects of alcoholism exceeds 2.5 million [Rehm J; 160-168]. In most countries of the world, alcoholism is one of the most widespread somatic diseases. For example, in the USA, 80,000 people die each year from alcoholic liver damage [F.Gao., 2019], in Russia more than 10 million patients with alcoholism are registered [Mendeleevich V.D., 2017]. In 2018, 615 patients with alcoholism were hospitalized in various clinics in Uzbekistan in Uzbekistan.

Thus, alcoholism around the world is one of the main causes of premature death of the population. Alcohol abuse negatively affects the functioning of almost all organs and systems of the body as a result of the toxic effects of ethanol, especially the liver, kidneys, heart, lungs, pancreas, peripheral and central nervous system [S.L.A. Rajbanshi., 2014, Omolola R.O., 2016; Erukainure O.L., 2011; A.Rezaee-Khorasany., 2019; M.R. Choi., 2017; Cerrillo I., 2019]. The violation of the structural and functional properties of biological membranes, the dysfunction of ion transport systems, the change in the metabolism of various organs and systems, the enzyme spectrum of blood and organs with alcohol damage have been proven. Ethanol toxicity may be associated with increased oxidative stress, lipid peroxidation (LP), excessive formation of free radicals that cause cell damage, and activation of cell apoptosis [X.Xie; 2018]. The metabolic processes that make up the molecular basis of alcoholic liver damage have been studied for many years. Alcohol and a number of other factors cause pathological changes that are diverse in the mechanisms of development and clinical manifestations in the liver, which is the main biochemical laboratory of the body. It is known that the action of alcohol disrupts the course of many diverse biochemical processes in the liver (carbohydrate, protein, lipid metabolism, pigment metabolism, as well as in the detoxification of numerous endogenous and exogenous substances) [I.A. Shikalova et al., 2012]. Ethanol metabolism mainly (75-98%) occurs in the liver in three ways to the formation of toxic acetaldehyde: mitochondrial NAD-dependent alcohol dehydrogenase (ADH) (up to 95%), cytochrome P450-dependent microsomal ethanol-oxidizing system (its share reaches 50-70% in chronic alcoholism) and catalase (about 2%) [A.F.Arafa., 2019]. Normally formed acetic aldehyde with the participation of FAD-dependent aldehyde oxidase or NAD-dependent acetaldehyde dehydrogenase (AlDH) is converted into

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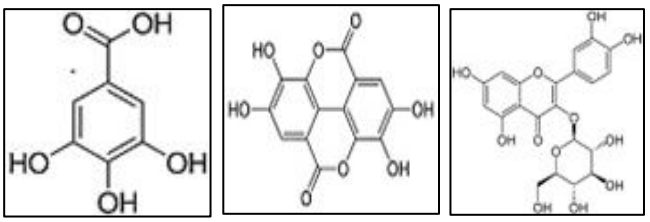
acetic acid and is included in the metabolic cycle. Since the rate of these reactions in hepatocytes is different, when high doses of ethanol are received, the highly toxic metabolite of acetaldehyde accumulates [Howida S.A.S., 2014]. Since alcohol is a leading etiological factor in liver damage, it is necessary to find new, more effective pharmacological preparations of a pathogenetic orientation with antioxidant and metabolic effects, which can significantly improve the quality of life of patients suffering from alcoholism. To date, hepatoprotective properties of various plant compounds have been studied and preparations based on them [Sh.Zou; 2019 Y. Guo; 2017; Arafa A.F., 2019; Omolola R. O., 2016]. Hepatoprotective drugs contain biological active complexes of plant or animal origin, essential phospholipids and drugs of different groups [Grishchenko E.B, 2013]. Despite the high effectiveness of hepatoprotectors, the search continues for plant-based hepatoprotectors with a wide spectrum of action. Currently, the interest of researchers in herbal preparations is high, since they have very low toxicity, a multilateral mechanism of action [MathurinP., 2015]. Carsil bioflavonoids, created on the basis of silymarin, the mechanism of the hepatoprotective action of which has been fairly well studied by many researchers, are widely used [Sh.Zou., 2019, Y.Guo., 2017; I.Shukla., 2017; N. Kumar et al., 2019]. Its action is associated with the competitive interaction of silymarin with toxins for the corresponding receptors on the hepatocyte membrane, suppression of the lipoxygenase binding pathway with oxygen free radicals, and accelerates the regeneration of affected hepatocytes. However, in rare cases, the drug causes nausea, dyspepsia, diarrhea, allergic reactions, the absorption of the drug in enterocytes is low, and high hepatobiliary circulation and excretion are detected, which significantly reduces the effectiveness of its action. Therefore, a search for new plant hepatoprotectors is underway. Promising in this regard are proanthacyanidins from Geranimum saxatile. Plants of the Geraniaceae family are widespread throughout the world. The main structural blocks of proanthocyanidins are (+) - catechin, (+) - gallocatechin, (-) - epicatechin and (-) epigallocatechin [A.Rauf., 2019]. According to the authors, di-, tri- and oligomeric proanthocyanidins may be simultaneously present in one plant, perform specific functions in plants, have a whole range of beneficial properties in mammals, have low toxicity and are considered as promising substances for the creation of medicines. In the literature there are reports of a number of its biological properties [A. Rauf., 2019]. Polymer proanthocyanidins (codenamed geranyl), allocated by the Institute of Plant Chemistry of Plant Substances (IHRV) of the Academy of Sciences of the Republic of Uzbekistan from the terrestrial part of the plant, have a molecular weight of 2000 to 70,000 D [Siddikov DR, 2013]. The antihypoxic and antioxidant properties of the isolated compounds have been established [Norbutaeva D.A, 2011; Norbutaeva D.A., 2012]. Thus, the object of this study was a new proanthocyanidin geranil isolated from the aerial part of the Geranimum saxatile plant. The development, study of the mechanism of their hepatoprotective action will not only expand effective domestic hepatoprotectors, but also introduce them into clinical practice.

Objective: to experimentally substantiate the feasibility of using geranil as a hepatoprotector in chronic alcohol intoxication.

1. Material and Methods

1.1. Research material.

To study the effect of herbal preparations on the liver under the conditions of its experimental alcoholic damage, carsil and geranyl were chosen. Carsil - isolated from the fruits of milk thistle (equivalent of silymarin), produced by the Bulgarian pharmacological company AO Sopharma. The drug is indicated for use in case of impaired liver function. Geranyl is isolated from the aerial part of the Geranium saxatile plant by employees of the Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan et al., 2013.]. The authors studied its chemical composition and identified gallic ($C_7H_6O_5$ - 3,4,5-trihydroxybenzoic acid), ellagic ($C_{14}H_6O_8$-dilactonehexahydroxydiphenic acid or 2,3,7,8-tetrahydroxy [1] benzopyrano [5,4,3-cde] [1] benzopyran-5,10-dione) and quercetin-3-O-glucoside ($C_{21}H_{20}O_{12}$ - 5,7,3 ′, 4′-tetrahydroxyflavon-3-O-glucoside).



gallic acid **ellagic acid** **quercetin-3-O-glucoside**

1.2. Design of experimental research.

In the experiment, 60 white outbred male rats weighing 180-220 g were used, which are on the standard diet of the central vivarium of the Central Scientific Research Laboratory at the Tashkent Medical Academy (50 experimental, 10 intact). All experiments conducted on animals were carried out in accordance with World Health Organization (WHO) recommendations for working with experimental animals, as well as safety precautions. Chronic alcohol intoxication in 50 rats was modeled by intragastric administration of 25% ethanol at a dose of 10 ml / kg for 28 days daily [Lieber CS., 1994]. In the early days of the experiment, the animals were excited, very active, and ate a large amount of food. On the 14-28th day of the experiment, the behavior of animals changed significantly, adynamia appeared, aggressiveness, which was often replaced by apathy, the hair of animals was ruffled, acquired a yellowish color, the appearance of some manifestations of hemorrhages was noted. By the end of 21 days, out of 50 animals, 2 (4%) died. An autopsy revealed visually pronounced changes in the liver in the form of atrophy, small-scale hemorrhages, and a small volume of fluid in the abdominal cavity. The surviving 48 experimental animals in accordance with the experimental design were divided into 3 groups: 2nd group (control) - 16 rats with a simulation of alcohol damage + 5 ml / kg of body weight H_2O intragastrically for 7 days; 3rd group (main) - 16 rats with a simulation of alcohol damage + geranyl at a dose of 100 mg / kg of weight also intragastrically for 7 days; 4th group (comparison group) - 16 rats with a simulation of alcohol damage + Carsil also at a dose of 100 mg / kg body

weight intragastrically for 7 days. Group 1 (intact) consisted of 10 rats not receiving ethanol and drugs. On the 28th day, 24 hours after the final injection of drugs, an etaminal sleep test was performed in all animals to evaluate the detoxifying function of the liver. The animals were injected subcutaneously with sodium etaminal at a dose of 40 mg / kg and the lateral position (sleep duration, min) was evaluated [Mavlanov Sh.R., 2016]. Rat euthanasia was performed after 14 hours of fasting with free access to water, in the morning, in accordance with existing documents and laws governing the use of laboratory animals in experimental studies in a cold room (0- + 2 ° C) under light ether anesthesia. Immediately after decapitation, blood was collected from animals.

1.3 Determination of the liver mass index.

To determine the liver mass index, animals of each group were weighed before and after the experiment, and liver mass was determined during slaughter. The liver mass index was determined by the formula [Z. Cai et al., 2018].

Liver mass index (%) = liver mass (g) / animal weight (g) * 100

1.4 Determination of biochemical blood parameters.

The content of bilirubin (μmol), cholesterol (mg / dl), glucose (mmol / l), total protein (g / l), albumin (g / l), globulins (g / l), their ratio were determined in blood serum; enzyme activity (U / L) alanine aminotransferase (Alt), aspartate aminotransferase (AcT), γ-glutamyl transferase (γ-GGT), alkaline phosphatase (alkaline phosphatase) on a biochemical automatic analyzer MINDRAYBA-88A (China) using commercial reagent firms from CYPRESS Diagnostics (Belgium).

Determination of malondialdehyde content.

The content of malondialdehyde (MDA) in the blood plasma of experimental animals was determined by the method of L.I. Andreeva et al. [Andreeva, 1988], based on the interaction of thiobarbituric acid with MDA, resulting from the oxidation of unsaturated fatty acids having 2-3 diene bonds. The optical density of the upper phase is measured at a wavelength of 535 nm against butanol on an SF-46 spectrophotometer. The content of products reacting with thiobarbituric acid was calculated taking into account the molar extinction of MDA equal to 1.56-106 mol cm-1 and expressed in micromol/l.

1.5. Statistical methods.

For statistical processing of the results, Exell and OriginPro7.5 software packages (OriginLab Corporation, USA) were used. The significance of differences between the indices of the control and experimental groups was determined by the student coefficient method (t), the significance of differences by the indicator P. At a significance level of P <0.05, the differences were taken as statistically significant.

2. RESULTS AND DISCUSSION

2.1 Geranil effect on animal liver index

Studies have shown that when exposed to ethanol, a decrease in body weight of animals by 40.83 ± 5.8 g relative to the initial mass was noted, while in intact rats an increase of this indicator by 38.7 ± 1.85 g was revealed. Moreover, the liver mass index in experimental animals it was 3.44 ± 0.45% with the value of this indicator in intact rats 2.70 ± 0.07%, which, apparently, was associated with edema of the liver parenchyma. Pharmacotherapy with proanthacyanidins and carsilum contributed to a slight increase in animal body weight relative to the indices of the untreated animal group, since the decrease in the initial body weight of rats was 24.00 ± 3.21 and 23.3 ± 8.67 g, respectively, of the preparations. At the same time, the liver mass index decreased slightly, amounting to 3.03 ± 0.12% and 3.17 ± 0.1%, respectively, of the above drugs, indicating a decrease in the phenomena of edema in the liver. Therefore, it can be said that the drugs we used reduced inflammatory processes in the liver of rats with alcohol intoxication.

Table 1

Changes in body weight and hepatic index in the pharmacotherapy of chronic ethanol poisoning

Experimental groups	Starting weight (g)	Last weight (g)	Difference between weights	Liver weight (g)	Liver index (%)
Group I	178,67±7,26	217,33±7,59	38,67±,861	5,895±0,33	2,70±0,07
Group II	235,33±10,15	194,50±14,42	-40,8±5,80	6,498±0,32	3,41±0,25 P_1<0,05
Group III	227,50±11,76	203,50±8,95	-24±3,21	6,13±0,18	3,03±0,12 P_1<0,01 P_2>0,05
Group IV	202,17±10,66	180,17±8,22	-23,3±8,68	5,688±0,15	3,17±0,09 P_1<0,01 P_2>0,05

Explanation: P1 is reliance on intact, P2 is reliability for untreated group.

2.2 The action of geranil on the metabolism of carbohydrates, lipids and proteins

Chronic poisoning with ethanol leads to a change in the metabolism of carbohydrates, lipids, proteins and other nitrogen-containing compounds. In our experiments, this is manifested by the development of hypoglycemia, hypercholesterolemia, hypoalbuminemia (Fig. 1). As can be seen from the above data, with alcohol intoxication (group 2) in the blood serum, the glucose content significantly decreased 1.5 times (P1 <0.001), cholesterol increased 1.24 times (P1 <0.001), and the albumin content a decrease in 1.44 times (P1 <0.001) relative to the indices of the intact group of rats.

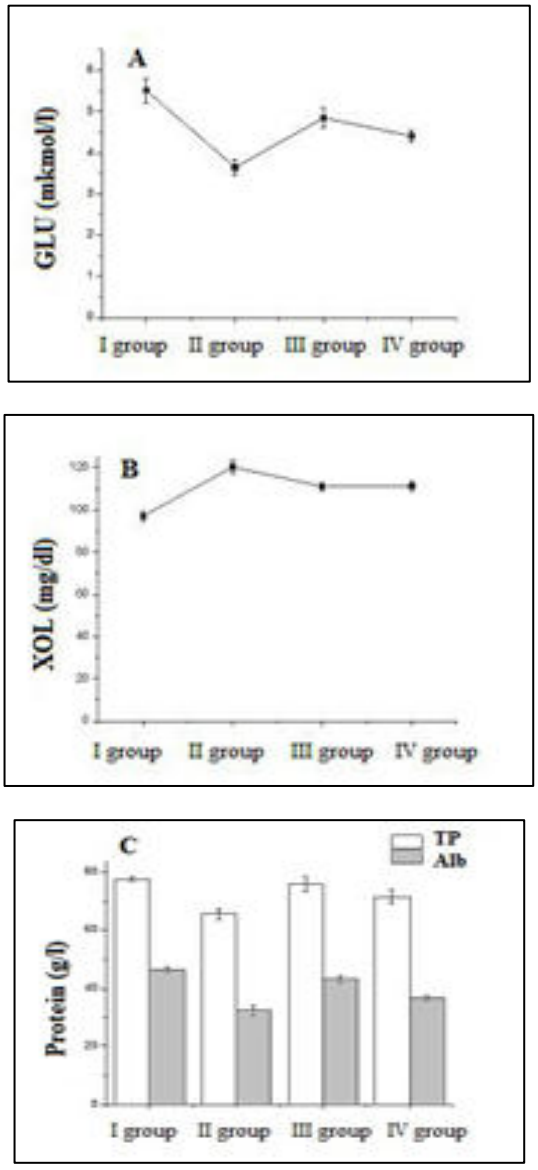
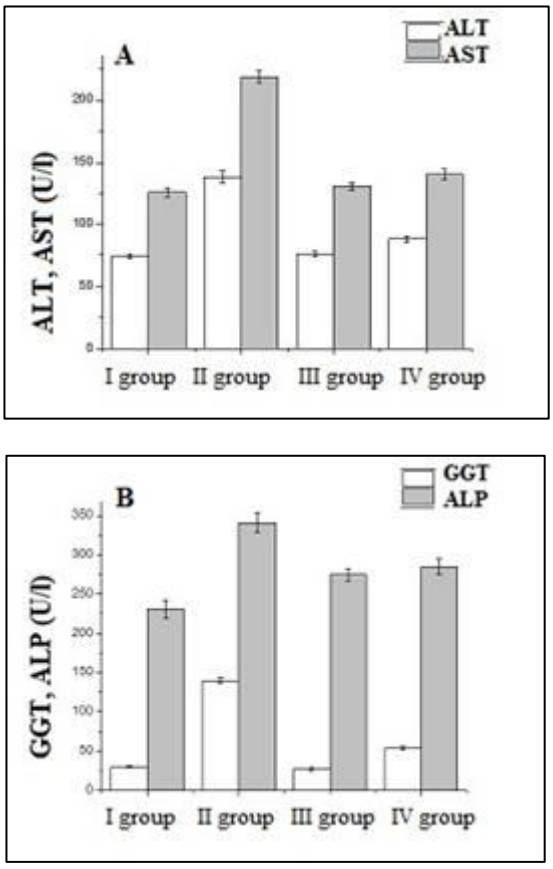


***Fig. 1**. The content of glucose (a), total cholesterol (b), total protein and albumin (c) in the blood serum of experimental animals with chronic ethanol intoxication and with the use of hepatoprotectors.*

Pharmacoteria by geranil (group 3) and carsil (group 4) of chronic toxic liver damage with ethanol led to a significant increase in low glucose levels of 1.33 (P2 <0.001) and 1.21 times (P2 <0.01), albumin 1.34 (P2 <0.001) and 1.13 times (P2 <0.05) and a decrease in high cholesterol concentrations of 7.5% and 6% (P2 <0.05) in blood serum relative to the values of the intact group of rats, indicating an improvement in the functional and metabolic parameters of hepatocytes. However, we did not observe their full restoration of the above indicators.

2.3 The effect of geranil on enzyme activity

Our studies showed that prolonged administration of ethanol leads to a violation of the integrity of the hepatocyte membranes, manifested by an increase in blood serum ALT by 1.86 times (P1 <0.001) and AST by 1.73 times (P1 <0.001) relative to the values of intact rats, respectively (Fig. 2a). The activity of GGT in rat blood serum with the introduction of ethanol significantly increased 4.67 times (P1 <0.001), the activity of alkaline phosphatase - 1.48 times (P1 <0.001) relative to the values of intact rats (Fig. 2b).



A B

***Fig. 2**. The activity of aminotransferases (a), GGT and alkaline phosphatase (b) in the blood serum of experimental animals with chronic ethanol intoxication and with the use of hepatoprotectors.*

Pharmacotherapy of chronic alcoholic liver damage with hepatoprotector geranil (group 3) and carsil (group 4) within 7 days significantly reduced high ALT and AST values: when using geranil, 1.83 and 1.67 times (P2 <0.001) when using carzil 1.58 and 1.55 times (P2 <0.001), relative to the values of the untreated group of animals. With the use of geranil, high GGT activity decreased by 5.18 times (P2 <0.001) and alkaline phosphatase - by 1.24 times (P2 <0.001), carzil - by 2.63 (P2 <0.001) and 1.2 (P2 < 0.01) times, relative to indicators of an untreated group of animals. As can be seen from the above data, both drugs reduced hyperfermentemia, however, this was more pronounced when using geranil. So, if with the use of geranil we observed the achievement of intact rats, then with the use of carcil they slightly exceeded them.

2.4 The effect of geranium on pigment metabolism.

In lower experiments, animals with alcohol intoxication showed hyperbilirubinemia (a 2.66-fold increase (P1 <0.001) relative to the values of intact rats (Fig. 3). It was mainly associated with a sharp increase in the level of

direct bilirubin (8.1 times, P1 <0.001), since the content of indirect bilirubin in the blood serum of experimental animals increased only 1.43 times (P1 <0.001) relative to the values of the intact group of rats. Pharmacological correction of geranil contributed to a decrease in the content of total, direct and indirect bilirubin by 2.19 (P2 <0.001); 4.45 (P2 <0.001) and 1.33 (P2 <0.001) times; carsilum - 2.11 (P2 <0.001); 4.42 (P2 <0.001) and 1.26 (P2 < 0.001) times, respectively, relative to the indices of the untreated group. The effectiveness of the above drugs did not differ significantly. If the content of indirect bilirubin approached the values of intact rats, then the level of direct and total bilirubin was significantly higher.

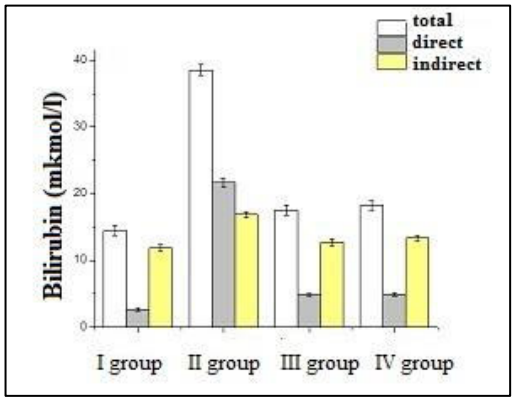


Fig. 3. *The content of total, direct and indirect bilirubin in the blood serum of experimental animals with chronic ethanol intoxication and with the use of hepatoprotectors.*

2.5 The effect of geranil on detoxifying liver function.

One of the tests that allow in the experiment to study the detoxifying function of the liver is a test for the duration of action of sleeping pills. For this, we used sodium ethaminal, metabolized in the liver with the participation of the cytochrome P450-dependent monooxygenase system. The studies showed an extension of the duration of etaminal anesthesia by 2.24 times (P1 <0.001), indicating a slowdown in the metabolism of this xenobiotic and an increase in its toxic effect on the body of experimental animals (Fig. 4).

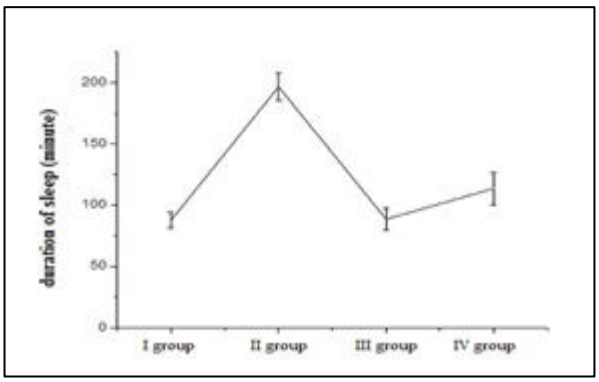


Fig. 4*. The duration of etaminal anesthesia (a) in experimental animals with chronic ethanol intoxication and with the use of hepatoprotectors.*

Experimental therapy of chronic alcoholic liver damage with geranil and Carsil significantly improved the detoxifying function of the liver, which showed a shortening of the duration of etaminal anesthesia by 2.22 (P2 <0.001) and 1.73 (P2 <0.001) times relative to the values of the untreated group of animals. In this case, the action of geranil was more pronounced, since the studied parameter approached the values of intact rats (P1> 0.05), while when using carzil we observed an excess of intact rats by 1.3 times (P1> 0.05).

2.6 The action of geranil on lipid peroxidation processes.

We determined the content of the lipid peroxidation - MDA product in the blood serum of rats with chronic ethanol intoxication. The studies showed a statistically significant increase of 2.49 times (P1 <0.001) in the content of MDA relative to indicators of intact rats (Fig. 5). Pharmacotherapy of chronic alcoholic liver damage with geranil (group 3) and carsil (group 4) significantly slowed lipid peroxidation processes, contributing to a decrease in blood serum MDA levels of 1.83 (P2 <0.001) and 1.57 (P2 <0.001) times relative to indicators of an untreated group of animals. However, it should be said that the MDA level still remained higher than the values of intact rats (exceeding 1.37 (P1 <0.001) and 1.59 (P1 <0.001) times), especially in the group treated with carlsyl. The data obtained indicate the presence of antioxidant properties of the compounds used, especially geranyl.

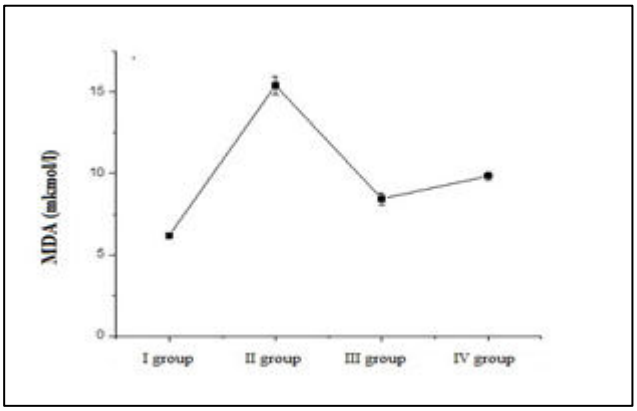


Fig. 5*. The content of MDA in the blood serum of experimental animals with chronic ethanol intoxication and with the use of hepatoprotectors.*

3 DISCUSSION

As can be seen from the above data, with alcohol intoxication, a significant decrease in body weight and an increase in the liver mass index of experimental animals were revealed. Therefore, chronic alcohol intoxication leads to the development of edema and inflammatory processes in the liver of experimental animals. The changes revealed by us can be related: as a decrease in ATP synthesis due to structural disorders in the mitochondria of hepatocytes; and a decrease in the concentration of NADPH due to an increase in the metabolism of ethanol in the liver with the participation of the microsomal ethanol oxidizing system [Y.Y.Chang., 2017]. Along with this, due to a decrease in carnitine content, β-oxidation of fatty acids in mitochondria slows down, and the lack of synthesis of apoB-100 protein contributes to the disruption of the formation of very low density lipoproteins and slows down the excretion of

endogenous triacylglycerides from the liver. Together, these changes lead to the development of steatohepatosis, which is confirmed in studies [Z.Cai., 2018; Y.Y.Chang., 2017]. Experimental pharmacotherapy of alcoholic liver damage with hepatoprotectors Carsil and Geranyl leads to positive changes in body weight and liver mass index, indicating a decrease in inflammatory processes, inhibit the development of steatohepatosis and liver edema. The main syndromes forming the laboratory diagnosis of the disease include the following syndromes: cytolysis, intracellular, intrahepatic and extrahepatic cholestasis, toxic damage to hepatocytes, insufficiency of synthetic processes in hepatocytes, slow inactivation of toxic compounds and inflammatory. In our experiments, hypoglycemia was observed due to inhibition of gluconeogenesis; hypercholesterolemia due to inhibition of transport forms of lipoproteins; hypoproteinemia, associated mainly with a violation of the synthesis of albumin in hepatocytes, due to insufficient synthetic functions of the liver. It is known that the liver is involved in the metabolism of lipoproteins [Ch. Li et al., 2017; X.X. Li., 2018, Y. Guo., 2017, Arafa A.F.; 2019], therefore, ethanol intoxication leads to the development of dyslipidemia. Another manifestation of liver damage under the influence of ethanol is a violation of the synthesis of hepatocytes of transport proteins, blood coagulation proteins, cholinesterase activity, etc. A classic indicator of this syndrome is a decrease in the content of total protein and its albumin fraction in liver lesions due to a decrease in the synthetic function of hepatocytes. This is manifested by a slowdown in the synthesis of albumin in the liver and hypoalbuminemia, the development of hypoglycemia, due to a slowdown in gluconeogenesis, an increase in total cholesterol, due to a decrease in its esterification, conversion to primary bile acids and excretion. Pharmacotherapy with geranil and Carsil, restoring the structural and metabolic parameters of hepatocytes, contributed to the improvement of the synthetic functions of hepatocytes, which was manifested in our experiments by an increase in the content of albumin, total protein, glucose and a decrease in cholesterol in the blood serum of experimental animals. The pathophysiological basis of cytolysis syndrome is a violation of the integrity of the plasma membrane of hepatocytes and their organelles with the development of hyperfermentemia. The increase in enzyme activity revealed by us in the experiment indicates hepatocellular damage to hepatocytes with the destruction of all its membrane structures, which is typical for alcoholic liver damage, and is associated with the toxic effect of acetaldehyde, which is formed in large quantities in the hepatocyte mitochondria and damages the functioning of these organelles [Gan D., 2012; Huang Y.S., 2011; J.B. Whitfield., 2018, A.Chabenno., 2014, Ch.Zhao., 2019]. This is confirmed by high AST values, since there are both cytoplasmic and mitochondrial isoforms of this enzyme, and a more pronounced increase in the mitochondrial isoform of the enzyme is characteristic of alcoholic steatohepatosis. Developing edema in the liver, an increase in the size of hepatocytes leads to compression of the bile ducts between the lobules of the liver and damage to the epithelium of the bile ducts, and the development of intracellular cholestasis. This is manifested in our experiment by an increase in blood activity of alkaline phosphatase and, especially, GGT, which are excretory enzymes. High GGT activity coincided with a sharp increase in direct bilirubin, an increase in cholesterol, indicating the development of intrahepatic cholestasis. Our data coincide with the literature, indicating that toxic liver damage is characterized by a marked increase in serum GGT activity without a significant increase in alkaline phosphatase activity [Tkachuk V.A. 2004; R. Yawalkar., 2018; I.Shukla., 2017]. The sharp increase in direct bilirubin observed by us is apparently associated with cytolysis of hepatocytes. At the same time, the content of indirect bilirubin in the blood serum of experimental animals increased to a lesser extent and, in our opinion, was associated with a slowdown in the capture of indirect bilirubin from the blood due to a violation of the absorption capacity of the liver. In rats with chronic alcohol intoxication, hepatocyte toxicity syndrome develops due to impaired mitochondrial function. In this case, a violation of ATP synthesis has a negative effect on the detoxification of endobiotics: neutralization of ammonia, hormones, and metabolic products of microorganisms in the intestine, causing poisoning of the body. Along with this, the neutralization of xenobiotics is observed, by the inhibition of their hydroxylation in the microsomal apparatus of hepatocytes. Apparently, this was due to the prolongation of the duration of etaminal anesthesia observed in our experiments more than 2 times relative to the values of intact rats. The mechanism of the toxic action of acetaldehyde is associated with its activating effect of lipid peroxidation, which leads to a violation of the structural and functional parameters of biological membranes, in particular hepatocytes [I.Shukla., 2017; M-Ch. Huang., 2009]. To clarify this issue, we determined an increase in the content of the lipid peroxidation - MDA product in the blood serum of rats with chronic ethanol intoxication. This leads to an increase in the permeability of cell membranes and a violation of the structural and functional parameters of hepatocytes. Analyzing the results, it should be said that in chronic alcoholic liver damage, the leading role belongs to acetaldehyde, which is formed in large quantities in the liver [Ch.Zhao., 2019]. This metabolite is a chemically active molecule capable of binding to macromolecules: albumin, hemoglobin, tubulin, actin, and other compounds with the formation of their acetyl derivatives. The latter are able to persist in the liver for a long time. The connection of acetaldehyde with cytoskeleton proteins leads to irreversible cellular damage, disrupting protein secretion and contributing to the formation of hepatocyte balloon dystrophy and edema, which leads to the development of intrahepatic cholestasis, manifested by the release of GGT and alkaline phosphatase. The following main effects can be distinguished in the mechanism of hepatocyte damage under the influence of ethanol: 1) increased lipid peroxidation causes damage to cell membranes, leading to an increase in their permeability, which was manifested by an increase in ALT and AST activity, hyperbilirubinemia, mainly due to direct bilirubin. An increase in the permeability of cell membranes causes a violation of transmembrane transport, the functioning of cell receptors and membrane-bound enzymes. 2) Chronic alcohol consumption reduces the activity of mitochondrial enzymes, leads to dissociation of oxidation and phosphorylation, which is accompanied by a decrease in ATP synthesis. Along with this, the oxidation of fatty acids, the synthesis of

phospholipids and the esterification of cholesterol, necessary for building cell membranes, are caused to a certain extent by the accumulation of lipid peroxidation products in lipoproteins, and the subsequent disruption of the distribution of cholesterol in lipoprotein particles, as well as disruption of the interaction of lipoproteins with cell receptors and inhibition of the process removing cholesterol from the body. This leads to the accumulation of fatty acids and increased synthesis of triacylglycerides, leading to fatty degeneration of the liver. 3) Suppression of DNA repairs in cells and activation of apoptosis due to the release of cytochrome c from mitochondria and immune-mediated mechanisms [M. Motaghinejad., 2017]. 4) Activation of the complement system and stimulation of superoxide production by neutrophils, further intensifying lipid peroxidation. In total, a vicious circle is created, leading to the aggravation of pathological damage to hepatocytes, the development of fatty degeneration and cirrhosis of the liver. In this regard, the breakdown of the vicious circle will allow preserving the structural and functional parameters of hepatocytes, protecting the liver from further destruction. Therefore, it was of interest in a comparative aspect to evaluate the effectiveness of the new drug geranil and the known drug carsil in the correction of identified violations. According to the literature, the leaders in the treatment of liver diseases are bioflavonoid drugs, in particular, containing silymarin (legalon, silymarin, carsil, silibor, etc.) as the main active ingredient [N. Kumaretal., 2019]. The carsil comparison drug we used was created on the basis of silymarin obtained from spotted milk thistle (Silybimariani). The hepatoprotective effect of silymarin is due to its antioxidant, membrane-stabilizing and stimulating repair potential of liver cells properties. The compounds that make up Geranil are also isolated from other plants and have been fairly well studied by scientists from far abroad, and neuroprotective properties have been established [L. Pogacnik., 2016]. In particular, quercetin belongs to flavonoids, reduces the neurotoxic ethanol, glutamate, regulates the secretion of neurotransmitters [L. Pogacnik., 2016], has an antioxidant, anti-inflammatory effect [N. Suganthy., 2016]. Gallic acid was isolated from some plants, antioxidant, neuroprotective properties were established [Akinrinde A.S., 2019; S.F. Nabavi., 2018]. Proanthocyanidins have a wide range of health benefits: antioxidant, antitumor, and immunostimulating properties, prevent platelet aggregation, and stabilize vascular endothelium [A.Rauf., 2019]. The above data allow us to state that geranyl prevents the development of cytolysis, cholestasis, mesenchymal inflammation and liver cell deficiency syndromes, improves the hepatocyte synthetic function, has antioxidant properties in rats with ethanol intoxication, and is superior to the known hepatoprotector carsil in its hepatoprotective activity. The presence of pronounced antioxidant properties is due to the presence in their composition of components that inhibit or reduce the intensity of free radical oxidation processes.

Study transparency
The study did not have sponsorship. Authors are solely responsible for submitting the final version of the manuscript to print.

Declaration of financial and other relationships
All authors took part in developing the concept of the article and writing the manuscript. The final version of the manuscript was approved by all authors. The authors did not receive an article fee.

Conflict of interest
Authors declare no conflict of interest.

4 CONCLUSION

Thus, the results of the study showed the development of structural and functional disorders of hepatocytes under the influence of ethanol and its metabolic products, leading to the development of cytolysis syndromes, intracellular, intrahepatic and extrahepatic cholestasis, toxic damage to hepatocytes, insufficiency of synthetic processes in hepatocytes, slowing inactivation of toxic compounds and inflammation. Experimental pharmacotherapy with a new drug from the group of geranyl proanthacyanidins and bioflavonoids - carsilum - slows down the lipid peroxidation intensity, causing restoration of the structural and functional parameters of hepatocytes. Geranil turned out to be more effective in this regard.

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