

Study Of the Effect of New Phytin Compounds In Experimental Hepatitis

Mirzaakhmedova K.T.

Tashkent State Medical University, Uzbekistan

Mirzamaxmudova N.M.

Tashkent State Medical University, Uzbekistan

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Abstract: Alcoholic liver disease (ALD) remains one of the leading causes of chronic liver pathology worldwide and includes fatty degeneration, alcoholic hepatitis, and liver cirrhosis. The present study aimed to evaluate the hepatoprotective activity of the drug Fitin-S in an experimental model of alcoholic hepatitis induced by ethanol administration against the background of toxic liver injury caused by carbon tetrachloride (CCl₄). Experimental alcoholic hepatitis was modeled in rats by preliminary administration of 50% CCl₄ solution followed by intragastric administration of increasing doses of ethanol. After induction of liver injury, animals received hepatoprotective therapy with Essentiale (20 mg/kg) and Fitin-S at doses of 20 mg/kg and 50 mg/kg for 10 days. Biochemical and histopathological parameters were assessed using standard laboratory methods. The experimental model resulted in significant hepatocellular and cholestatic liver damage characterized by elevated ALT, AST, alkaline phosphatase, bilirubin, prolonged prothrombin time, decreased total protein levels, and severe fatty degeneration of hepatocytes. Treatment with Fitin-S significantly reduced cytolysis and cholestasis markers, improved protein-synthesizing and detoxification functions of the liver, normalized prothrombin time, and decreased the severity of fatty liver degeneration. The most pronounced therapeutic effect was observed at a dose of 20 mg/kg, demonstrating efficacy comparable to the reference hepatoprotector Essentiale. Histological findings confirmed the biochemical results, indicating substantial restoration of liver structure and function. The obtained data suggest that Fitin-S possesses significant hepatoprotective activity and may be considered a promising agent for the correction of alcoholic liver injury of mixed hepatocellular-cholestatic type.

Keywords: Alcoholic hepatitis, experimental modeling, hepatoprotectors, cytolysis, cholestasis.

Introduction: Alcoholic liver disease (ALD) is a group of various morphological forms of liver damage that occur with the consumption of hepatotoxic doses of alcohol and the resulting clinical manifestations. Three main forms of ALD are distinguished: fatty degeneration, alcoholic hepatitis, and cirrhosis of the liver. The prevalence of ALD can be judged by statistical data that reflect the average per capita annual alcohol consumption and the scale of medical consequences [1]. Alcoholic hepatitis (AH) is classified (K 70.1) as one of the forms of alcoholic liver disease (K70 according to ICD 10). According to WHO data, alcoholic liver disease develops in individuals consuming more than 8 liters of

alcohol per year (calculated as pure ethanol). A single intake of large doses of alcohol is more dangerous than the same total dose consumed over several days [2]. According to domestic clinical observations, alcoholic hepatitis is the cause of a significant number of work losses, patient disability, as well as liver cirrhosis and fatal complications [3,4]. Materials and methods of the study. Rectified ethyl alcohol was administered to rats with liver damage caused by the preliminary administration of a 50% solution of carbon tetrachloride CCl₄ in vegetable oil at a rate of 1 ml / kg of body weight, since it is known that hypertension can often develop against the background of hepatopathy

of non-alcoholic etiology. The surviving rats, on the 3rd day, were administered rectified ethyl alcohol in the form of 40% ethanol in doses of 7 g / kg for 3 days, 10 g / kg for 3 days once, after which, two days later, the duration of hypertension development in this case is 7 days [5]. The use of this scheme makes it possible to model the acute form of hypertension; however, it is impossible to differentiate liver pathology by severity with this experimental setup, since continued administration of ethanol in increasing doses after the formation of hypertension did not cause further aggravation of liver pathology. After cessation of alkalization, rats were administered the hepatoprotectors Essentiale at a dose of 20 mg/kg and Fitin-C at doses of 20 mg/kg and 50 mg/kg intramuscularly for 10 days. The animals were then euthanized, and material was collected for biochemical and pathomorphological parameters. Biochemical and pathomorphological parameters of hypertension were determined using standard methods [6].

Statistical analysis of the obtained results was performed using Student's t-test.

Results and discussion. Using a scheme for the formation of hypertension against the background of pre-induced liver pathology caused by the administration of CCl₄, it was found that the administration of CCl₄ led to the development of liver pathology in rats, characterized by the development of fatty degeneration of hepatocytes, hyperbilirubinemia, and activation of cholestasis (Table 1). Histological studies revealed the presence of moderate focal, large-droplet fatty degeneration of the liver. Subsequent administration of ethanol at doses of 7 and 10 g/kg to rats with underlying liver pathology resulted in the following changes: a dose-dependent increase in the degree of bile duct damage, as evidenced by a significant increase in the activity of cholestasis (AP) enzyme markers; a tendency toward an increased degree of cytolysis—an increase in transaminase and bilirubin activity; increased toxic liver dystrophy; and an increase in severe focal, large-droplet fatty liver degeneration.

Hepatoprotectors used in the model of ethanol-induced hypertension against the background of toxic liver damage (mixed-type hypertension). As alkalization progressed through intramuscular administration of increasing doses of ethanol, biochemical and histological parameters progressed in rats. As shown in Table 1, by the end of the alkalization period, an increase in the activity of enzymes characterizing the cytolysis process—ALT and AST—and ALP cholestasis, was observed. Hypercholesterolemia, which is characterized by increased cytolysis, was also observed. In clinical

practice, an increase in ALT and AST activity of less than 5 times the upper limit of normal is considered moderate, 5 to 10 times the upper limit of normal is considered moderate, and over 10 times the upper limit of normal is considered severe. This allows the pathology that developed by day 10 of the alkalization experiment to be classified as moderate hypertension.

As can be seen from the data presented in Table 1, administration of ethanol to control animals in the presence of CCl₄-induced liver pathology leads to damage to hepatocyte membranes, disrupts function, and is accompanied by an increase in the activity of the marker enzymes alanine and aspartate aminotransferases (cytolytic effect) by 23-98% and the cholestasis marker alkaline phosphatase by 64%.

Liver damage is of a mixed hepatocellular/cholestatic nature, as confirmed by the ALP/ALT ratio (R) of 1.22.

As can be seen from the data presented in Table 1, the duration of anesthesia in rats after intraperitoneal administration of hexenal in the control group increased from 48±4.1 minutes to 190±16.4 minutes, or 3.96 times. The bromsulfalein (BSF) test, which indicates the excretory and detoxifying function of the liver, increased from 2.2±0.21 to 7.8±0.51 in the control group. Total, direct, and indirect bilirubin levels increased by 2.2, 1.1, and 2.4 times, respectively, while the bilirubin glucuronidation coefficient decreased from 0.117 to 0.083, or 1.41 times, indicating a reduced ability of hepatocyte enzymes to catalyze conjugation reactions.

The effect of mixed hypertension on the protein-synthesizing function of the liver was assessed by total protein content, and the liver's involvement in procoagulant synthesis was assessed by prothrombin time in the plasma of control animals. As can be seen from the data presented in Table 1, protein content decreased from 95.1±3.9 to 59.0±1.6 g/L, or by 38%, and prothrombin time increased 3.8-fold, from 19.0±1.5 to 72.5±4.55 seconds, indicating low levels of procoagulants (VII IX X) in the blood plasma of control rats.

The mechanism of the pathogenic action of mixed-type hypertension is associated with the conversion of the cytochrome P-450-dependent monooxygenase system into free radicals and electrophilic intermediates that covalently bind the biomacromolecules of centrilobular hepatocytes. Treatment of animals with mixed hypertension with Fitin-C at doses of 20 and 50 mg/kg and the reference drug Essentiale at a dose of 20 mg/kg, administered intramuscularly for 10 days, reduced transaminase levels, respectively: ALT – by 1.98 and 2.1 times with Fitin-C; 2.3 times with Essentiale, compared to the control. The ratio of AST

and ALT indicators – the de Ritis coefficient (AST/ALT) – increased under the influence of Fitin-C at doses of 20 and 50 mg/kg from 1.4 (control) to 4.6 and 3.9, respectively, and to 3.3 with Essentiale, indicating a decrease in the severity of liver damage. In the intact group, it was 2.9. Average alkaline phosphatase levels in animals treated with Fitin-S at doses of 20 and 50 mg/kg and Essentiale at 20 mg/kg were 14-25% lower than in the control group and slightly higher than in intact animals (57 ± 3.5 , 59 ± 4.0 , and 52 ± 3.2 U/L, respectively; the norm is 47 ± 2.8 U/L).

The effect of Fitin-S on the liver's protein-synthesizing function was assessed by total protein content, and the liver's involvement in procoagulant synthesis was assessed by prothrombin time in the plasma of control animals. As can be seen from the data presented in Table 1, the protein content, compared to the control group of animals, increased with the administration of Essentiale to 75.0 ± 2.6 g/L, and with the drug "Fitin-S"

to 85.0 ± 2.6 and 75.0 ± 2.6 g/L, respectively.

Prothrombin time decreased with the administration of Essentiale from 72.5 ± 4.5 sec (control) to 22.0 ± 1.7 , and with the administration of the drug "Fitin-S" to 23.7 ± 1.8 and 21.25 ± 1.8 sec, respectively, indicating complete restoration of the synthesis of procoagulants in the liver of the experimental animals, with the norm being 19.0 ± 1.5 sec.

The results obtained, presented in Table 1, indicate that Fitin-S exerts a hepatoprotective effect on the overall condition of experimental animals with mixed hypertension. The most pronounced effect was observed at a dose of 20 mg/kg. Fitin-S's efficacy was comparable to that of the reference drug, Essentiale.

The biochemical analysis data are confirmed by the liver pathological studies presented in Table 2. These data indicate that administration of Essentiale and Fitin-S at doses of 20 and 50 mg/kg respectively reduces the severity of fatty degeneration.

Table 1

The effect of the drug "Fitin-S" and the comparison drug Essentiale on the parameters characterizing hepatocyte damage in mixed-type alcoholic hepatitis

Biochemical parameters	Intact	Control CCl ₄ + ethanol	Essentiale- 20	"Fitin-S" / dose mg/kg	
				20	50
Hexenal sleep, min.	$48 \pm 2,1$	$190 \pm 16,4$	$140 \pm 7,9$	$96 \pm 8,2$	$60 \pm 8,2$
Bromsulfalein test	$2,2 \pm 0,21$	$7,8 \pm 0,51$	$3,9 \pm 0,26$	$4,2 \pm 0,32$	$4,2 \pm 0,32$
Total bilirubin, mmol/L	$8,2 \pm 0,6$	$18 \pm 1,4$	$13,5 \pm 1,1$	$14,1 \pm 1,2$	$15,0 \pm 1,2$
Direct bilirubin, mmol/L	$1,4 \pm 0,10$	$1,5 \pm 0,13$	$1,65 \pm 0,14$	$2,2 \pm 0,16$	$1,9 \pm 0,14$
Bilirubin glucuronidation coefficient (direct/total)	0,117	0,083	0,122	0,156	0,126
Indirect bilirubin, mmol/L	$7,0 \pm 0,65$	$16,5 \pm 1,20$	$11,85 \pm 0,7$	$11,9 \pm 1,1$	$13,1 \pm 1,1$
Relative liver mass,	$27 \pm 2,3$	$38,6 \pm 2,8$	$42,3 \pm 2,2$	$31,0 \pm 1,8$	$29,0 \pm 1,8$
ALT, U/L	$32,0 \pm 3,1$	$63,3 \pm 3,9$	$27,5 \pm 1,8$	$32,0 \pm 2,1$	$30,0 \pm 2,1$
AST, U/L	$93,0 \pm 2,1$	$114,0 \pm 10,2$	$89,5 \pm 6,3$	$148 \pm 6,4$	$116 \pm 6,4$
De Ritis coefficient AST/ALT	2,9	1,8	3,3	4,6	3,9
Alkaline phosphatase, U/L	$47 \pm 2,8$	$77 \pm 4,6$	$52 \pm 3,2$	$57 \pm 3,5$	$59 \pm 4,1$
ALP/ALT	1,47	1,22	1,9	1,78	1,97
Total protein, g/L	$95,1 \pm 3,9$	$59,0 \pm 1,6$	$75,0 \pm 2,6$	$85,0 \pm 2,6$	$75,0 \pm 2,6$
Glucose, mmol/L	$4,1 \pm 0,22$	$6,27 \pm 0,44$	$6,5 \pm 0,36$	$4,05 \pm 0,32$	$4,05 \pm 0,32$
Prothrombin time, sec	$19,0 \pm 1,5$	$72,5 \pm 4,5$	$22,0 \pm 1,7$	$23,7 \pm 1,8$	$21,25 \pm 1,8$

Table 2

The effect of the drug "Fitin-S" and the comparison drug Essentiale on histological parameters in mixed-type alcoholic hepatitis

Experimental Groups, doses mg/kg	Severity of pathomorphological changes in points		
	Fatty degeneration	Sclerotic dystrophy	Inflammatory changes
Intact animals	0	0	0
Untreated animals	II-III	I	I

Treated with Essentiale - 20	I	I	I
Treated with Fitin-S - 20	I	I	1
Treated with Fitin-S - 50	I	I	I

Conclusions

Analyzing the results of the study, we can conclude that Fitin-S has a pronounced hepatoprotective effect in mixed alcoholic hepatitis when administered intramuscularly at doses of 20 and 50 mg/kg. The most effective dose was 20 mg/kg administered 10 times intramuscularly. The drug's efficacy was comparable to that of Essentiale.

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