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Efficiency of Gum Resin Ferula Asafetid in Correction of Disturbances of the Liver in Acute Paracetamol-Induced Hepatitis in Rats

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Abstract Acute toxic hepatitis induced by paracetamol (APIH) in adult white male rats 180-200 g., experimental therapy with gum-resin Ferula asafoetida (GRFA) at doses 50 mg/kg led to a clear elimination of reduced bile secretion, assessed by the intensity of exocrine liver function and the chemical composition of bile, in which bile secretion increased by 101.7%, quantity of bile acids by 46.6%), cholesterol by 54.6% and bilirubin by 56.1%. The doubling of the dose of the medicine (100 mg/kg) did not cause to increase the effect. The positive therapeutic effect of GRFA is also confirmed in the results of the study of "liver function tests" in blood serum. The medicine eliminated the phenomena of hypoproteinemia, hyperbilirubinemia, cytolytic and cholestatic syndromes in rats with acute drug-induced hepatitis. At the same time, GRFA surpasses the reference hepatoprotector - Legalon by its pharmacological activity.

Keywords Acute drug hepatitis, Paracetamol, Bile, Liver function tests

1. Introduction

Liver damage by the influence of various etiological factors is one of the most common pathologies of the hepatobiliary system. In order to restore the functional state of the liver, the substances using in practical medicine do not always satisfy clinicians [1]. In this regard, searching for and developing new compounds with a high therapeutic effect in liver pathology is an actual task of pharmacologists. Literature data indicate that even in highly developed countries, drugs with a hepatotoxic effect are taken without permission, without appropriate supervision of medical personnel [2,3].

Since the vast majority of drugs are eliminated by hepatocytes, an increase in the hepatotoxicity of drugs can be expected. Among the latter, paracetamol occupies one of the important places due to its different pharmacodynamic effect (antipyretic, analgesic) [4,5,6,7]. However, its metabolite N - acetyl - n - benzoquinone imine, which binds glutathione, exhibits hepatotoxic, nephrotoxic effects (necrosis of hepatocytes and renal tubules). At the same time, the drug is widely used in pediatric practice as an analgesic and antipyretic agent. In economically developed countries, such as the USA, Great Britain, paracetamol is the most common reason of acute liver failure [6,8,9].

The aim of this work was to study the effect of gum-resin Ferula asafoetida (GRFA) on the functional state of the liver in acute hepatitis induced by paracetamol in comparison with the well-known hepatoprotector Legalon. The functional state of the liver was judged by the intensity of the exocrine function of the liver, the chemical composition of bile and biochemical parameters of the blood ("liver tests").

2. Material and Methods

2.1. Experiments

The technology of obtaining gum-resin from plants Ferula asafetida L.. (GRFA) was described by us in previous studies [10,11].

The experiments were carried out on sexually mature male rats with an initial weight of 180-200 g. The maintenance of laboratory animals corresponded to the sanitary rules for the design, equipment and maintenance of experimental biological clinics. Feeding was carried out with natural and briquetted food, in accordance with the norms. After passing 14 days of quarantine, several groups of animals were formed, 6 animals in each, taking into account body weight.

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The experiments were carried out in accordance with the rules of a good laboratory practice (GLP) for preclinical research, as well as the rules and International Recommendations of the European Convention for the Protection of Vertebrate Animals used in Experimental Research (1986). The approval of Ethic Committee of Republic of Uzbekistan was taken before beginning of the experiment (protocol No 6/17-1579, 23/09/2021).

Acute drug-induced hepatitis was reproduced by intragastric administration of paracetamol at a dose of 1500 mg/kg once a day for two days [12]. One day after the last administration of paracetamol, experimental therapy was carried out for six days. For this, GRFA was administered at doses of 50 and 100 mg/kg, and Legalon - 100 mg/kg. 24 hours after the final administration of medicines, the bile excretion function of the liver was investigated by inserting a polyethylene catheter into the common bile duct of anesthetized animals (intraperitoneal administration of sodium ethaminal at a dose of 50 mg/kg) [13]. The choleric activity of various doses of GRFA and Legalon was judged by the total amount of excreted bile for 4 hours of the experiment, as well as by the concentration and amount of its components: bilirubin, cholesterol and bile acids [14,15]. In hourly portions, the concentration (mg%) and the total amount (mg per 100 g of body weight) of bile acids, cholesterol and bilirubin were determined [15,16].

In the second series of experiments, various biochemical markers characterizing liver function were determined in the blood according to the "Guidelines for conducting preclinical studies of drugs" [17]. Determination of the amount of total protein, albumin, total bilirubin, as well as the activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) in blood serum was carried out photometrically on a semi-automatic biochemical analyzer (China, 2014 Mindray) using kits from Human (Germany) and Cypress diagnostics (Belgium).

2.2. Statistical Analysis

The data obtained were processed by the method of variation statistics using the paired Student's test and one-way analysis of variance using the standard software package BIOSTAT 2009 with an assessment of the significance of indicators (Mean±Std error). Differences in the compared groups were considered significant at a significance level of 95% $p < 0.05$, in the case of $0.05 < p < 0.10$, the differences were assessed as a trend.

3. Results and Discussion

Paracetamol had a expressed hepatotoxic effect in the used dose in rats. So, the exocrine function of the liver was significantly reduced by more than two times under influence of paracetamol and there were an almost two times decreasing of quantity of chelates (by 41.1%), cholesterol (by 44.5%) and bilirubin (by 50.7%) in the excreted bile. These data confirm the results of our earlier studies [18].

Consequently, paracetamol caused a significant depression of the functional state of the liver in rats, which was assessed by the specific bile excretory function of liver (Table 1).

Experimental therapy with GRFA had a distinct therapeutic effect, which was manifested not only by the stimulation of bile secretion (by 101.7%), but also by the excretion of bile acids (by 46.6%), cholesterol (by 54.6%) and bilirubin (by 56.1%). %). The doubling of the dose of the medicine (100 mg/kg) did not cause to increase the effect. We observed a similar therapeutic effect in animals treated with Legalon, but the effect of the medicine was somewhat inferior then activity of GRFA, which was used in half-dose. The obtained results indicate some superiority of GRFA over Legalon.

Table 1. Study of the therapeutic effect of GRFA and Legalon on the bile excretory function of the liver and its biochemical composition in rats with acute paracetamol-induced hepatitis (Mean±Std error, n=6) (calculated for 100 g of body weight of rats for 4 hours of experiment)

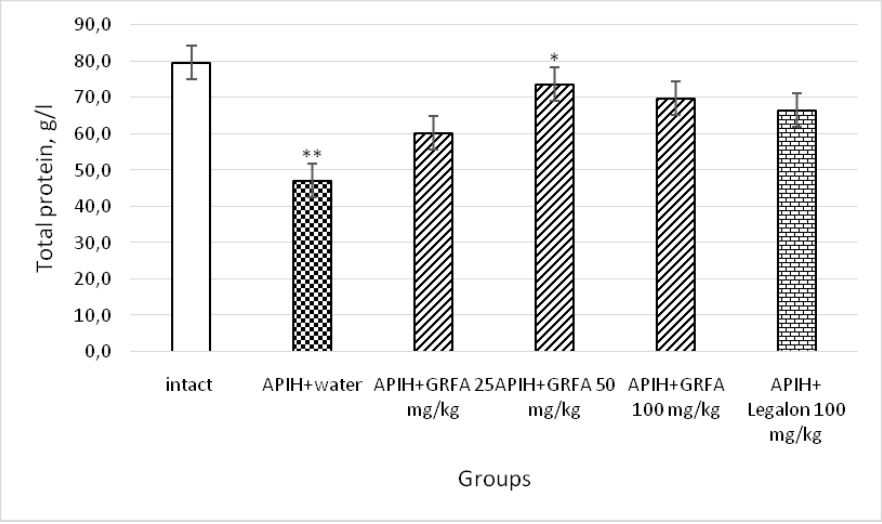
Indicators / Groups	Dose, mg/kg	Volume of bile, ml	Bile acids, mg	Cholesterol, mg	Bilirubin, mcg
Intact	-	1,31± 0,03	6,33 ± 0,44	0,254 ± 0,027	128,46 ± 15,96
APIH + water	-	0,58 ± 0,08	3,71 ± 0,36	0,141 ± 0,009	63,26 ± 6,07
P		<0,001	<0,01	<0,01	<0,02
APIH + GRFA	50	1,17± 0,08	5,44 ± 0,37	0,218± 0,016	98,77 ± 6,01
P		<0,05	<0,05	<0,05	<0,05
P_1		<0,01	>0,05	>0,01	>0,01
APIH + GRFA	100	1,08 ± 0,12	5,14 ± 0,44	0,192± 0,012	89,52 ± 8,63
P		>0,05	>0,05	>0,05	>0,05
P_1		<0,02	<0,05	<0,02	<0,05
APIH + Legalon	100	1,03 ± 0,14	5,19 ± 0,31	0,206 ± 0,014	84,15 ± 9,56
P		<0,05	>0,05	>0,05	<0,05
P_1		<0,05	<0,01	<0,01	<0,05

Note: P – statistically significant in comparison with intact group,
P_1 - statistically significant in comparison with untreated group.

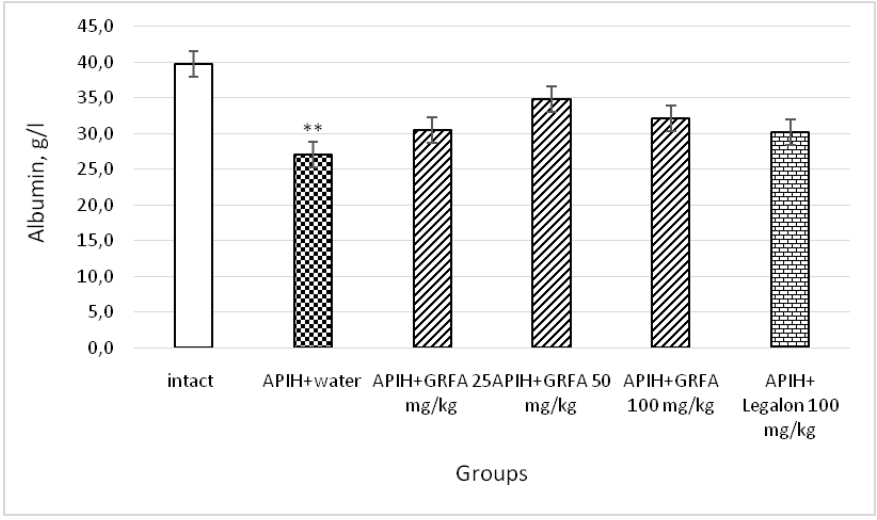
Table 2. Study of the therapeutic effect of GRFA and Legalon on some biochemical parameters of blood serum in rats with acute paracetamol-induced hepatitis (Mean ± Std error, n=6)

Indicators / Groups	Dose, mg/kg	ALT, U/l	AST, U/l	ALP, U/l	GGT, U/l
Intact	-	69,98 ± 5,92	96,70 ± 9,48	289,35 ± 19,47	3,83 ± 0,29
APIH + water	-	250,45 ± 19,73	288,51 ± 17,78	790,63 ± 52,25	6,67 ± 0,54
P		<0,001	<0,01	<0,001	<0,01
APIH + GRFA	50	91,21 ± 8,16	174,50 ± 10,44	422,63 ± 30,93	4,33 ± 0,48
P		<0,05	<0,01	<0,02	>0,05
P_1		<0,001	<0,001	<0,002	<0,05
APIH + GRFA	100	137,58 ± 12,62	270,60 ± 11,22	474,50 ± 40,27	4,83 ± 0,46
P		<0,01	<0,001	<0,01	>0,05
P_1		<0,01	<0,002	<0,01	<0,05
APIH + Legalon	100	129,16 ± 11,13	193,97 ± 9,63	465,05 ± 35,49	4,67 ± 0,41
P		<0,01	<0,001	<0,01	>0,05
P_1		<0,01	<0,001	<0,01	<0,05

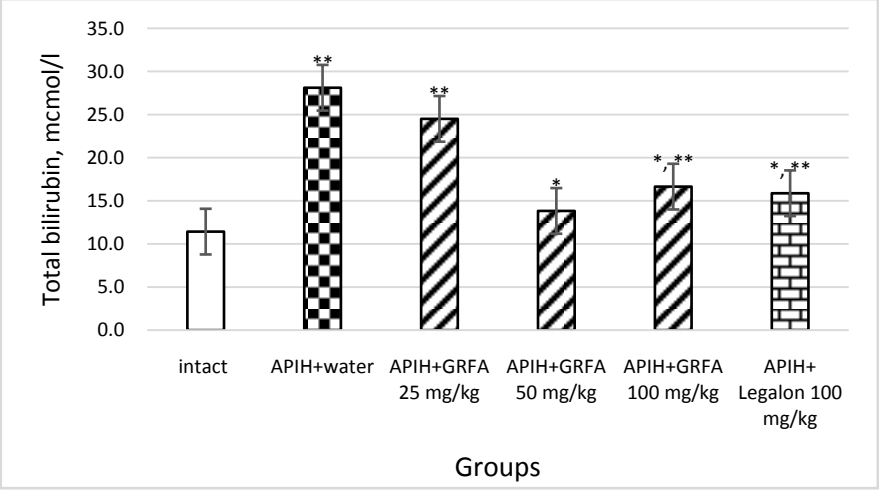
Note: P – statistically significant in comparison with intact group,
P_1 - statistically significant in comparison with untreated group.



Picture 1. Influence of GRFA and Legalon on the total protein content in blood serum in rats with acute paracetamol-induced hepatitis. * – statistically significant in comparison with control group, ** - statistically significant in comparison with intact group



Picture 2. Influence of GRFA and Legalon on the content of albumin in the blood serum of rats with acute paracetamol-induced hepatitis. * – statistically significant in comparison with control group, ** - statistically significant in comparison with intact group



Picture 3. Influence of GRFA and Legalon on the content of total bilirubin in blood serum in rats with acute paracetamol-induced hepatitis. * – statistically significant in comparison with control group, ** - statistically significant in comparison with intact group

Thus, significant disturbances of the exocrine function of the liver and the chemical composition of bile are clearly eliminated by the therapeutic use of GRFA in paracetamol-induced hepatitis.

Previously, we found that GRFA had a significant therapeutic effect on the functional state of the liver in carbon tetrachloride- and heliotrin-induced hepatitis [19,20]. The therapeutic effect of pharmacological agents in a clinical condition is assessed not only by an improvement of the patients' state and a decrease the patients' complaints, but also by the normalization of the biochemical parameters of blood, reflecting the degree of development of a number of syndromes in the pathology of the hepatobiliary system. A number of biochemical tests are used as an objective and reliable criterion for assessing the severity of pathology and the effectiveness of the carried out treatment in clinical practice, in [21]. Proceeding from this, we carried out biochemical studies for evaluating the activity of enzymes reflecting the functional state of the liver in a separate series of experiments. Thus, acute hepatitis induced by paracetamol in rats led to an increase in the activity of ALT and ASAT by 258.0 and 198.3%, respectively, which indicates a significant degree of development of cytolytic syndrome. Against this background, there was an increase in ALP activity by 173.2% and GGT by 74.1%, which reflected the development of cholestatic syndrome. Along with this, a decrease in the levels of total protein and albumin by 21.3% and 23.0%, respectively, was revealed, indicating the development of hypoproteinemia. These changes were accompanied by a significant increase in the content of total bilirubin by 223.4% in blood.

Thus, substantially development of cytolytic and cholestatic syndrome is noted in acute paracetamol-induced hepatitis, which is accompanied by hyperbilirubinemia and hypoproteinemia.

Analysis of the results of the experimental studies showed a distinct therapeutic effect of GRFA. Thus, the activity of ALT, AST, ALP, GGT in animals receiving GRFA at a dose of 50 mg/kg decreased compared with the untreated group by 63.4%, 67.6%, 46.5% and 35.1%, respectively. The positive effect of GRFA in the elimination of cytolytic and cholestatistical syndrome was clearly visible. At the same time, the studied dose of the drug 50 mg/kg was somewhat effective than 100 mg/kg. It is characteristic that the degree of changes in the noted parameters under the influence of Legalon did not significantly differ from the action of the medicine in a higher dose. Along with this, there was an increase in total protein by 22.7% and albumin by 27.3% in the treated animals with GRFA, especially at a dose of 50 mg/kg, which indicates the restoration of the protein-synthesizing function of hepatocytes. GRFA significantly eliminated the phenomenon of jaundice, so it decreased quantity of total bilirubin almost two times in the blood. A similar, but to a slightly lesser extent, we noted in the group of rats receiving GRFA and Legalon for therapeutic purposes at doses of 100 mg/kg.

Thus, experimental therapy of animals with the acute paracetamol-induced hepatitis by GRFA clearly eliminates the degree of cytolytic and cholestatic syndromes, hypoproteinemia and jaundice. At the same time, the medicine has some high activity compared to Legalon. The mechanism of the therapeutic action of GRFA is probably associated with followings that on the one hand, it has antioxidant properties [22,23,24], and on the other hand, the drug enhances the energy potential of hepatocytes [25], because the bile-forming function of the liver requires a large amount of energy consumption. Based on the results of this work, and also taking into account that GRFA is a low-toxic compound [26], it can be concluded that GRFA can be recommended as an effective therapeutic agent in the treatment of toxic hepatitis, including those drug- induced damage ones.

4. Conclusions

1. GRFA clearly enhances the exocrine function of the liver and the chemical composition of bile in rats with acute paracetamol- induced hepatitis.

2. The therapeutic effect of GRFA is also confirmed in the results of biochemical blood tests, which indicate the elimination of cytolytic and cholestatic syndromes.
3. Judging by the increase in the excretion of bilirubin in the composition of bile and the decrease in its concentration in the blood serum, it can be stated that the GRFA has a hypobilirubinemic effect.
4. GRFA, with therapeutic use, eliminates hyproproteinemia in rats with drug-induced hepatitis.

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