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Therapeutic Effects of the Pharmaceutical Product - Phenomenon at Experimental Liver Cirrhosis

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Abstract

Article provides results of investigation carried out on lad. Rats with CCl4-induced liver cirrhosis and treated with differend drugs (Phenomenon and S-ademethioninein). Treatment efficacy was evaluated according to the biochemical parameters: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Sodium phosphatase (ALP), total bilirubin (TBIL), Cholesterol, serum Creatinine (CREA), Blood glucose, superoxide dismutase (SOD) and morphology of liver tissue. Investigations showed that the better therapeutic effects were detected at treatment with phenomenon, especially at combination phenomenon+honey compared to the data of the animals treated with S-ademethionine. **Conclusion:** phenomenon reveals antioxidant, membrane-stabilizing, hepatoprotective properties, decreases lipid peroxidation, inhibits damage of hepatocytes, and improves liver functions in CCl4 induced liver cirrhosis in lab rats.

Key words: Phenomenon, liver cirrhosis, alanine aminotransferase, sodium phosphatase, Aspartate aminotransferase

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Introduction

Liver cirrhosis is a chronic and progressive disease, a global health concern with a high prevalence worldwide. Replacement of healthy liver tissue with fibrous tissue disrupts the normal function of the liver. As the disease progresses the liver's ability to perform detoxification, metabolism, and protein synthesis is severely compromised. The complications associated with liver cirrhosis, such as portal hypertension, ascites, hepatic encephalopathy, and increased risk of liver cancer, pose significant challenges in terms of treatment [1-4]. The primary goal of treatment is to slow down the progression of liver damage, manage complications, and improve the patient's quality of life. Despite advancements in medical research, the development of effective pharmacological therapies for liver cirrhosis has been limited. The treatment outcome depends on the individual's response and the extent of liver damage. Complete reversal of cirrhosis is currently not possible, and liver transplantation remains the only curative option for end-stage cirrhosis. While there are medications available to manage these complications, they may not provide complete resolution. Although, several clinical trials are underway to explore potential treatments targeting fibrosis, inflammation, and other pathways involved in the progression of cirrhosis, more research is needed to develop safe and efficacious therapies that could limit, or reverse liver fibrosis.

Coming from the aforesaid we were aimed to study therapeutic efficacy of the drug "Phenomenon" and S-ademethionine in case of CCl4-induced liver cirrhosis.

Objects and methods of research: Experiment was conducted on white male laboratory rats with a body weight 200-250 g. The conditions of keeping and caring for the animals corresponded to the internationally established norms and conditions (animals had free access to food and water). The research protocol was approved by the Ethics Committee of Animal Research of TSMU. After a week of adaptation, the animals randomly were divided into 5 study groups: Group I - healthy rats; Group II – control (rats with CCl4-induced liver cirrhosis, untreated); Group III - rats with CCl4-induced liver cirrhosis and treated with the S-ademethionine; Group IV - rats with CCl4-induced liver cirrhosis and treated with the drug Phenomenon; Group V - rats with CCl4-induced liver cirrhosis and treated with Phenomenon + honey.

10 animals were placed in each study group. For the disease modeling 0.1 ml of CCl4 was injected intraperitoneally into the research animals 2 times a week during 1 month. Treatment of the animals was started by the time, when liver cirrhosis was morphologically confirmed. In the group III rats, S-ademethionine (5 mg/kg) was injected intraperitoneally, once a day. In the group IV the Phenomenon (12 mg/kg) was administered orally once a day, and in the group V, Phenomenon diluted in 1.5 ml of honey was administered orally once a day. All study group animals were treated during 20 days. Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Sodium phosphatase (ALP), total bilirubin (TBIL), Direct bilirubin (DBIL), Cholesterol, Triglycerides, Creatinine (CREA), Blood glucose has been assessed by spectrophotocolorimetric method with a closed system fully automated device Roche cobas e111 and Antioxidant superoxide dismutase (SOD) were studied by ELISA method. For morphological investigation the liver samples were stained with Hematoxilin and Eosin. Factorial variance analysis (Factorial ANOVA) was used for data processing. Statistical software package SPSS was used for calculations and visualization of results.

Results: ALT, AST, ALP, TBIL, cholesterol and triglycerides are highly sensitive diagnostic markers of liver function and their elevated levels are reliable indicators of liver damage. By determining serum

creatinine we get information about protein synthesis in the liver and the state of kidney function. Superoxide dismutase is a natural antioxidant and decreased level indicatesthe lipid peroxidation [5-8].The results of biochemical investigations showed that in the group II animals (control, CCl4-induced liver cirrhosis) AST, ALT, ALP, TBIL, cholesterol and triglycerides were significantly increased while, serum creatinine and superoxide dismutase were decreased compared to the data of healthy rats.

According to the above-mentioned it is clear that hepatocytes in case of CCl4-induced liver cirrhosis are damaged by oxidative stress. Massive necrosis of hepatocytes and accompanied inflammatory processes alters/decreases the major functions of the liver. In particular, the detoxification functions of the liver, the metabolism of cholesterol, bilirubin and triglycerides are disordered, protein synthesis decreased, glycogen synthesis is inhibited and the level of glucose in the blood increased.

As a result of the treatment, the studied parameters were improved. In particular, the functional parameters of the liver (ALT, AST, ALP, TBIL), as well as serum creatinine and superoxide dismutase indicators were improved, which correlated with the results of the morphological study of the liver.

Statistical analysis of the data obtained after the treatment showed that better therapeutic effects were detected in case of treatment with Phenomenon,especially in case of combination Phenomenon+honey compared to the data of the animals treated with S-ademethionine). Phenomenon decreases lipid peroxidation, inhibits the damage of hepatocytes and improve liver functions.

Although the treatment with Phenomenon+honey showed the best therapeutic effect, one important fact must be mentioned. Namely, when treated with this regimen, higher levels of glucose were observed in the blood of animals compared to the control group animals. If we take into account that animals of the group V were constantly fed with honey-containing preparation for 20 days, the high glucose level is natural. With high probability, we assume that in case of treatment in clinic, the glucose level in humans will be maintained within the normal range. However, at treatment of patients with diabetes mellitus, it may have some effect on blood sugar levels. To overcome this problem, it is necessary to determine the optimal dose of dilution of phenomenon with honey.

Fig.1. Average values of AST and its 95% confidence interval in different research groups on the 10th and 20th day of treatment

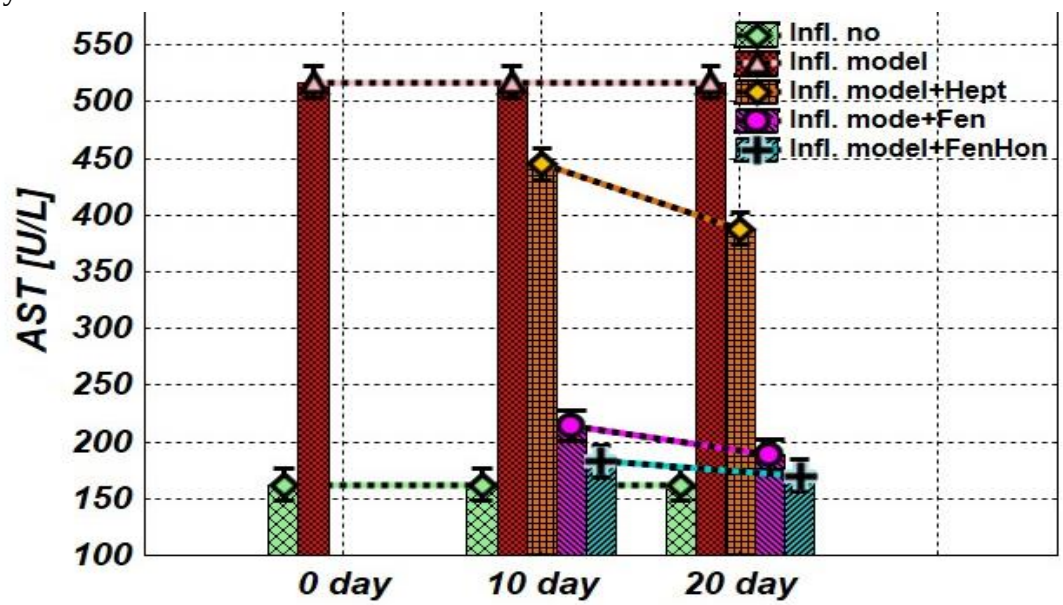


Fig.2. Mean values of ALT and its 95% confidence interval in different research groups on the 10th and 20th day of treatment

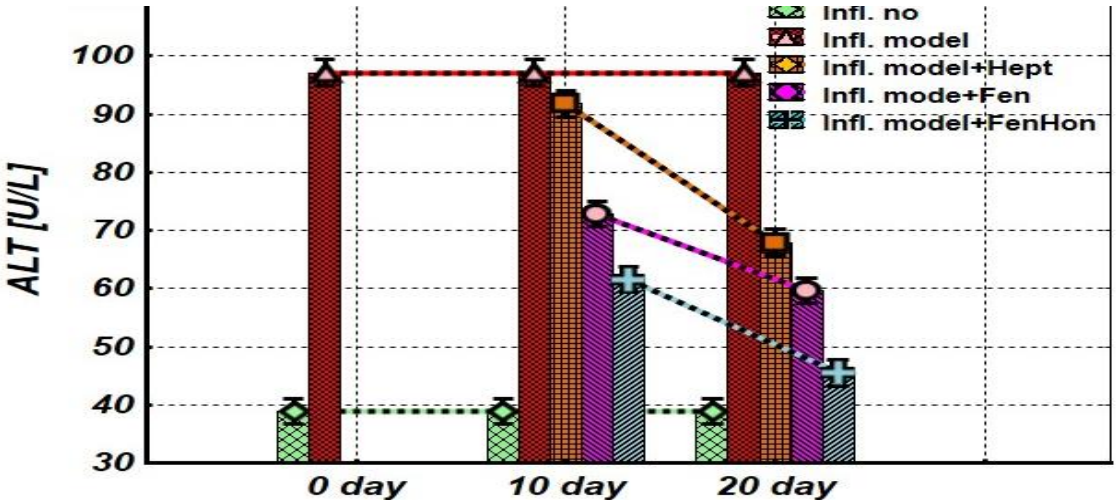


Fig.3. Average values of ALP and its 95% confidence interval in different research groups on the 10th and 20th day of treatment (Rhombus-healthy; triangle-model; square - model+S-Ademethionine - model+phenomenon, the cross - model+phenomenon+honey).

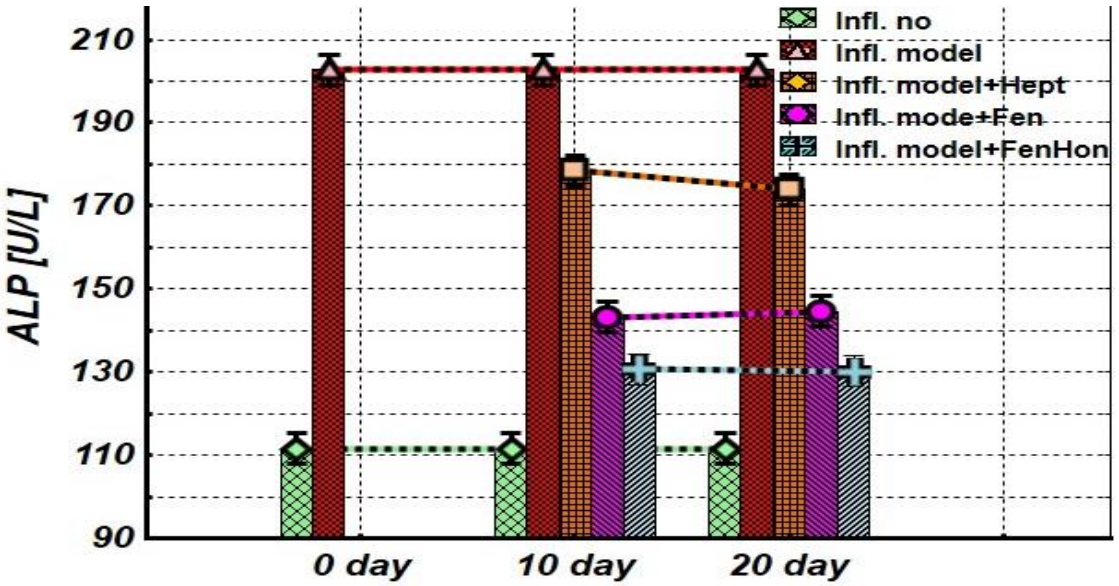


Fig.4. Mean values of CHOLESTEROL in different research groups and its 95% confidence interval, on the 10th and 20th day of treatment

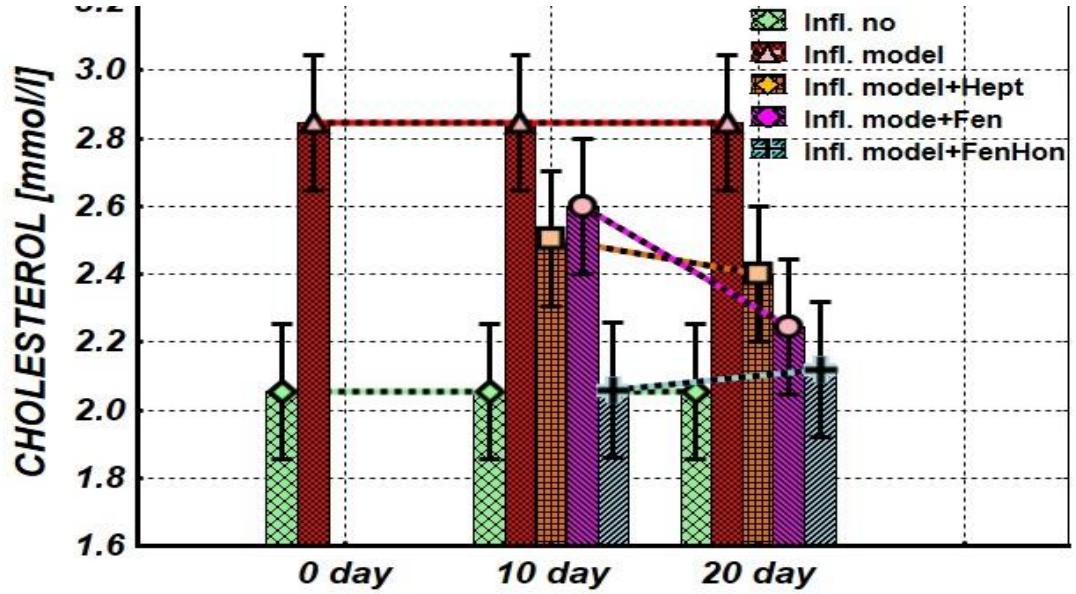


Fig. 5. Mean values of TRIGLYCERIDE and its 95% confidence interval in different research groups, on the 10th and 20th day of treatment

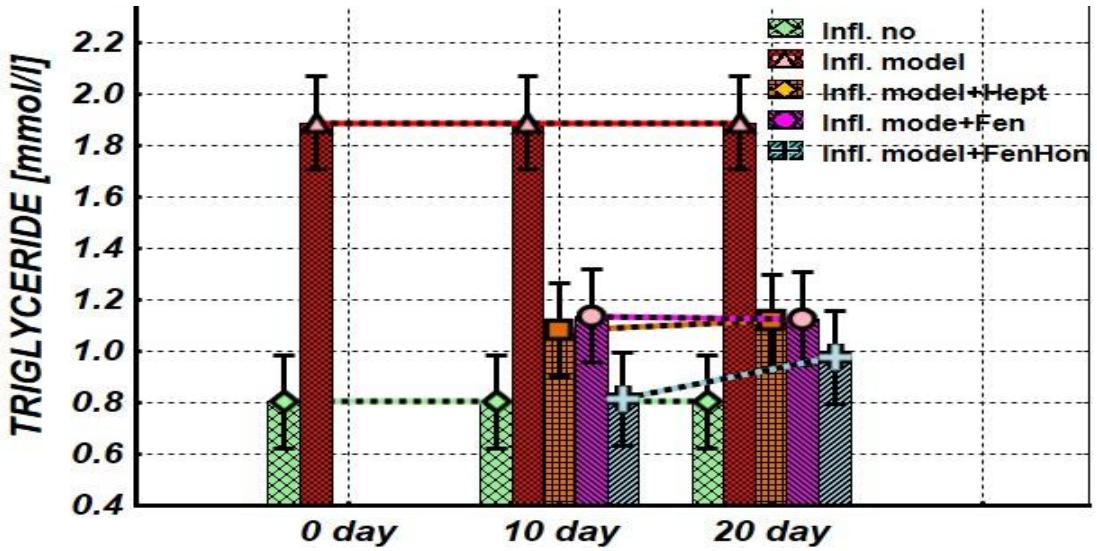


Fig.6. Average values of SOD in different research groups and its 95% confidential interval, on the 10th and 20th day of treatment

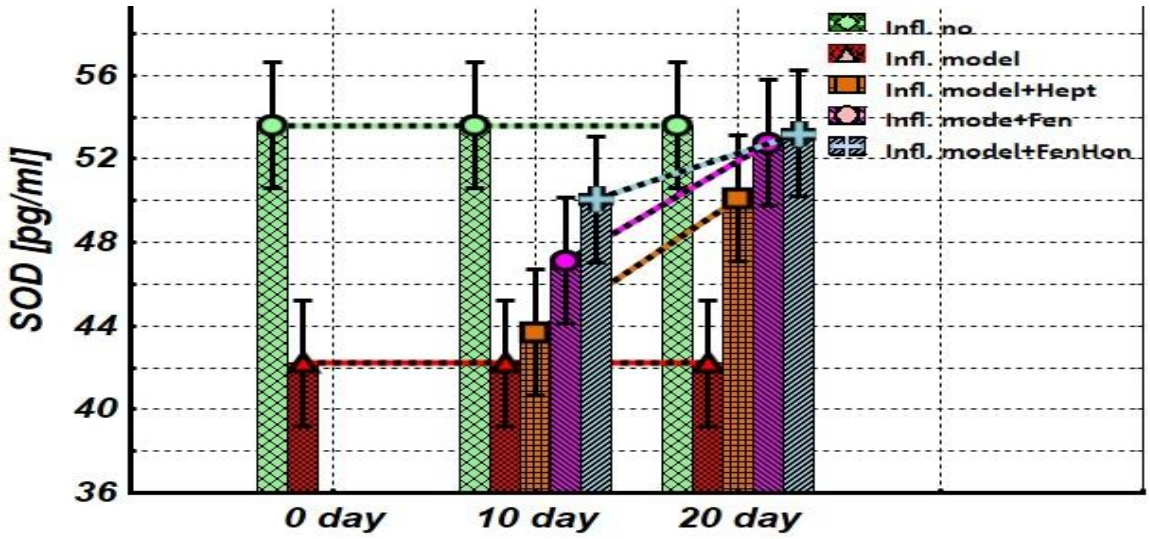


Fig.7. Mean values of GLUCOSE and its 95% confidence interval in different research groups on the 10th and 20th day of treatment

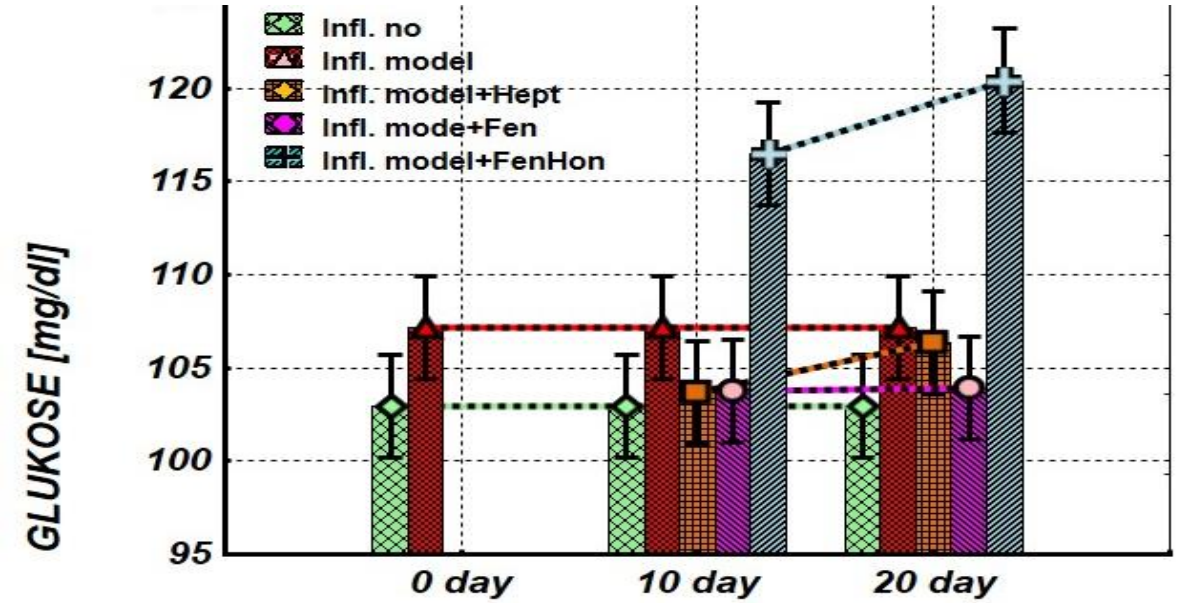


Fig.8. Mean values of TBIL and its 95% confidence interval in different study groups on the 10th and 20th day of treatment

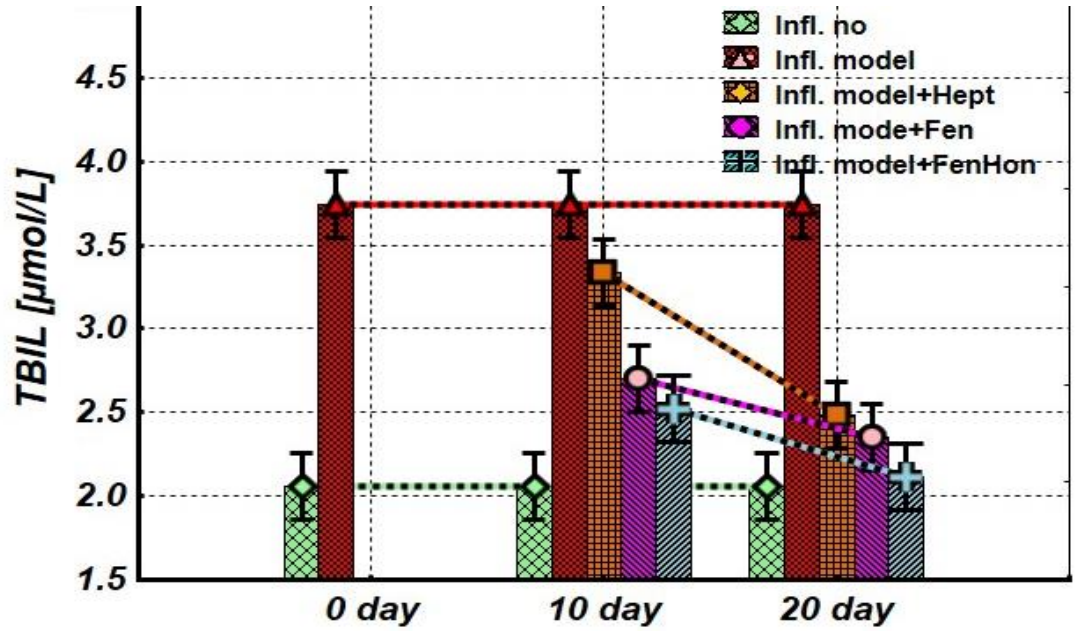


Fig.9. Average values of CREATINIINE and its 95% confidence interval in different research groups on the 10th and 20th day of treatment

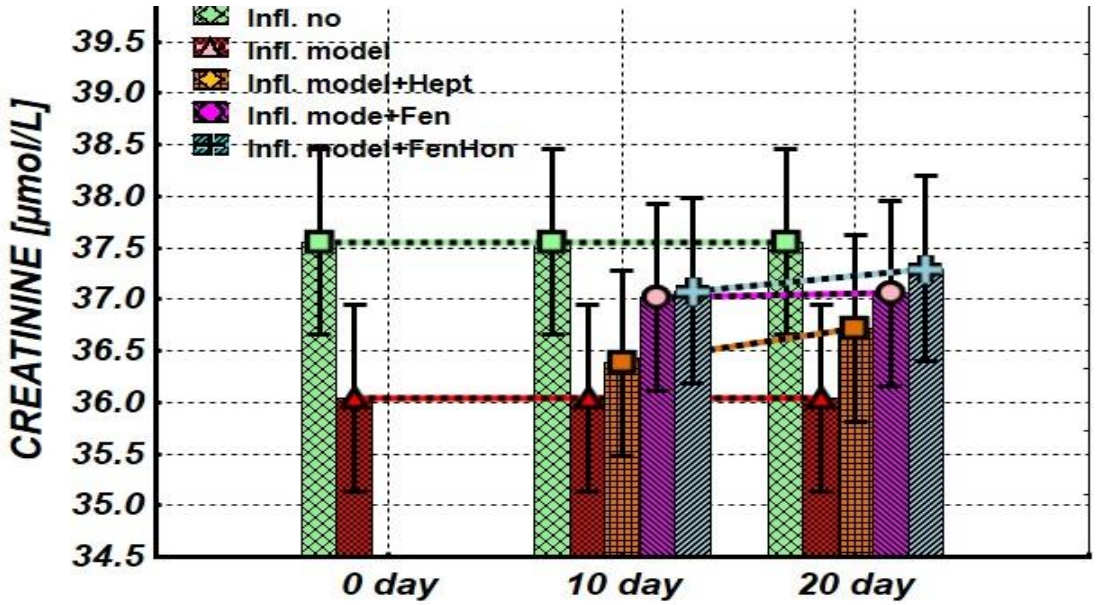
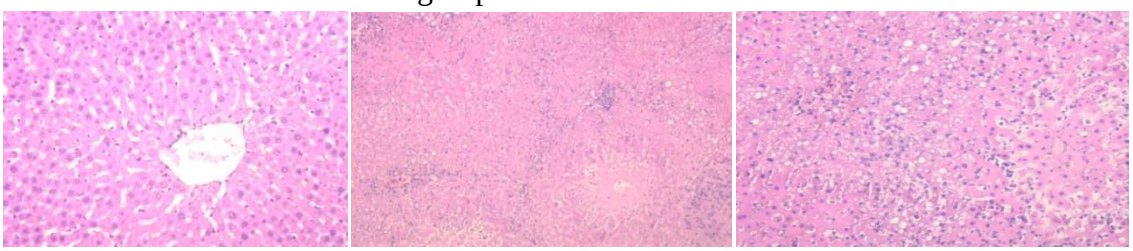
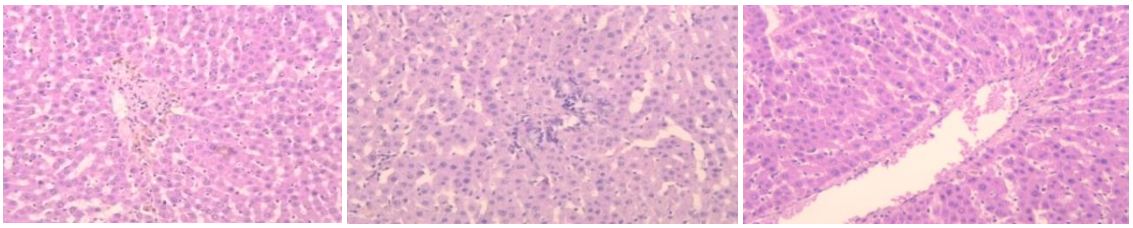


Photo N 1. The liver tissue of the control group rats with liver cirosis



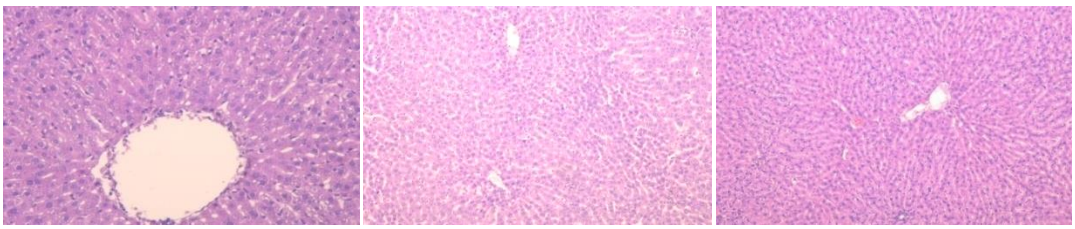
a b c



d e f

a) Central vein with disorganization and necrosis of surrounding hepatocytes, fibrosis and chronic inflammatory changes; **b**) Foci of periportal multiple lobular necrosis with acute inflammatory changes on the periphery; **c**) perinecrotic fatty degeneration with acute inflammatory changes; **d**) Central vein with disorganization and necrosis of surrounding hepatocytes, fibrosis and chronic inflammatory changes, sharp dilatation of sinusoids; **e**) Inflammatory infiltration of the portal triad, disorganized hepatocytes, marked sinusoid dilatation; **f**) Central vein with disorganization and necrosis of surrounding hepatocytes, fibrosis and chronic inflammatory changes, H&E, x200.

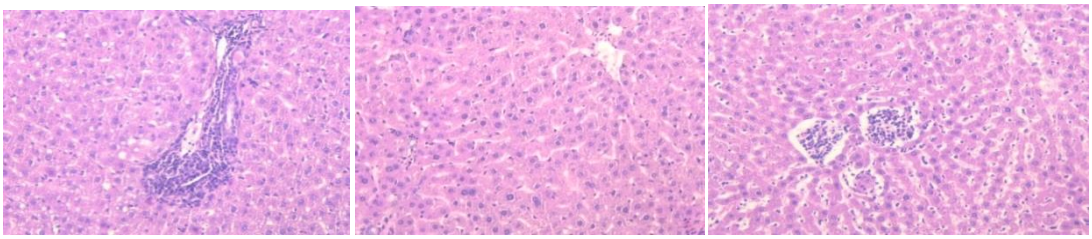
Photo N2. Liver tissue of rats after after 10 days of treatment (S-Ademethionine, Phenomenon, Phenomenon+honey).



a b c

a) s-Ademetionine- regenerative hyperplasia of liver lobule with mild inflammatory infiltration with events of droplet hepatosis, H&E, X400. (Liver #3); b) Phenomenon - regenerative changes of the perilobular triad with mild inflammatory changes, H&E, X200; c) Phenomenon+honey - regenerative type processes, with hyperplasia of macrophages (Kupffer cells), H&E, X100

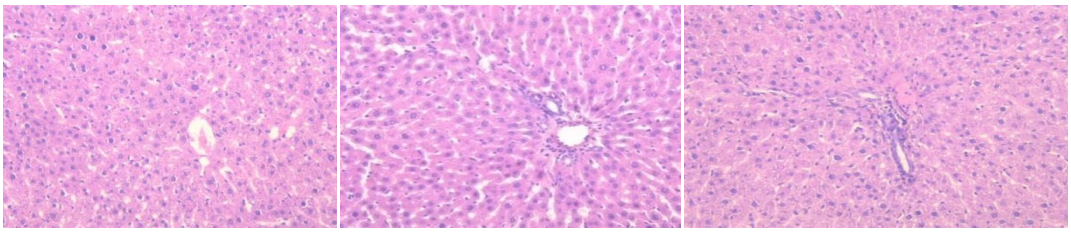
Photo N3. Liver tissue of rats after 20 days of treatment with S-Ademethioine



a b c

a) Moderate inflammatory infiltration of the portal triad, with hyperplasia of Kupffer cells; b) Dilatation of the canaliculi near the central vein, hyperplasia of Kupffer cells with mild inflammatory changes. Hypertrophy of hepatocyte nuclei with multiple nuclei, binucleated hepatocytes (regenerative type); c) Inflammatory infiltration of the portal triad, dilatation of canaliculi near the central vein, hyperplasia of Kupffer cells with mild inflammatory changes. Hypertrophy of hepatocyte nuclei with multiple nuclei (regenerative type), H&E, 200.

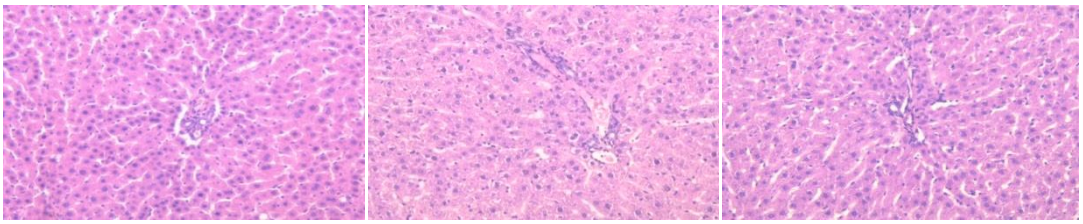
Photo N4. Liver tissue of rats after after 20 days of treatment with Phenomenon



a b c

a - Dilatation of canaliculi near the central vein, hyperplasia of Kupffer cells with mild inflammatory changes. Hypertrophy of hepatocyte nuclei with multiple nuclei, binucleated hepatocytes (regenerative type); b, c -Mild inflammatory infiltration of the portal triad, regenerative type hepatocytes. H&E, 200.

Photo N5. Liver tissue of rats after 20 days treatment with Phenomenon+honey



a b c

a, b, c - Mild inflammatory infiltration of portal triad, regenerative type hepatocytes H&E, 200.

Conclusion: Phenomenon reveal antioxidant, membrane-stabilizing and hepatoprotective properties.The Phenomenon+honey showed the best therapeutic effect improving liver functional parameters (ALT, AST, ALP) and normalizing creatinine, TBIL and SOD concentration. Also, it should be noted that liver functional tests in control and experimental groups were correlated with liver morphological pictures in appropriate study groups.

Thus, the drug Phenomenon could be suggestedas hepatoprotective and antioxidant agent for liver pathologies such as hepatitis, fatty dystrophy, and cirrhosis

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