Diet-Induced Animal Models for Non-Alcoholic Fatty Liver Disease (NAFLD), Pathogenesis and Natural Product Gossipol for Prevention and Treatment

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Background: Non-alcoholic fatty liver disease (NAFLD) is a major public health crisis. Non-alcoholic fatty liver disease (NAFLD) is a major public health crisis affecting approximately 25% of the world's population [1,2,3]. Non-alcoholic fatty liver disease (NAFLD) is one of the manifestations of metabolic syndrome. The diagnosis of NAFLD remains a diagnosis of exclusion, requiring confirmation of hepatic steatosis by imaging or histology and the absence of alternative etiologies, including alcohol consumption, although in many patients both metabolic and alcoholic components contribute to liver injury [4,5]. Additional factors may also contribute to liver fat accumulation. Non-alcoholic steatohepatitis (NASH), which is the presence of hepatic steatosis with associated hepatocellular injury and inflammation, remains a histologic diagnosis. The spectrum of NAFLD ranges from mild steatosis to steatohepatitis with fibrosis; development of cirrhosis is possible [6].

Purpose. To study the effect of a gossypol derivative on biochemical indices of liver function in rats using a model of fatty hepatosis

Materials and methods. The experiments were conducted on 120 white rats weighing 160-200 g. Fatty liver disease is modeled by a high-fat diet. During the study, the animals were divided into 4 groups: 1st - intact (healthy), 2nd - rats that received a high-fat diet and in which a model of fatty hepatosis developed over 14, 18 and 20 weeks, 3rd - rats that received treatment with the traditional hepatoprotector Karsil for fatty hepatosis, and 4th - rats that received treatment with a new hepatoprotector, a gossypol derivative, for fatty hepatosis for 30 days. A biochemical blood test was conducted to determine the indices of hepatocellular insufficiency syndrome.

Results. When studying the 14-day results of the triglyceride (TG) level in intact rats, its level was 0.4±0.01 mmol/l, and in hepatosis it increased to 0.93±0.07 mmol/l, but there was no statistically significant difference between them. The amount of TG in the gossypol derivative decreased by 0.75±0.02 mmol/l compared to the control, while in the Karsil preparation its amount was 0.87±0.01 mmol/l, which shows a result close to hepatosis. The indicators reached statistical differences only compared to the intact group, while no differences were observed in relation to hepatosis. On the 28th day of the experiment, TG was 0.42±0.01 mmol/l in intact animals and 2.48±0.03 mmol/l in hepatosis, the differences between them were statistically significant ($r1<0.005$). In the gossypol derivative and the drugs, TG was 0.5±0.03 and 0.7±0.01, respectively, and

increased with statistically significant differences from the control (r<0.005), but decreased compared to the rats of the intact group, reaching statistically significant differences (for both, r1<0.005). When studying the level of high-density lipoproteins (HDL) in the blood serum of rats after 14 days, its level in intact animals was 1.3±0.05 mmol/l, and in hepatosis its level was higher - 0.93±0.10 mmol/l, and the difference between them was statistically significant (r<0.05). For the gossypol derivative, this indicator was 1.085±0.05 mmol/l, which is significantly higher than the control (r<0.05) and demonstrates results close to the indicators of intact animals. The drug Karsil was 0.97±0.16 mmol/l, which is higher than the indicators of the control and intact groups of animals, and a statistically significant difference was observed only in comparison with the intact group of animals (r<0.01). During the examination after 28 days, the HDL level in hepatosis was 0.75±0.04 mmol/l, which was statistically significantly lower (r<0.005) compared to intact animals (1.3±0.05). For the gossypol derivative, this indicator was 1.25±0.05 mmol/l, which was significantly lower than the control (r<0.05) and showed results close to the indicators of intact animals. The drug Karsil was 1.08±0.16 mmol/l, which was higher compared to the control and intact groups of animals, and a statistically significant difference was observed only from the intact group of animals, and compared to the gossypol derivative, a smaller increase was observed (r<0.01). When studying the level of low-density lipoproteins (LDL) in the blood serum of experimental rats after 14 days, it was 1.07±0.05 mmol/l in intact animals, and 2.14±0.04 mmol/l in hepatosis, a statistically significant difference was observed when comparing. In the gossypol derivative, its content was 1.75±0.14 mmol/l and increased compared to intact animals with statistically significant differences (r<0.05); and decreased in hepatosis (r<0.01). A similar result was observed for the comparison drug Carsil (1.94±0.07 mmol/l) (r<0.05; r<0.005, respectively). When examining after 28 days, the LDL values in intact animals were 1.075±0.04 mmol/l, which was statistically significantly lower (r<0.005) compared to intact animals (1.3±0.05). For the gossypol derivative, this indicator was 1.25±0.05 mmol/l, which was significantly lower than the control (r<0.05) and showed results close to the indicators of intact animals. The drug Karsil was 1.08±0.16 mmol/l, which was higher compared to the control and intact groups of animals, and a statistically significant difference was observed only from the intact group of animals, and compared to the gossypol derivative, a smaller increase was observed (r<0.01). When studying the level of low-density lipoproteins (LDL) in the blood serum of experimental rats after 14 days, it was 1.07±0.05 mmol/l in intact animals, and 2.14±0.04 mmol/l in hepatosis, a statistically significant difference was observed upon comparison. In the gossypol derivative, its content was 1.75±0.14 mmol/l and increased compared to intact animals with statistically significant differences (r<0.05); and decreased in hepatosis (r<0.01). A similar result was observed for the comparison drug Carsil (1.94±0.07 mmol/l) (r<0.05; r<0.005, respectively). When examined after 28 days, the LDL values in intact animals were 1.075±0.04 mmol/l, which in hepatosis was statistically significantly higher than in

intact animals (4.3±0.05) (r<0.005). For the gossypol derivative, this indicator was 1.05±0.05 mmol/l, which was significantly lower than the control (r<0.05) and showed results close to the indicators of intact animals. The drug Karsil was 1.78±0.16 mmol/l, which is higher compared to the control and intact groups of animals, and compared to the gossypol derivative, a smaller decrease was noted (r<0.01). The atherogenicity coefficient was

Conclusions. Thus, when analyzing the results of the experiment by TG indices by the 28th day, the studied drugs, the gossypol derivative and Karsil, surpassed the control by a statistically significant difference. According to the UZLP indices, the gossypol derivative achieved statistically significant differences from the control on the 14th and 28th days of the experiment, showing results close to those in intact animals. Although the PDZLP indices were higher in the studied samples compared to the group of intact animals, they reduced its quantitative indices, having statistically significant differences from the control. The levels of triglycerides and LDL were higher in the group with hepatosis. The obtained results indicate that the gossypol derivative and the comparison drug Karsil had a certain positive effect on the lipid indices of blood serum of rats with fatty hepatosis. Thus, the use of the Gossypol derivative is advisable, which makes it possible to use this drug in non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome.

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