

# Choleretic Activity Of Rutana At Therapeutic Application In Rats With Heliotrin Hepatitis

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## ANNOTATION:

*The experiment established a high hepatoprotective and choleretic activity of Rutan polyphenol isolated from the tannin-bearing plant Rhus coriaria L. in heliotrinic hepatitis. It is believed that Rutan can be recommended in practical medicine as a means of pathogenetic treatment of hepatitis of various etiologies, including infectious toxic pathologies of the hepatopancreatobiliary system.*

*Key words: heliotrin, hepatitis, bile secretion, pharmacotherapy.*

## 1. INTRODUCTION :

Improving the quality and safety of the pharmacotherapy of diseases of the hepatobiliary system is an urgent problem of modern clinical hepatology, because despite the progress achieved, liver diseases remain one of the most common pathologies in the clinic of internal diseases [1,2,3,4]. In the pharmacotherapy of these diseases, hepatoprotectors occupy an important place [1,5,6].

Along with a significant increase in the number of patients suffering from liver diseases of various etiologies (viral, toxic, medicinal, alcoholic, etc.), today the question of the need to use hepatoprotective drugs also in the complex therapy of liver diseases against the background of such common comorbid conditions such as obesity, diabetes mellitus and metabolic syndrome [7].

Numerous assortment of hepatoprotectors does not allow to completely solve the problem of successful treatment of hepatitis of various etiology [1,8]. These circumstances determine one of the important tasks of domestic pharmacology - the creation and development of effective means of treating diseases of the hepatopancreatobiliary system. Promising in this direction is the search for medicines among plants growing in great diversity in the Republic of Uzbekistan.

It should be borne in mind that the biologically active substances contained in medicinal plants are optimally balanced by nature itself, which are easily absorbed by the body and are less toxic than synthetic drugs. In this regard, our attention was drawn to a polyphenolic compound isolated from the tannin-bearing plant Rhus coriaria L., which has a high antiviral activity

This choice was based on the fact that polyphenolic compounds are antioxidants, and therefore have a positive effect on the course of pathological processes in the pathogenesis of which an important role is played by free radical oxidation of membrane lipids. However, the influence of Rutan on the functional state of the liver in its acute lesions has not been studied. In terms of establishing the effectiveness of new means of treatment for liver pathologies, a model of paralysis of this organ reproduced by the alkaloid - heliotrin contained in the seeds of the plant *Heliotropium lasiocarpum* - heliotrope is used, has a selective damaging effect on hepatocytes, causing the development of pathologies, very similar in morphological changes hepatitis occurring in humans [10,11].

The aim of this work was to study the choleric activity of Rutan during therapeutic use in rats with heliotrinic hepatitis. The biliary function of the liver is specific only for this organ, therefore, a violation of the exocrine function of the liver and the chemical composition of bile are one of the sensitive and objective indicators reflecting the functional state of the organ.

## **2. MATERIALS AND RESEARCH METHODS.**

The experiments were carried out on outbred white rats, males weighing 160-210 g. The experimental animals were divided into 4 groups, each group consisted of 6-7 animals. The therapeutic effect of the drug was studied. After 48 hours after a single subcutaneous injection of a freshly prepared solution of heliotrin hydrochloride salt at a dose of 250 mg / kg, experimental therapy was carried out for six days. Rutan was administered to one group of animals once a day by mouth at a dose of 10, and to the other at a dose of 25 mg / kg.

The control group of rats during this period received an equivalent volume of drinking water. 24 hours after the final administration of the drugs, the biliary 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).

The choleric activity of the drug 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). In hourly portions of bile, the concentration (mg%) and total amount (mg per 100 g of body weight) of bile acids, cholesterol and bilirubin [12,13]. All experiments were carried out in compliance with the requirements of the European Convention "On the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes" (Strasbourg 1986).

The results of the study were statistically processed using the Biostat 2009 software package. The data are presented as the mean (M) and standard error of the mean (m). The difference at a probability level of 95% and more ( $p < 0.05$ ) was taken as a statically significant change.

## **3. RESEARCH RESULTS AND THEIR DISCUSSION.**

In the composition of the pubescent alcolloids isolated from the aerial part of the plants, heliotrin, along with heliotrin and lazioarpine, contains saponins, N - heliotrin oxide, N-lazioarpine oxide and other derivatives of the gelurin and eupopin bases, which causes significant changes in the hemodynamics of the organ, which leads to severe pathology. After a single injection of an alkaloid, the animals suffered death (20-25%), especially on the second day. When the abdominal cavity of the animals was opened, a large amount of ascitic fluid of a dark purple light, a dense liver, and a dark cinnamon light were noted.

Morphological studies have shown that the liver, when exposed to heliotrin, slightly decreases in mass, on a nutmeg-type section, hemorrhage is noted in places. Microscopically,

the destruction of the walls of the central veins and capillaries, their sharp thickening are noted. In some places in the central parts of the lobules, the walls of the blood vessels are completely indistinguishable. Trabecula gradually thin out towards the center of the lobules. The kufer cells disappear. In the center of the lobules, obstacles are created for the blood flow of the portal vein (blood clots are often found). The foregoing served as the basis for many scientists to draw a conclusion that heliotrin poisoning is morphologically similar to toxic liver dystrophy in Botkin's disease. At the same time, the death of blood vessels is considered to be a factor playing a decisive role in this liver pathology [10]

The exocrine function of the liver is specific for hepatocytes and its disorders are associated with the functional state of this organ. Therefore, as an indicator of the therapeutic and prophylactic action of new compounds intended for the treatment of hepatitis in experimental studies, the study of exocrine organ activity is widely used [12,13].

The results of the studies showed that in acute hepatitis induced by heliotrin, the exocrine function of the liver is significantly reduced (more than twice, by 57%), which was accompanied by a decrease in the total content of bile acids in bile by 64%, cholesterol by 60 % and bilirubin - by 63.3%. We can confidently assume that heliotrin produces significant changes in hepatocytes leading to inhibition of the functional state of the liver, which are clearly manifested in a decrease in the excretion of bile and its components.

As you know, the active secretion of bile components by parenchymal cells of the liver requires significant energy costs. The energy required for secretory mechanisms is generated due to biological oxidation and glycolysis, since against the background of suppression of tissue respiration of the liver, the intensity of bile formation decreases. Consequently, it is justified to believe that tissue respiration of the liver and associated oxidative phosphorylation is the main energy source of bile formation.

Indeed, studies by a number of authors have established that heliotrin in rats causes degradation of oxidative phosphorylation in mitochondria and causes the development of a pronounced low-energy state [14], in which biosynthetic processes are substantially suppressed.

The results of experiments to study the effect of the therapeutic effect of various doses of Rutan on the exocrine liver function in acute hepatitis hepatitis showed that under the influence of the studied doses of the drug, the course of hepatitis hepatitis was more favorable than in untreated animals. It is noteworthy that in the group of rats receiving the study drug, there was a decrease in lethal outcomes. At the same time, in rats treated with Rutan at a dose of 10 mg / kg, the biliary function of the liver in comparison with the indices of untreated animals is statistically significantly increased by 33%.

Against this background, the level of bile acids in bile increases by 71.4%, cholesterol by 24.2% and bilirubin by 69%. However, this positive effect was insufficient to achieve the values of healthy rats. Therefore, it was of practical interest to establish the effect of the drug at a higher dose. As can be seen from the data in the table, after pharmacotherapy with Rutan at a dose of 25 mg / kg, the volume of excreted bile for 4 hours of the experiment increased by 99.4% compared to the control, and was only 14% less than the values of healthy animals.

It is noteworthy that this effect of the drug was accompanied by an increase in the content of bile acids, cholesterol and bilirubin in bile as compared to untreated animals by 128, 109 and 128%, respectively, and did not differ significantly from the values of healthy animals. The data presented clearly demonstrate the presence of a pronounced choloretic activity in Rutan.

Since the secretion of bile is a process provided exclusively by liver cells, it can be assumed that under the influence of Rutan in acute toxic hepatitis induced by heliotrin, damage to the biological membranes of liver cells is eliminated, which made it possible to restore their function and organ as a whole.

The influence of Rutan on the biliary function of the liver in rats with acute toxic hepatitis induced by heliotrin(for 4 hours of experience per 100 g of body weight)

| Groups                             | Bile, ml         | Bileacidsmg     | Cholesterol mg   | Bilirubin, mcg |
|------------------------------------|------------------|-----------------|------------------|----------------|
| Intact                             | 1,102 + 0,0585   | 6,28 + 0,34     | 0,1710 + 0,0126  | 119,5 + 15,1   |
| Hepatitis                          | 0,475 + 0,0466*  | 2,27 + 0,23*    | 0,0691 + 0,0084* | 43,9 + 5,08*   |
| -----                              | -----            | -----           | -----            | -----          |
| Hepatitis +<br>Rutan<br>10 mg / kg | 0,630 + 0,0380*  | 3,89 + 0,28*#   | 0,0858 + 0,0058* | 74,2 + 6,84*#  |
| Hepatitis +<br>Rutan 25<br>mg / kg | 0,947 + 0,0254*# | 5,17 + 0,22 * # | 0,1444 + 0,0050# | 100,1 + 2,99#  |

Note: \* statistically significant differences compared to intact animals  
 # - statistically significant differences in comparison and hepatitis.

The positive effect of Rutan on the functional state of the liver, and in particular on the bile-forming process, is probably associated with the suppression of the processes of free radical oxidation of lipids of the membranes of hepatocytes, because the drug is a polyphenolic compound characterized by the presence of antioxidant properties. Under these conditions, membrane damage is eliminated and favorable conditions are created for reparative and biosynthetic processes. This assumption is in good agreement with the data of the authors who studied the effect of rutan on the functional and metabolic parameters of rat liver mitochondria under heliotrin intoxication.

So, if in rats with hepatitis induced by heliotrin there is a slowdown in respiration, a decrease in the efficiency of phosphorylation with low respiratory control, then treatment with Rutan eliminated the disturbances in the functional and metabolic parameters of liver mitochondria not only during the oxidation of FAD-dependent substrates, but also NAD-dependent substrates. At the same time, protein biosynthesis is restored in rats treated with Rutan by 19-30.5% [11].

The latter, in our opinion, is of particular importance in the therapeutic effect of Rutan, since during heliotrinic intoxication, the process of protein biosynthesis is inhibited due to damage to the mitochondrial genome, since according to the literature [10], heliotrin specifically damages the nuclear-nucleolar apparatus of cells, causing protein dystrophy liver. It can be assumed that under the influence of rutan, the synthesis of mitochondrial proteins, including the enzymes of this organo-noid, is enhanced, which leads to an increase in energy production and the maintenance of a high degree of conjugation of the processes of oxidative phosphorylation.

As you know, the process of synthesis of bile acids from cholesterol and conjugation of bilirubin with glucuronic acid occurs in the cytoplasmic reticulum of hepatocytes, where the monooxygenase enzyme system is localized. The functional activity of the latter during intoxication with heliotrin is significantly inhibited, which manifests itself in a significant decrease in the exogenous secretory function of the liver and the content of bile acids, cholesterol and biolirubin in bile [14,15].

Considering the fact that pharmacotherapy with Rutan in rats with heliotrinic hepatitis restores the biliary function of the liver, it can be argued that under the influence of Rutan, the functional and metabolic parameters of not only mitochondria, but also the cytoplasmic network of hepatocytes are restored. All this ensures the functioning of the liver at the level of healthy animals. Thus, based on the results of the experimental studies, it can be concluded that Rutan has a distinct choleric property, which is also manifested under conditions of significant inhibition of the functional state of the liver induced by heliotrin

#### 4. CONCLUSIONS.

1. Acute toxic hepatitis induced by heliotrin is accompanied by a significant decrease in the exocrine function of the liver and the content of the main components of bile.
2. Rutan exhibits distinct choleric activity in acute hepatitis induced by heliotrin.
3. Under the influence of Rutan, the course of those biochemical processes that lead to the development of circulatory histotoxic hypoxia under the influence of heliotrin are restored.
4. Restoration of the exocrine function of the liver and the chemical composition of bile is an objective criterion for the high therapeutic effectiveness of Rutan in acute toxic hepatitis.
5. A decrease in the intensity of lipid peroxidation processes, which causes the restoration of the functional metabolic state of mitochondria and the cytoplasmic network of hepatocytes, are probable mechanisms of the effective therapeutic action of Rutan in acute liver damage with heliotrin.

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