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# THE EFFECT OF NEW PLANT HEPATOPROTECTORS ON THE LEVEL OF PROINFLAMMATORY CYTOKINES IN ACUTE TOXIC LIVER DAMAGE

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***Abstract:*** *Purpose of the research: a comparative study of the molecular mechanisms of the anti-inflammatory action of catacin, geranium, cavergal in comparison with carlsil in a model of acute toxic liver damage with heliotrin. Material and methods. Studies were carried out on 118 adult male rats. The model of acute toxic damage (ATD) was reproduced by a single subcutaneous injection of heliotrin at a dose of 200 mg / kg of animal body weight in 110 rats, 8 rats made up the intact group. On the 3rd day of the toxicant administration, the surviving animals were divided into 5 groups: 1) ATD + physiological saline at a dose of 0.5 ml / 100 g body weight (control) of 20 rats; 2) ATD + carsil (comparison group) 19 rats; 3) ATD + catacin 19 rats; 4) ATD + geranyl of 19 rats; 5) ATD + cover 18 rats. The drugs were administered intragastrically daily in the morning at 100 mg / kg for 6 and 12 days. 24 hours after the final administration of the plant preparations, the animals were killed under mild anesthesia. The development of toxic hepatitis was judged by the activity of ALT and AST, the content of bilirubin and its fractions in serum using a MINDRAYBA-88A biochemical analyzer (China) using commercial reagent kits from CYPRESS Diagnostics (Belgium). The content of IL-1β, IL-6 and TNF-α was determined by enzyme-linked immunosorbent assay on an ELYZA apparatus (Germany) using Bender Medsystems kits. For statistical processing of the results, Exell and OriginPro7.5 software packages (OriginLab Corporation, USA) were used. Results. The results of the study showed a sharp increase in the level of pro-inflammatory cytokines in ATD rats, especially those responsible for the humoral immunity. Experimental pharmacotherapy with new drugs from the group of flavonoids and proanthacyanidins leads to a decrease in the production of proinflammatory cytokines, and catacin and geranyl preparations turned out to be more effective in this regard. Conclusion: the studied new herbal preparations catacin and geranyl in rats with ATD significantly suppressed the high level of pro-inflammatory cytokines, which may indicate their anti-inflammatory activity.*

***Keywords:*** *acute hepatitis, heliotrin, pharmacotherapy, carsil, geranyl, catacin, kavergal, pro-inflammatory cytokines.*

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## I. Introduction

Damage arising from pathological processes in the liver under the influence of various factors leads to serious metabolic disorders, immune response, detoxifying liver function and antimicrobial protection. Although many of them end in recovery, it still leaves a "trace" of metabolic disturbance, which, after many years, can lead to chronic liver damage requiring hepatoprotectors. These drugs not only restore metabolic disorders, but also increase the resistance of hepatocytes to damaging agents. Hepatoprotective properties are possessed by drugs that suppress free radical processes, antihypoxants that protect mitochondrial enzymes and microsomes from damaging effects, slow down collagen synthesis, etc. [12]. The interest of researchers in herbal preparations is high due to their very low toxicity and multilateral mechanism of action [25]. In rare cases, causes nausea, dyspepsia, diarrhea, allergic reactions. On the other hand, the absorption of the drug in enterocytes is low, and high hepatobiliary circulation and excretion somewhat reduce the effectiveness of the action of bioflavonoids. This necessitates the search for new plant hepatoprotectors. Promising in this regard are proanthacyanidins from Geranimum saxatile, consisting of (+) - catechin, (+) - gallocatechin, (-) - epicatechin and (-) epigallocatechin, have low toxicity and are considered as promising substances for the creation of medicines [27]. Polymer proanthocyanidin, isolated by employees of the Institute of Plant Substances Chemistry of the Academy of Sciences of the Republic of Uzbekistan from the terrestrial part of the plant [15], has antihypoxic and antioxidant properties [13, 14]. In this regard, the development, study of the mechanism of their hepatoprotective and anti-inflammatory effects will allow them to be introduced into clinical practice.

In response to tissue damage by endothelial cells, leukocytes and macrophages, a number of proinflammatory factors are triggered that trigger a cascade of tissue reactions: activation of chemotaxis, increased capillary permeability, formation of a focal point of inflammation, phagocytosis, lysis, apoptosis, followed by restoration of damaged tissue [5]. An important role in this complex cascade of reactions is played by pro-inflammatory chemokines and cytokines (tumor necrosis factor-alpha (TNF-α), interleukins (IL) IL-1, IL-6, IL-8, adhesion molecules, integrins and other physiologically active compounds whose gene expression is via transcription factors [2, 16, 24]. Milk thistle flavonoids exhibit immunomodulating properties in alcoholic liver disease, helping to reduce the cytotoxic link (CD8 + cytotoxic lymphocytes), decrease β-globulin production and increase blah speed lymphocyte transformation [17]. Despite the presence of anti-inflammatory properties in liver damage, their effectiveness remains low, which necessitates the development of new highly effective hepatoprotectors and the study of their anti-inflammatory effects. All of the above was the subject of an upcoming study.

**Purpose of the research:** a comparative study of the molecular mechanisms of the anti-inflammatory action of catacin, geranium, caverga compared to carlsil in a model of acute toxic liver damage with heliotrin.

## II. Material and methods

### Experimental Design

To achieve this goal, studies were conducted on 118 sexually mature male rats. The model of acute toxic damage (ATD) was reproduced by a single subcutaneous injection of heliotrin at a dose of 200 mg / kg of animal body weight in 110 rats, 8 rats made up the intact group. Mortality for 1-3 days was 13.6%. On the 3rd day of the

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introduction of the toxicant, the surviving animals were divided into 5 groups: 1) ATD + physiological saline at a dose of 0.5 ml / 100 g body weight (control) of 20 rats; 2) ATD + carsil (comparison group) 19 rats; 3) ATD + catacin 19 rats; 4) ATD + geranyl of 19 rats; 5) ATD + cover 18 rats. The drugs were administered intragastrically daily in the morning at 100 mg / kg for 6 and 12 days. 24 hours after the final administration of herbal preparations of animals by simultaneous decapitation, they were killed under anesthesia in compliance with the rules outlined by the European Convention for the Protection of Vertebrate Animals.

**Research methods**

The animals collected blood, isolated serum. The development of toxic hepatitis was judged by the activity of ALT and AST, the content of bilirubin and its fractions in the serum using a MINDRAYBA-88A biochemical analyzer (China) using commercial reagent kits from CYPRESS Diagnostics (Belgium). The content of IL-1, IL-6 and TNF-α was determined by enzyme-linked immunosorbent assay on an ELYZA apparatus (Germany) using Bender Medsystems kits. The “sandwich” variant of enzyme-linked immunosorbent assay was used in the kits.

For statistical processing of the results, Excel and OriginPro7.5 software packages (OriginLab Corporation, USA) were used. The significance of differences between the indices of the control and experimental groups was determined by the Student's t-test coefficient (t), the significance of differences by the indicator P. At a significance level of $P < 0.05$, the differences were taken as statistically significant.

## III. Results

The studies showed a sharp increase in the content of IL-1 in the blood serum with ATD in 5.15 and 6.48 times relative to the values of intact animals, according to the study time (table. 1). Experimental pharmacotherapy of ATD with a carsil comparison drug for 6 days led to a significant decrease in the level of this cytokine by 1.47 times relative to the values of the untreated group. A longer administration of carsil further reduced the high IL-1 values by 2.69 times. Despite these positive changes, the content of IL-1 in the blood serum of this group remained high, exceeding the indices of intact rats by 3.5 and 2.41 times, respectively, the duration of the study. Experimental pharmacotherapy with catacin led to a more pronounced decrease in the level of this cytokine: 3.12 and 4.45 times relative to the indices of the untreated group, 2.12 and 1.65 times compared with the comparison group. In animals of this group, we observed only a slight significant excess of intact rats of 1.65 and 1.46 times, respectively, the treatment time.

Table 1

The content of interleukin 1 (pg/ml) in the blood of rats with acute toxic hepatitis during treatment with herbal preparations.

| Groups and deadline of the study | The deadline of the study, a day from the start of treatment | | | | | |
|---|---|---|---|---|---|---|
| | 6 days | | | 12 days | | |
| | M± m | max :min | P $_1$/$P_2$ | M± m | max :min | P $_1$/$P_2$ |

| | | | | | | |
|---|---|---|---|---|---|---|
| Intact, n=8 | 1,18 ±0,10 | 1,8 : 1,0 | | 1,18 ±0,10 | 1,8 : 1,0 | |
| ATD+$H_2O$, n=10 | 6,08 ±0,10 | 5,4 : 6,5 | < 0,001 | 7,65 ±0,34 | 6,1 : 9,1 | < 0,001 |
| ATD+carsil, n=9-10 | 4,13 ±0,21 | 3,2 : 4,9 | < 0,01 < 0,01 | 2,84 ±0,09 | 2,4 : 3,2 | < 0,05 < 0,01 |
| ATD+ catacin, n=9-10 | 1,95 ±0,06 | 1,7 : 2,3 | < 0,05 < 0,001 | 1,72 ±0,08 | 1,1 : 2,0 | < 0,05 < 0,001 |
| ATD+ geranium, n=9-10 | 1,48 ±0,15 | 1,0 : 2,0 | > 0,05 < 0,001 | 1,65 ±0,15 | 0,9 : 2,3 | < 0,05 < 0,001 |
| ATD+kavergal, n=9 | 3,99 ±0,22 | 2,9 : 4,9 | < 0,05 < 0,01 | 2,99 ±0,10 | 2,5 : 3,4 | < 0,01 < 0,01 |

Note: $P_1$ - significance of differences between the indices of the experimental and intact groups, $P_2$ - significance of differences between the indices of the treated and untreated groups.

Experimental pharmacotherapy of ATD with geranium for 6 and 12 days led to a decrease in the level of IL-1 by 4.11 and 4.64 times relative to the indices of the untreated group, by 2.79 and 1.72 times compared with the comparison group 1.25 and 1.4 times higher than the values of intact rats, respectively, the duration of treatment. The use of the antihypoxant kavergal for the treatment of ATD had a less pronounced effect: relative to the indices of the untreated group, 1.62 and 2.56 times, and did not significantly differ from the indices of the comparison group. Moreover, the level of this cytokine still significantly exceeded the values of intact rats by 3.38 and 2.53 times, respectively, the study time.

More pronounced changes were characteristic of IL-6 (table. 2). So, with ATD, its level increased statistically significantly by 14.39 and 15.12 times, respectively. Experimental pharmacotherapy of ATD with carsil led to a decrease in the level of this cytokine by 1.87 and 1.4 times relative to the indices of animals of the untreated group, still significantly higher than the values of intact rats by 7.71 and 10.78 times, respectively, with the duration of treatment. The use of catacin in rats with ATD led to a more pronounced decrease in the level of this cytokine:

7.25 and 5.65 times relative to the values of the untreated group, 3.88 and 4.02 times compared with the comparison group, and 1.98 and 2.68 times the value of intact rats.

Table 2

The content of interleukin 6 (pg/ml) in the blood of rats with acute toxic hepatitis during treatment with herbal preparations.

| Groups and deadline of the study | The deadline of the study, a day from the start of treatment | | | | | |
|---|---|---|---|---|---|---|
| | 6 days | | | 12 days | | |
| | M± m | max :min | $P_1/P_2$ | M± m | max :min | $P_1/P_2$ |
| Intact, n=8 | 2,05 ±0,29 | 0,9 : 3,0 | | 2,05 ±0,29 | 0,9 : 3,0 | |
| ATD+$H_2O$, n=10 | 29,5 ±0,55 | 27,0 : 33,0 | < 0,001 | 31,0 ±0,68 | 27,0 : 33,4 | < 0,001 |
| ATD+carsil, n=9-10 | 15,8 ±1,71 | 9,4 : 22,0 | < 0,001 < 0,01 | 22,1 ±1,34 | 16,1 : 28,0 | < 0,001 < 0,05 |
| ATD+catacin, n=9-10 | 4,07 ±0,33 | 3,0 : 5,6 | < 0,001 < 0,001 | 5,49 ±0,66 | 3,3 : 7,9 | < 0,01 < 0,001 |
| ATD+ geranium, n=9-10 | 3,94 ±0,24 | 3,1 : 4,9 | < 0,01 < 0,001 | 4,13 ±0,46 | 3,0 : 7,7 | < 0,01 < 0,001 |
| ATD+kavergal, n=9 | 16,1 ±1,28 | 11,0 : 22,9 | < 0,001 < 0,01 | 21,3 ±1,84 | 13,3 : 31,0 | < 0,001 < 0,01 |

Note: $P_1$ - significance of differences between the indices of the experimental and intact groups, $P_2$ - significance of differences between the indices of the treated and untreated groups.

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Experimental pharmacotherapy of ATD with geranium for 6 and 12 days also had a more pronounced effect on the level of IL-6: the high level of this cytokine significantly decreased by 7.49 and 7.51 times relative to the indices of untreated group, by 4, 01 and 5.35 times compared with the performance of the comparison group. The values of this cytokine did not significantly differ from those of animals treated with catacin, and only slightly (1.92 and 2 times) exceeded the values of intact animals. The use of kavergal for the treatment of experimental ATD had a weaker effect: the IL-6 values decreased 1.83 and 1.45 times relative to the values of the untreated group, did not significantly differ from the action of carsil and therefore significantly exceeded the indices of intact rats in 7, 85 and 10.39 times, respectively.

The content of TNF-α in the blood serum of experimental animals with ATD also statistically significantly increased by 7.67 and 11.1 times, respectively, the duration of the study (table. 3). Pharmacotherapy of ATD with carsil for 6 and 12 days contributed to a decrease in high TNF-α value of 1.61 and 1.98 times, however, these parameters remained statistically significantly higher than the values of intact rats by 4.76 and 5.61 times, respectively, terms. The use of catacin for the treatment of ATD had a more pronounced effect: the values of this cytokine significantly decreased 2.86 and 3.83 times relative to the values of the untreated group, 1.78 and 1.94 times compared with the rats treated with the comparison drug carsil. Despite these positive changes, the level of this cytokine significantly exceeded the indices of intact rats by 2.68 and 2.9 times, respectively, terms.

Table 3

The content of TNF-α (pg/ml) in the blood of rats with acute toxic hepatitis during treatment with herbal preparations.

| Groups and deadline of the study | The deadline of the study, a day from the start of treatment | | | | | |
|---|---|---|---|---|---|---|
| | 6 days | | | 12 days | | |
| | M± m | max :min | $P_1/P_2$ | M± m | max :min | $P_1/P_2$ |
| Intact, n=8 | 3,17 ±0,41 | 2,0 : 4,9 | | 3,17 ±0,41 | 2,0 : 4,9 | |
| ATD+$H_2O$, n=10 | 24,3 ±1,06 | 21,0 : 29,5 | < 0,001 | 35,2 ±1,92 | 29,7 : 44,4 | < 0,001 |
| ATD+carsil, n=9-10 | 15,1 ±1,42 | 10,0 : 22,1 | < 0,001 < 0,05 | 17,8 ±1,14 | 14,1 : 25,0 | < 0,001 < 0,01 |
| ATD+catacin, n=9-10 | 8,50 ±0,41 | 7,1 : 10,0 | < 0,001 < | 9,20 ±0,57 | 5,9 : 11,2 | < 0,001 < |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | 0,001 | | | 0,001 |
| ATD+geranium, n=9-10 | 7,54 ±0,53 | 5,4 : 9,9 | < 0,001 < 0,001 | 8,92 ±0,58 | 6,9 : 12,0 | < 0,001 < 0,001 |
| ATD+kavergal, n=9 | 15,4 ±1,46 | 10,1 : 22,2 | < 0,001 < 0,05 | 18,2 ±0,85 | 14,0 : 21,2 | < 0,001 < 0,01 |

Note: $P_1$ - significance of differences between the indices of the experimental and intact groups, $P_2$ - significance of differences between the indices of the treated and untreated groups.

Pharmacotherapy of ATD with geranium for 6 and 12 days on the content of TNF-α had the same positive effect as catacin. The level of this compound significantly decreased 3.22 and 3.95 times relative to the values of the untreated group, 2 and 1.99 times compared with the comparison group, but still significantly exceeded the values of intact rats 2.38 and 2.81 times , according to the timing. The level of TNF-α in the blood serum of rats with ATD treated with kavergal for 6 and 12 days statistically significantly decreased 1.58 and 1.93 times relative to the indices of the untreated group and did not significantly differ from the values of the comparison group. The content of this cytokine significantly exceeded the values of intact rats by 4.86 and 5.74 times, respectively, terms.

Thus, the studied new herbal preparations catacin and geranyl in rats with ATD significantly suppressed the high level of pro-inflammatory cytokines, which may indicate their anti-inflammatory activity.

## IV. Discussion

Analyzing the data obtained, it should be said that the direct cause of liver failure in many pathological conditions is a decrease in oxygen supply, an imbalance in oxidative processes, activation of the immune-mediated and mitochondrial apoptosis pathways, fibroblast growth factors, leading to irreversible fibrosis processes leading to chronic pathological process [19, 22]. Damage and destruction of hepatocytes is the starting point in the activation of other cell populations, which, in turn, initiate an inflammatory reaction, an adaptive immune response with the development of reactive liver fibrosis. Previous morphological studies that we performed showed the development of massive centrallobular necrosis and hemorrhages; in the periportal liver tissue, an expansion of sinusoids, Disse spaces, and foci of inflammatory lymphohistiocytic infiltration around necrosis and vessels of portal tracts were revealed [8]. Under these conditions, apparently, the accelerated synthesis of IL-1, IL-6, and TNF-α observed by us leads to accelerated synthesis of polypeptides by endothelial cells of the liver vessels, stimulating cell migration and proliferation, causing the release of vascular inflammatory mediators. The high values of the above cytokines revealed by us activate the formation of arachidonic acid with increased synthesis of prostaglandins, thromboxanes, prostacyclins and leukotrienes - active inducers of the inflammatory process, leading to liver damage. Indeed, IL-1 is a powerful pro-inflammatory cytokine, enhances the proliferation of CD4 + cells, the growth and differentiation

of B cells, induces the production of IL-2 and the expression of its receptor, promotes the activation of antibody production and is one of the first to be included in the body's protective response under the action of pathogenic factors ( cytokines). Activation of Th1 producing IFN-γ, IL-2, TNF-α leads to stimulation of the functions of T-lymphocytes and macrophages and the development of an immune response according to the cell type, activation of Th2, secreting IL-4, IL-5, IL-6, IL -9, IL-10 and IL-13, stimulate mainly the humoral immunity. An imbalance in the production of cytokines, the ratio of the number of Th1 / Th2 cells, is important in the immunopathogenesis of the progression of chronic hepatitis [10]. In this regard, we analyzed the ratio of the level of TNF-α to the content of IL-6. Studies have shown a more pronounced activation of the humoral immunity compared to the cellular link in rats with ATD, since a decrease in this indicator from 1.74 + 0.27 in intact rats to 0.82 + 0.03 and 1.14 +0.06 - with ATD on the 6-12th day of the study. Apparently, a more pronounced increase in the level of IL-6 is associated with the action of the transcription factor NF-κB, which targets genes of chemokines, cytokines, immune receptors, cell adhesion molecules, which initiate a powerful pro-inflammatory effect, enhanced synthesis of leukotriene and prostaglandins, which sharply activate the humoral immunity [32]. It has been proven that IL-6 is a factor in the differentiation of B-lymphocytes into AT-producing cells, which leads to the induction of acute phase protein synthesis, especially a significant increase in the c-sis gene mRNA in cultured human endothelial cells, which can mediate inflammatory vascular effects [17]. According to some authors, increased serum IL-6 production is an independent factor in the progression of fibrosis and kidney damage in patients with hepatitis C [9]. The increase in the content of TNF-α revealed by us in rats with ATD causes aggregation of receptors, which leads to the formation of various adapter proteins (kinases, proteases, caspases). On the other hand, mitochondria are the target for TNF-α-initiated signals that cause the cell to die, due to the release of the active forms of oxygen, cytochrome oxidase, and other factors inducing apoptosis from mitochondria and ultimately contribute to induce cell destruction [21].

According to the literature, the leaders in the treatment of liver diseases are drugs of a bioflavonoid nature, in particular, containing silymarin (legalon, silymarin, carsil, silybor, etc.) as the main active substance [26]. Most flavonoids have an anti-inflammatory effect, inhibiting the enzymes responsible for the synthesis of pro-inflammatory cytokines, prostaglandins, thromboxanes and leukotrienes [2]. According to the authors, the metabolic effect of this group of hepatoprotectors is associated with stimulation of protein biosynthesis and acceleration of regeneration of damaged hepatocytes, due to specific stimulation of RNA polymerase 1, activation of transcription and translation, which leads to an increase in the number of ribosomes and activation of biosynthesis of structural and functional proteins [2]. It should be said that the mechanism of the protective action of flavonoids is associated with an increase in the activity of antioxidant enzymes, restoration of hepatocyte cell membranes, their participation in the processes of molecular transport, cell division and differentiation, stimulation of the activity of various enzyme systems, slowdown of collagen synthesis and an increase in collagenase activity, which underlies their antifibrotic effect [5]. The decrease in the high level of proinflammatory cytokines in ATD rats that we detected when using flavonoids and proanthacyanidins was apparently associated with inhibition of transcription factors leading to blocking the synthesis of cytokines and their receptors [20, 23], inhibition of the enzymatic cascade of arachidonic acid [23], a decrease in neutrophil adhesion due to inhibition of the production of adhesive molecules by endothelium [28, 33]. However, the severity of the decrease in the level of pro-inflammatory cytokines depended on the chemical structure of the compounds we used. The highest pro-inflammatory activity was shown by catacin and geranyl. At the same time, we observed a more pronounced decrease in the level of IL-6, which led to an increase in the rate of TNF-α / IL-6 from 0.82 + 0.03 and 1.14 + 0.06 to 2.17 + 0.15 and 1.86 + 0.23 when using catacin, up to

1.94 + 0.12 and 2.30 + 0.21 - when using geranium, respectively, treatment periods of 6 and 12 days. At the same time, the effect of carcil and kavergal was weaker, the level of pro-inflammatory cytokines remained higher, especially IL-6. Apparently, catacin and geranium suppressed the NF-κB transcription factor, which is responsible for the expression of genes for chemokines, cytokines, cell adhesion molecules, leukotrienes and prostaglandins, more pronouncedly.

The carlsil comparison product we used was created on the basis of silymarin obtained from spotted milk thistle (Silybimariani). The hepatoprotective effect of silymarin is due to its antioxidant, membrane-stabilizing and stimulating repair potential of the liver cells. A decrease in the high level of pro-inflammatory cytokines in ATD rats with carcil is probably due to activation of the Keap/Nrf2/ARE system under the influence of flavonoids [6, 30]. According to O.V. Azarova and Galaktionova, the presence of 4'- and (or) 3', 4'-hydroxyl groups in ring B determines their inhibitory activity against histamine, tryptase, IL-6 and IL-8 released by macrophages and mast cell culture [2].

In the studies of Abdullaev G.R. (2016) in rats with emotional pain stress, a decrease in lipid peroxidation processes using catacin was found, the drug increased the energy potential of cells [1, 3]. This drug has an antihypoxic effect in various forms of hypoxia and is superior in activity to known antihypoxants. A study of the chronic toxicity of catacin showed a lack of cumulative properties [11].

The proanthacyanidins that make up geranil are also isolated from other plants and have been studied quite well by scientists from far abroad, neuroprotective, antioxidant, anti-inflammatory, antitumor, and immunostimulating properties have been established, they prevent platelet aggregation, and stabilize vascular endothelium [31]. Our previous studies showed a decrease in the rates of cytolysis syndrome, cholestasis, mesenchymal inflammation and liver cell failure, an improvement in the synthetic function of hepatocytes, antioxidant properties in rats with ethanol intoxication, and its hepatoprotective activity is superior to the known hepatoprotector carsil [7]. The presence of pronounced antioxidant properties is due to the presence in their composition of components that inhibit or reduce the intensity of free radical oxidation processes. According to Tarakhovskaya Yu.S. et al. (2013), this is due to the chemical structure of these compounds [16, 18, 29]. Proanthocyanidin geranium exhibited antihypoxic properties in a carotid artery occlusion model [14]. Apparently, the more pronounced hepatoprotective properties of catacin and geranium obtained by us are related to their antihypoxic and antioxidant effects; they are not inferior in their hepatrotective properties to the well-known drug carsil.

In recent years, the drug kavergal, which is used as a corrector of hypoxic conditions in various pathologies, has gained particular popularity on the pharmaceutical market of Uzbekistan. It has a pronounced antihypoxic and antioxidant activity and membrane-protective action, increases the body's resistance to adverse environmental factors, potentiates the effects of anti-inflammatory and antibacterial agents, and increases the effectiveness of treatment of patients with chronic pyelonephritis [4].

**Study transparency**

The study did not have sponsorship. Authors are solely responsible for providing the final version of the manuscript in print.

Declaration of financial and other relationships

All authors took part in developing the concept of the article and writing the manuscript. The final version of the manuscript was approved by all authors. The authors did not receive an article fee.

**Conflict of interest**

The authors declare no conflict of interest.

## V. Conclusion

Thus, the results of the study showed a sharp increase in the level of pro-inflammatory cytokines in ATD rats, especially those responsible for the humoral immunity. Experimental pharmacotherapy with new drugs from the group of flavonoids and proanthacyanidins leads to a decrease in the production of pro-inflammatory cytokines, and catacin and geranyl preparations turned out to be more effective in this regard.

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