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Research Article

# Selank and semax as potential hepatoprotectors in medical treatment of tuberculosis

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## Abstract

**Introduction:** Drug-induced hepatitis is common in clinical practice. This problem is particularly relevant in the treatment of tuberculous infection, because for this purpose, up to 5–6 hepatotoxic drugs are used simultaneously for a long time, which often (in 15–20% of cases) leads to medical liver lesion. To protect the liver, Semax and Selank are offered – drugs of regulatory peptides group.

**Materials and Methods**: The research was conducted on 96 outbred white male rats weighing 180–220 g. The experimental group included about 10 animals. Drug-induced hepatitis was simulated through the combined 21-day administration of isoniazid, rifampicin and ethanol. Semax and Selank, as well as Essentiale N and Mexidol (comparison drugs) were administered once a day during the experiment. Healthy control animals with experimental hepatitis were used for comparison. Subsequently, the obtained biochemical and histomorphological parameters were evaluated.

**Results and Discussion:** In the experiment, Semax and Selank showed a greater therapeutic activity than the recognized hepatoprotectors – Essentiale and Mexidol. Only in the case of administering Selank and Semax, there was parallelism between the restoration of biochemical parameters of blood and histomorphological parameters of the liver. Selank was also characterized by an increased activity of regenerative processes.

**Conclusion:** Administering Selank and Semax to patients with tuberculosis would significantly reduce the number and severity of hepatotoxic reactions.

## Keywords

tuberculosis, hepatoprotection, hepatoprotector, drug-induced liver lesions, Semax, Selank.

## Introduction

The recent decades have seen a growth in liver diseases due to a hectic pace of life lined with stress and overwork, industrialization and environment pollution, professional and household hazards, an increased consumption of abused drugs and alcohol, imbalanced diets, an increase in the number of tuberculosis patients and uncontrolled medication intake (Kovtun et al. 2011, Poluchova et al. 2018, Topchiy and Toporkov 2013). Among the most widespread liver infections are acute and chronic viral hepatitis (for example, nearly 170 million people in the world have chronic hepatitis C), and among non-infectious ones – non-alcoholic fatty liver disease (Kolesnikova and Nikiforova 2014, Lazo et al. 2013, Vernon et al. 2011, Williams et al. 2011). Alcoholic liver disease is of great concern in the the Russian Federation, for 14–20 thousand people die from it annually (Homeriki and Homeriki 2012).

In recent years, drug-induced and toxic hepatitis have occured more and more often (up to 30% of all acute hepatitis) (Bandegi et al. 2014, Shapiro and Lewis 2007). Drug-induced liver disease may develop due to drug properties, patients' body features, their liver condition, a diet and other factors. According to the world statistics, drug-induced liver lesion (DILL) make up from 0.7% to 20% of cases, with every seventh patient with this pathology dying (Chalasani et al. 2008, Kovtun et al. 2011, Topchiy and Toporkov 2013). Drug hepatotoxicity is the main reason in the development of liver failure requiring liver transplantation (Kovtun et al. 2011).

The main groups of drugs causing DILL appeared to be anti-infections drugs influencing the central nervous system, locomotor system (for example, nonsteroidal anti-inflammatory drugs) and gastrointestinal tract (Chalasani et al. 2008). The liver lesion is described for more than 1,000 drugs (Bandegi et al. 2014).

Drug-induced lesion of liver caused by the use of antibacterial remedies are characterized with considerable variability in both frequency and type of liver lesion. Very often hepatitis occurs as a complication after administering anti-tuberculosis drugs (for example, up to 2,000 per 100,000 prescriptions of isoniazid) (Ivanova and Borisov 2017, Zuckerman 2011).

A considerable increase in the number of rapidly progressing and widespread forms of tuberculosis. as well as the growth of polyresistant forms of mycobacteria of tuberculosis (MBT) make it imperative that a combination of 5–6 drugs is used in chemotherapy, which provokes the development of toxic hepatitis (Federal Clinical Recommendations 2014).

It is known that major anti-tuberculosis drugs (isoniazid, ethambutol, ethionamide, pyrazinamide and rifampicin) have hepatotoxical properties and provoke the development of toxic hepatitis, and their combined administration intensifies the toxic effect. The frequency of DILL during polychemotherapy of tuberculosis is 15%-20%, which creates risks for administering a complete course of chemotherapy. Irregular administration of anti-tuberculous drugs reduces treatment efficacy and leads to forms of tuberculosis with wide drug resistance, as well as to an increase in the reservoir of tuberculous infection (Drobin 2014, Ivanova and Borisov 2017, Mordyk et al. 2014, Testov et al. 2014).

In tuberculous therapy, isoniazid is most often used, which after acetylation becomes hydrazine, from which a potent combination is formed in the liver, leading to destruction of hepatocytes. The toxic action of isoniazid is increased if administering it along with inducers of cytochrome enzyme system, for example with rifampicin, as well as with alcohol, anaesthetics and paracetamol (Cai et al. 2012, Kazakov et al. 2018).

The treatment of DILL requires abolishing all other drugs, except for the life-saving ones. For pathogenic therapy, hepatoprotectors are used, selected in accordance with the main mechanism of the disease development (Minushkin et al. 2016). The effect of hepatoprotectors is aimed at restoration of homeostasis in the liver, increasing its resistance to pathogenic factors, normalization of functional activity and stimulation of reparative-regenerative processes in the liver (Kovtun et al. 2011, Kucheryavyy and Morozov 2012, Vyalov 2013). The biochemical mechanism of protective action of most hepatoprotectors includes membrane stabilizing (increased activity and membrane fluidity, decreased density in the mosaic matrix of phospholipid element membranes and normalization of their penetration, activation of phospholipid-dependant ferments), anti-oxydative (inhibition of lipid peroxidation, a decreased rate of free radical synthesis), anti-phibrotic, regenerative (an increasing in ribonucleic acid and albumin synthesis by hepatocytes) and hypolipidemic effects (Yakovenko et al. 2017).

Practically all liver toxins stimulate several pathogenic ways, leading, as a rule, to necrotic death of liver cells (mediator-hormonal imbalance, activation of POL, oxidation stress, damage to phospholipids of cellular and mitochondrial membranes, etc.). At the same time, hepatoprotectors have their own role in the pathological process, without overlapping all the pathogenesis links of drug-induced hepatotoxicity, which requires combining several drugs with each other or using their maximum dosage. Unfortunately, such an approach to prescribing hepatoprotectors leads not only to an increase in the therapy efficacy, but also to a considerable increase in the number of side effects (Vyalov 2013).

What is more, the hepatoprotective therapy itself has some negative aspects: adverse side effects, drug interaction, and the variability of clinical effects of drugs by different producers, a rather narrow spectrum of therapeutic efficacy, which makes it necessary to combine drugs of different groups (Babayan and Havkin 2013, Crocenzi and Roma 2006, Matveev et al. 2011).

Another negative aspect is as follows: drugs containing the same substance may be produced in different countries, and clinical experience shows that the therapeutic actions they have are far from being similar. Phytogenic drugs may act differently depending on places where the herbs used for their production grew (Matveev et al. 2011, Minushkin et al. 2016).

One of the ways to solve this problem is to introduce into medical practice the drugs that, on t home hand, have versatile physiological effects, and, on the other hand, provide a high degree of safety. Such hepatoprotective drugs as glyprolines, possessing properties of regulatory peptides (RP), meet these requirements. In case of various diseases, RPs activate the self-regulation processes and self-repair of disrupted functions of affected organs and systems. An important aspect of using regulatory oligopeptides is their capacity to normalize the level of tissue trophic factors which, on the one hand, inhibit various mechanisms of a pathological cascade, but, on the other hand, stimulate reparative processes (Myasoedov 2016).

The typical representatives of the RP class are Semax and Selank, belonging to the glyproline family (Myasoedov 2016). Semax is a synthetic peptide based on fragments of adrenocorticotropic hormone (ACTH) 4–7 (Met-Glu-His-Phe), whereas the structure of Selank is based on peripheral immunomodulator taftsin (H-Thr-Lys-Pro-Arg-OH). To protect from the hydrolysed action of peptidases, tripeptide Pro-Gly-Pro, which has a cytoprotective activity, was added to them in C-position (Myasoedov 2016). The introduction of Semax and Selank to the body promotes activation of the peptidergic system and secondary synthesis of a wide range of regulatory peptides (Solovyev et al. 2011). They prevent the liver damage in stress situations (Ivanov et al. 2017). They contribute to regulation of inflammatory processes due to reducing the level of cytokine imbalance and normalizing the activity of the kinin and bradikinin system, and also reduce the activity of apoptosis in the damaged tissues. The drugs are characterised with a high level of safety (Myasoedov 2016).

The purpose of this research is to study a hepatoprotective effect Selank and Semax in liver damage caused by anti-tuberculous drugs.

# Materials and methods

The research was conducted on 96 outbred white male rats, each weighing 180–220 g. The experimental group included at least 10 animals. The laboratory animals were treated according to the Rules of Laboratory Practice (On the Approval of Rules of Laboratory Practice, Order no. 708n of the Ministry of Healthcare and Social Development of the Russian Federation of August 23, 2010). All the animals were kept in the identical standard conditions of care.

Drug-induced hepatitis was simulated through a combined administration of isoniazid (100 mg/kg, intragastrically), rifampicin (130 mg/kg, intragastrically) and a 25% ethanol solution (3gr/kg, intragastrically) for 21-days. A number of biochemical parameters were studied in the blood of the animals on the 22$^{nd}$ day after the start of administering liver toxicants. These biochemical parameters were combined into functional groups: cytolysis markers (activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDG)); indicators of protein-synthetic activity of hepatocytes (total protein, albumins, globulins), carbohydrate metabolism (the activity of total and pancreatic alpha-amylase, the content of glucose), lipid metabolism (the activity of lipase, the content of triglycerides (TG), total cholesterol (Ch.T), cholesterol of high-density lipoproteins (HDL) and low-density lipoproteins (LDL)), and detoxification function of liver (contents of direct bilirubin). The osmotic resistance of erythrocytes (ORE) was studied with a standardized method.

During histomorphological research, the general evaluation of preparations was carried out by hematoxilin and eosin staining; collagen fibers were shown by Masson staining; elastic fibers were stained by fukselin (with Hart's staining), and reticuline fibers – by Foot's silver impregnation. A stereometrical study of liver was done to define the correlation between different tissue compounds.

Semax and Selank were administered intranasally 0.04 ml in each nasal passage; the dosage was 0.2 mg/kg. For comparison, hepatoprotectors were used, such as Essentiale N and Mexidol (administered hypodermically at 1 ml/kg and 50 mg/kg, respectively). All the drugs were administered once a day during the whole experiment. Comparison was made between the healthy control groups and the animals with simulated hepatitis (the rats were administered saline solution).

All the calculations were done using Biostatistics software (StatPlus Professional 5.8). The number of measurments of each parameter in different experiments was 10–18. For intergroup comparison, there was used Student's t-criterion (in case of normal distribution) and a non-parametric Wilcoxon criterion (with no normal distribution); for multiple comparisons, Student criterion with a Bonferroni's adjustment was used. The significance of intragroup differences was defined by paired Student's t-criterion. The difference was considered significant at $p<0.05$.

# Results and discussion

The analysis of dynamic activities of cytolytic enzymes in blood showed (Table 1) that in the case of toxic hepatitis there was a statistical increase in AST and ALT by 46% and 21%, respectively, and a tendency towards a 15% increase in total LDH activity, but, at the same time, the activity of GGT remained unchanged. All this points at moderate hepatocytes cytolysis. Administration of Essentiale and Mexidol for hepatitis treatment did not prevent the destruction of hepatocytes, but the level of cytolysis somewhat decreased: Essentiale prevented an increase in the AST activity in blood (though the ALT activity remained 35% higher than usual), and Mexidol prevented an increase in ALT (with AST increasied by 36%,

**Table 1.** The Influence of Tested Drugs on Hepatocytes Cytolysis Activity.

| Groups | ALT un/L | AST un/L | GGT un/L | LDG un/L |
|---|---|---|---|---|
| intact | 103.3±11.5 | 136.5±6.7 | 5.46±0.76 | 628±58 |
| control | 150.6±14.5* | 164.5±11.1* | 5.98±0.74 | 722±74 |
| hepatitis + Semax | 102.2±21.1 | 114.5±9.8** | 5.78±0.46 | 356±41*/** |
| hepatitis + Selank | 132.7±15.6 | 149.7±6.5 | 5.44±0.74 | 647±81 |
| hepatitis + Essentiale | 139.3±10.1* | 138.5±7.7 | 6.28±0.56 | 433±20*/** |
| hepatitis + Mexidol | 129.5±11.8 | 185.2±19.1* | 6.72±0.86 | 472±43** |

**Note:** * – statistical difference with intact animals ($p<0.005$); ** – statistical difference with control animals ($p<0.05$); ALT – activity of alanine aminotransferase, AST – aspartate aminotransferase, GGT – gamma-glutamyltransferase, LDG – lactate dehydrogenase.

$p<0.05$). On the contrary, Selank and Semax prevented an increase in the activity of blood transaminases: as for AST, Semax decreased its activity statistically by 30% as compared to that in the control group.

Protein metabolism imbalance is a typical effect for liver damage. The 21-day administration of hepatotoxic drugs (Table 2) to the control rats caused a statistical decrease in the total protein level in blood by 16% due to a drop in albumin concentration (-23%, $p<0.05$); no statistical changes in the globulin concentration in blood were registered. Administering Selank and Essentiale normalized all disrupted indices. Semax had almost no influence on the total protein content in blood, but somewhat increased the albumin level (by 15%, $p>0.05$) as well as statistically decreased the globulin concentration in blood by 21% in the intact animals. Mexidol administration was not effective.

During hepatitis simulation, there was a statistical reduction in amylase activity by 17%, with glucose content in blood remaining at the normal level (Table 3). Out of the tested drugs, only administration of Selank caused the normalisation of amylase activity. Semax, Mexidol and Essentiale did not influence the activity of alpha-amylase (the recorded decrease was 16–23%), but a decrease in the level of glucose in blood by 22% was observed after administering Essentiale.

**Table 2.** The Influence of Tested Drugs on Synthesis of Protein in Liver Against the Background of Simulated Hepatitis.

| Groups | Total protein g/L | Albumins g/L | Globulins g/L |
|---|---|---|---|
| intact | 64.3±1.2 | 33.7±0.6 | 30.6±0.5 |
| control | 54.2±2.7* | 26.0±1.1* | 28.2±1.2 |
| hepatitis + Semax | 53.9±2.5* | 29.8±1.0* | 24.1±0.8*/** |
| hepatitis + Selank | 59.6±2.1 | 31.6±1.1** | 28.0±1.2 |
| hepatitis + Essentiale | 62.6±1.5** | 32.3±0.5** | 30.3±0.6** |
| hepatitis + Mexidol | 51.4±4.2* | 29.0±1.0* | 22.4±1.0*/** |

**Note:** * – statistical difference with intact animals ($p<0.005$); ** – statistical difference with control animals ($p<0.05$).

**Table 3.** The Influence of Tested Drugs on the Carbohydrate Metabolism Rate in Case of Simulated Hepatitis.

| Groups | Alpha amylase un/L | Alpha-amylase pancreatic un/L | Glucose mmol/L |
|---|---|---|---|
| intact | 2173±94 | 1218±53 | 8.6±0.4 |
| control | 1796±60* | 1012±41* | 8.7±0.4 |
| hepatitis + Semax | 1776±92* | 991±51* | 8.5±0.9 |
| hepatitis + Selank | 2024±104** | 1135±61 | 8.1±0.3 |
| hepatitis + Essentiale | 1656±65* | 935±40* | 6.7±0.4 */** |
| hepatitis + Mexidol | 1493±67*/** | 796±63*/** | 8.6±0.6 |

**Note:** * – statistical difference with intact animals ($p<0.005$); ** – statistical difference with control animals ($p<0.05$).

The liver is the key organ in lipid metabolism: cholesterol and lipoproteins, its transporters, are synthesized in hepatocytes; it is also the place of most synthesis of phospholipids and endogenic triglycerides. When simulating toxic hepatitis in rats (Table 4), there was a decrease in blood lipase activity (-57% at $p<0.05$) against the background of a statistical increase in the triglyceride concentration (+43%) in blood and a tendency towards an increase in the total cholesterol level (+20% at $p<0.05$).

Administering Semax, Selank and Essentiale prevents the disruption of lipid metabolism in simulated hepatitis, whereas Mexidol only normalizes the lipase activity, but does not prevent a 78% growth in triglyceride concentration in blood (at $p<0.05$) and, above all, with its administration statistically decreases the level of high-density lipoprotein cholesterol by 28%.

One of main functions of the liver is detoxification: the organ detoxicates both exogenous and endogenous toxic products. The latter include direct bilirubin, the level of which increased by 27% (Table 5) in the sick rats. The use of Essentiale was not effective, and the administration of Mexidol decreased detoxification properties of the liver: concentration of direct bilirubin in blood statistically increased by 41% compared to control and by 79% as compared to the intact animals. The administration of Semax and Selank restored the detoxification function of hepatocytes. Semax was the most active, as it statistically decreased the level of direct bilirubin in blood by 1.5 times as compared to the control group.

The osmotic resistance of erythrocytes (ORE) is an integral indicator of the body's resistance to lipid peroxidation; there is also a close connection between changes in the permeability of erythrocyte membranes and of the membranes of cells affected by a pathological process (Zakharova et al. 1991).

When simulating toxic hepatitis, there was a statistical decrease in ORE by 30% in the animals. Gliprolines and Mexidol prevented an increase in the erythrocytes hemolysis level under hypo-osmotic conditions; Essentiale, though it increased the erythrocytes resistance to a 0.5% solution of NaCl (by 21% at $p<0.05$ as compared to the control group), with ORE remaining lower (by 15%) than in the intact rats. The obtained results made it possible to suppose that the tested drugs, while limiting the activity of free-radical oxidation of lipids, prevent the impairment of cytoplasmic membrane func-

**Table 4.** The Influence of Tested Drugs on the Lipid Metabolism in Simulated Hepatitis.

| Groups | Lipasa un/L | Triglyceride mmol/L | Total cholesterol mmol/L | LDL mmol/L | HDL mmol/L |
|---|---|---|---|---|---|
| intact | 220.0±50.6 | 0.54±0.03 | 1.60±0.13 | 0.87±0.07 | 0.43±0.05 |
| control | 94.8±7.6* | 0.77±0.10* | 1.93±0.11 | 0.90±0.07 | 0.46±0.03 |
| hepatitis + Semax | 464.6±120.6** | 0.71±0.15 | 1.70±0.22 | 0.74±0.17 | 0.37±0.08 |
| hepatitis + Selank | 378.0±106.2** | 0.56±0.06** | 1.71±0.14 | 1.09±0.06** | 0.40±0.04 |
| hepatitis + Essentiale | 261.2±90.4 | 0.49±0.10 | 1.63±0.11 | 0.81±0.06 | 0.37±0.03** |
| hepatitis + Mexidol | 375.2±141.6 | 0.96±0.18* | 1.66±0.16 | 0.63±0.08*/** | 0.38±0.09 |

**Note:** * – statistical difference with intact animals ($p<0.05$);** – statistical difference with control animals ($p<0.05$); HDL – high-density lipoproteins; LDL – low-density lipoproteins.

tions, limiting cytolysis and disturbance of metabolic processes in the liver.

The simulation of drug-induced hepatitis revealed significant histomorphological changes in the liver structure. In the liver, there developed a sharp hyperaemia of the arterial and venous networks; there was an expansion of sinusoids and lymphatic channels. At the same time, extralobular stroma was infiltrated by mononuclear cells, neutrophils and eosinophils; besides, a growth of fibrous connective tissue was also observed, including that in vessels (arteries and branches of the portal vein) and bile ducts. Hepatocytes underwent hydropic protein degeneration, sometimes turning into focal necrosis, which caused a decrease in the specific area of parenchyma. The specific area of hepatocytes decreased 1.3 ($p<0.001$) times as compared to the control group. And vice versa, the specific area of sinusoids increased 1.3 ($p<0.001$) times, and the specific area of the stroma increased 1.2 ($p<0.05$) times (Table 6). On the whole, the morphological picture may be characterized as chronic active hepatitis with fibrosis of stroma, and hepatitis in the experiment in its structural manifestations fully complied with that observed in clinical practice.

After administering Selank and Semax, a regress of pathological changes in the liver tissue was observed: inflammatory hyperaemia of inflow and outflow blood vessels of liver, as well as of sinusoids, decreased sharply; sclerotic changes in bothe arterial walls and in portal vein branches decreased equally well, and their tonus returned to normal. Besides, the usual lobular stricture of liver was preserved, and there were no signs of liver cell damage, such as degeneration and necrosis. A considerable difference of Selank from Semax was the reinforcement of regeneration processes in liver parenchyma, which showed in an increase in and hyperchromatosis of cellular nuclei and the emergence of dual-core forms, as well as considerably less expressed inflammatory infiltration of portal tracts and a noticeable decrease in the sclerosis level and the area of the portal stroma.

After administering Essentiale, minor positive dynamics was observed in the rats. The differences mostly concerned the liver parenchyma, in which there were no signs of serious damage in the form of small foci of necrosis; at the same time dystrophic changes in liver cells were expressed as much as in the control group. Inflammatory infiltration, sclerotic process in the portal stroma and vascular walls of arteries and veins showed no involution. When administering Mexidol, no considerable morphological differences were observed.

A stereometrical study showed that (Table 7) all the tested drugs prevented a statistical decrease in the specific area of hepatocytes as compared to the sick animals. However, normalization of this indicator is only observed when administering Selank and Semax, which statistically increased it as compared to the control group by 22 and 20% ($p<0.01$), respectively. An increase in the specific area of sinusoids by 21–31% occurred when administering all the tested drugs, but it was observed to a lesser extent when using Selank (there was a 9%, decrease; $p>0.05$). Also, only Selank and Semax prevented an increase in the area of the stroma? with Selank statistically decreasing it by 14% as compared to the control group. That is, this can mean the anti-fibrotic activity of the drugs in question.

Lethality of the animals is the most important integral indicator of the effect of toxic agents on the organism. While simulating toxic hepatitis, there was a 20% lethality of animals. Administration of Semax, Selank and Essentiale completely prevented it, whereas Mexidol was ineffective.

The research showed that when simulating drug-induced hepatitis in white rats by means of hepatotoxic agents (isoniazid, rifampicin and ethanol), a universal link of the mechanism of liver tissue damage was activated, that is lipid peroxidation, which resulted in the disruption of the integrity of liver cell membrane structures, a cytolytic syndrome, necrotic death of some hepatocytes and subsequent fibrosis. This led to a protein, carbohydrate and lipid metabolic imbalance, as well as to a impaired detoxification function of the liver. The disruption of biochemical processes was accompanied by obvious morphological changes in the liver.

**Table 5.** Influence of Tested Drugs on the Detoxification Functions of Liver Indices in Simulated Hepatitis.

| Groups | Direct bilirubin mkmol/L |
|---|---|
| intact | 0.52±0.02 |
| control | 0.66±0.05* |
| hepatitis + Semax | 0.44±0.06** |
| hepatitis + Selank | 0.56±0.09 |
| hepatitis + Essentiale | 0.70±0.08* |
| hepatitis + Mexidol | 0.93±0.11*/** |

**Note:** * – statistical difference with intact animals ($p<0.05$); ** – statistical difference with control animals ($p<0.05$).

**Table 6.** Influence of Tested Drugs on Osmotic Resistance of Erythrocytes (ORE) in Simulated Hepatitis.

| Groups | ORE (% of hemolysis) |
|---|---|
| intact | 55.1 ± 3.2 |
| control | 78.1 ± 4.6* |
| hepatitis + Semax | 59.2±4.7** |
| hepatitis + Selank | 62.3±4.2** |
| hepatitis + Essentiale | 64.8 ± 3.5*/** |
| hepatitis + Mexidol | 60.7 ± 4.1** |

**Note:** * – statistical difference with intact animals ($p<0.05$); ** – statistical difference with control animals ($p<0.05$).

**Table 7.** Stereometrical Research of Liver Tissue in Intact and Control Group of Rats (%).

| Groups | Hepatocytes | Sinusoids | Stroma |
|---|---|---|---|
| intact | 58.2±2.3 | 29.6±1.2 | 8.5±0.3 |
| control | 46.7±2.1* | 38.8±2.0* | 10.3±0.4* |
| hepatitis + Semax | 55.1±2.4** | 37.6±1.8* | 9.1±0.5 |
| hepatitis + Selank | 56.9±2.2** | 35.7±1.7* | 8.9±0.3** |
| hepatitis + Mexidol | 52.0±2.2 | 38.6±2.1* | 10.3±0.5* |
| hepatitis + Essentiale | 54.2±2.4 | 38.2±2.0* | 10.0±0.6* |

**Note:** * – statistical difference with intact animals ($p<0.05$); ** – statistical difference with control animals ($p<0.05$).

In the treatment of drug-induced hepatitis, Semax and, especially, Selank showed a greater therapeutic activity than the recognized hepatoprotectors – Essentiale and Mexidol. All the four drugs promoted the normalization of biochemical indicators in blood of the sick animals to a greater (with Selank and Semax) or smaller (with Essentiale and Mexidol) degree. However, only in the case of administering Selank and Semax, the restoration of biochemical indicators of blood took place along with the restoration of hystomorphological parameters of the liver. And only Selank contributed to an increase in the activity of regenerative processes.

The research proved that administering Selank and Semax to patients with pulmonary tuberculosis who already receive a massive antibacterial therapy would make it possible to decrease the number and intensity of hepatotoxical reactions, to optimize the duration and scheme of polychemotherapy, and also to prevent the development of polyresistance of tuberculosis mycobacteria.

# Conclusion

Selank and Semax have a pronounced hepatoprotective activity, superior to that of Essentiale and Mexidol. In view of their hepatoprotective activity, the drugs are rated as follows: Selank>Semax>Essentiale>Mexidol.

While administering Selank and Semax, a certain parallelism was observed between the restoration of biochemical parameters of blood and histomorphological parameters of the liver, but an increase in the activity of regenerative processes was characteristic only of Selank.

# Conflict of interests

The authors state no conflict of interests concerning the present submitted manuscript.

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