REPUBLIC OF AZERBAIJAN

On the rights of the manuscript

THE EFFECT OF THE NEW COMPLEX COMPOUND BASED ON PALLADIUM AND MEKSIDOL ON LIVER METABOLISM AND ANTIOXIDANT STATUS

ABSTRACT

of the dissertation for the degree of Doctor of Philosophy (Doctor of Science)

Specialization: 2406.02 – «Biochemistry»

Scientific field: «Biology»

Applicant: İsmayil Mammad Bagirov

BAKU-2025

The work was performed at the Scientific Research Center of the Azerbaijan Medical University.

Scientific supervisor: doctor of biological sciences, professor
Arif Mustafa Efendiyev

doctor of biological sciences, associate professor
Rena Anvar Jafarova

Official opponents: doctor of biological sciences, associate professor, senior researcher employee
Hasan Garib Babayev

doctor of biological sciences,
Suleyman Ifkhan Allahverdiyev

doctor of biological sciences, professor
Adalat Nurulla Farajov

doctor of biological sciences, professor
Panah Zulfugar Muradov

One-time Dissertation Council BED 4.33 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Azerbaijan Medical University

Chairman of the dissertation council:
doctor of biological sciences, professor
Arif Mammad Mammadov

Scientific secretary of the dissertation council:
doctor of philosophy in biological sciences, associate professor
Agil Hasan Orujov

Chairman of the scientific seminar:
doctor of biological sciences, associate professor
Namig Oruj Qudratov

İMZANI TƏSDİQ EDİRƏM
Azərbaycan Tibb Universitetinin
ELMİ KATİBİ
Tibb üzrə fəlsəfə doktoru, dosent
Rəşad Şəmsəddin oğlu Talışınskiy
26.09.2025 il

GENERAL CHARACTERISTICS OF THE WORK

The relevance of the problem and the degree of its development. Today, toxic liver injury ranks among the widely prevalent diseases among the population and creates life-threatening complications[1]. Liver cirrhosis, which is the peak of this complication, is considered a leading cause of death in Western countries[2].

Regardless of economic development, the number of people suffering from toxic hepatitis is dynamically increasing in all countries of the world.

The widespread spread of the disease and its life-threatening complications and the dynamic increase in the number of deaths from these complications have made toxic hepatitis the main problem of modern medicine. It has been established that toxic hepatitis is a polyetiological disease[3].

According to modern understanding, various types of viruses, liver metabolism disorders, environmental pollution, household chemicals, radiation, drugs, alcohol, etc. are the main etiological factors of toxic hepatitis[4,5]. It has been established that they have a more serious effect on the physiological functions of the liver and cause the development of hepatitis. In particular, by blocking the detoxification function of the liver, they create oxidative stress[6].

---

[1] Sundran V., Bjornsson E.S. Drug-induced cholestasis // Hepatol. Commun. – 2017, 1 (8), – p.726-735.

[1] Звягинцева Т.Д., Чернобой А.И. Токсические поражения печени: Современные представления и патогенетическая коррекция. // Здоровья Украіni, – 2017, – с.19-24.

[1] Губергриц Н.Б., Беляева Н.В., Клочков А.Е. [и др.]. Лекарственные поражения печени: от патогенеза к лечению. // Вестник клуба панкреатологов. – 2020, февраль, – с.72-80.

[1] Стрельникова Т. Влияние климатических изменений на заболеваемость населения и экономическое развитие регионов // Экономист – 2018, № 12, – с. 31-36.

[1] Трухан Д.И., Мазуров А.Л. Лекарственные поражения печени: актуальные вопросы диагностики и лечения // Медицинский совет – 2016, №5, – с.70-73.

[1] Louvet A., Mathurin P. Alcoholic liver disease: mechanisms of injury and targeted treatment // Nature Reviews Gastroenterology Hepatology. – 2015, Vol.12, – p. 231-242.

Free lipid peroxidation products, on the other hand, have a hepatotoxic effect and cause destructive changes in the liver tissue. In this regard, it is recommended to use drugs that have antioxidant properties in addition to hepatoprotectors in the treatment of hepatitis[7].

Clinical observations have shown that in chronic liver diseases, including toxic hepatitis, the use of drugs that have antioxidant and hepatoprotector properties does not give the expected result in restoring the impaired integrity of hepatocytes. On the other hand, the range of drugs that combine both properties (antioxidant and hepatotropic) is quite small.

These data presented in the literature emphasize the need for the synthesis of new drugs that combine hepatoprotective antioxidant properties.

Consequently, a major objective in modern medical and pharmaceutical sciences is the synthesis of pharmaceutical drugs with a broad spectrum of action and the investigation of their impact on pathological processes. In this context, many chemists and pharmacologists give preference to coordination compounds[8,9].

In this regard, the complex compound (mexidazole) synthesized by Professor Kh.I. Hasanov at the Scientific Research Center (SRC) of the Azerbaijan Medical University based on palladium and mexidol is a biologically active substance that meets the requirements of today. Because this substance combines palladium, which has hepatotropic properties, and mexidol molecules, which are used as an antioxidant drug.

The theoretical basis of mexidazole synthesis is that any toxic substance entering the body creates oxidative stress. Oxidative stress

---

[7] Мусаев Д.М., Самадов Б.Ш., Дубинина Н.В. [и др.]. Антиоксидантная коррекция фармакометаболизирующей функции печени при экспериментальном токсическом гепатите. // Вестник науки и образования, – 2020, №14 (92), Часть 1, – с.63-70.

[8]Кузнецов Н.Б., Кузнецов П.Е. Прогнозирование биологической активности лигандов каппа-опиоидного рецептора. // Auditorium, – 2015, № 4, – с. 8-18.

[9] Гасанов Х.И., Мирзаи Дж.И., Мамедова И.Ш. [и др.]. Координационные соединения платины (II) и палладия (II) с серо-кислород содержащими биологически активными лигандами. / Баку, – 2021. Təbib nəşriyyatı. – 143 с.

weakens the antioxidant defense system (ADS) by intensifying the free peroxidation of lipids in mitochondria. It has been proven that as a result of the weakening of the antioxidant defense system, ATP, which is considered the main energy source of the body, and its products, decrease.

This also reduces the body's resistance to the pathological process. In this regard, the synthesized complex compound gives hope for its future use as a pathogenetic treatment. In this regard, we consider it appropriate to study its effect on the enzymatic and non-enzymatic metabolism of the liver, which is more susceptible to metabolic disorders, as well as on oxidative stress (OS) in liver tissue.

Object and subject of the study:

1. White rats of unknown sex, weighing 120-140 g, bred in vivarium conditions,
2. White rats, in which a model of drug hepatitis, toxic hepatitis, alcoholic hepatitis was created,
3. White rats exposed to X-rays,
4. Changes in their liver,
5. Investigation of the effect of mexidazole on liver metabolism in norm and pathology.

Purpose of the study: Determination of the state of liver metabolism in non-viral hepatitis and clarification of the role of mexidazole in its regulation.

Objectives of the study:

1. Determination of the norm of enzymatic, non-enzymatic metabolism, OS and ADS markers characterizing the liver of white rats;
2. Selection of the optimal dose of mexidazole for the effect of mexidazole on enzymatic, non-enzymatic metabolism, free lipid peroxidation and ADS markers in the liver of white rats;
3. Study of changes in the amount of enzymatic and non-enzymatic metabolism, free lipid peroxidation products, and ADS markers in the liver after the creation of a drug hepatitis model in white rats, and determination of their duration;
4. Study of enzymatic, non-enzymatic metabolism, intensity of free lipid peroxidation and the role of mexidazole in the recovery

of ADS in the liver of white rats in which a drug hepatitis model was created, and the relationship of the results obtained with the duration of administration of the complex compound to the body;

5. Study of changes in the amount of enzymatic, non-enzymatic metabolism, free lipid peroxidation products and ADS markers in the liver after the creation of a toxic hepatitis model in white rats, and determination of their duration;

6. Study of the relationship between enzymatic, non-enzymatic metabolism, intensity of free lipid peroxidation and the duration of administration of mexidazole in the recovery of ADS in the liver of white rats in which a toxic hepatitis model was created;

7. Study of changes in the amount of enzymatic metabolism, free lipid peroxidation products and ADS markers in the liver after the creation of an alcoholic hepatitis model in white rats, and determination of their duration;

8. Determination of the role of mexidazole in the liver of white rats, the intensity of free lipid peroxidation and the recovery of ADS, and the dependence of the results obtained on the duration of administration of the complex compound;

9. Study of the effects of X-rays on enzymatic, non-enzymatic, free lipid peroxidation and changes in the amount of ADS markers in the liver of white rats and their duration;

10. Determination of the dependence of the intensity of enzymatic, non-enzymatic, metabolism, free lipid peroxidation and the recovery of ADS in the liver of white rats irradiated with X-rays;

11. Determination of the effect of the drug cysteplatin on liver metabolism and a comparative analysis of the results obtained with the results of mexidazole.

Methodology and methods of the study: The methodological basis of the study was the research conducted by foreign and domestic scientists in the field of biochemistry, pharmacology and hepatology, medical statistics. During the study, experiments were conducted, their documentation and comparison with the control group were carried out. To determine the results of the experiments, markers reflecting enzymatic and non-enzymatic metabolism of the liver in the blood, OS and ADS in the liver tissue

were determined. To create a pathological process, drug hepatitis, toxic hepatitis, alcoholic hepatitis, hepatitis models created using X-rays were used.

The main provisions of the dissertation presented for defense:

1. In the hepatitis model created regardless of its etiological factors, metabolic disorders in the liver tissue are associated with the intensification of oxidative stress in hepatocytes.

2. The introduction of mexidazole into the body at a dose of 0.02 mg/kg blocks the free radical process by activating the antioxidant defense system in the liver tissue and thus plays an important role in the restoration of impaired liver metabolism.

3. The regulation of impaired liver metabolism by Mexidazole depends on the duration of its administration to the body.

4. X-rays weaken the antitoxic function of the liver, leading to the development of oxidative stress and creating real conditions for toxic liver damage.

5. Since the development of oxidative stress in the liver of white rats, in which a drug hepatitis model was created, metabolic disorders take a more serious form compared to other models.

Scientific novelty of the study:

– The mechanism of action of Mexidazole on impaired liver metabolism has been clarified.

– The dependence of the level of impaired liver metabolism on the etiological factors of hepatitis has been determined.

– The role of oxidative stress in liver tissue in the mechanism of development of liver pathology has been determined.

– The optimal dose of Mexidazole in the restoration of hepatocytes has been determined.

– A specific relationship between Mexidazole and the synthesis of ALT and LDH enzymes has been revealed.

Theoretical and practical significance of the study:

– The importance of extinguishing oxidative stress in the disruption of enzymatic and non-enzymatic metabolism of the liver, regardless of the etiological factors of non-viral hepatitis, has been proven.

– The extinguishing of oxidative stress in the liver during non-viral hepatitis by mexidazole will restore the impaired function of hepatocytes.

– Mexidazole, which combines hepatoprotective and antioxidant properties, is expected to be an effective treatment for liver pathology.

Relationship of the study to the problem plan of medical sciences:

The topic of the dissertation was carried out on the basis of the plan of scientific research works of the ETC.

Reliability and approbation of the results:

The reliability of the results obtained was ensured by the statistical analysis of the quantitative indicators obtained during the experiment based on the works of domestic and foreign scientists. 12 scientific works were published on the topic of the dissertation in the register of the Higher Attestation Commissions and in journals included in the international indexing database.

Articles prepared on the basis of the dissertation materials were discussed at the following local and international scientific meetings.

– 90th anniversary of the establishment of the Azerbaijan Medical University December 19-20. Baku.

– Oncology – XX Century. XXIII International Scientific Conference April 28-May 5, 2019.

– XXXII – International Multidisciplinary Conference Prospects and Key Tendencies of Science in Contemporary World: Proceedings of the conference (June, 2023) Bubok Publishing S.L., Madrid, Spain 2023. 118 p.

– VIII International European conference on interdisciplinary scientific research, July 13-15, 2023, (Rome, Italy).

– IV International Liberty Interdisciplinary studies Conference, August 2023, New York.

– International scientific and practical conference on the topic "Modern medicine: innovations and modern approaches" dedicated to the 100th anniversary of the National Leader Heydar Aliyev, Baku, 2023, pp. 200-201.

The results of the dissertation were heard and discussed at the

meeting of the Methodological Council of the Azerbaijan Medical University ETC, at the scientific meeting of the Faculty of Public Health.

The results of the dissertation were presented and discussed at the meeting of the Methodological Council of the Scientific Research Department of Azerbaijan Medical University and at the scientific assembly of the Faculty of Public Health.

Application of research results:

The results of the research, especially the modeling of drug hepatitis, toxic hepatitis, alcoholic hepatitis, are applied at the ETC of AMU.

The organization where the dissertation work was performed: The dissertation was completed at the ETC of Azerbaijan Medical University.

The structure and volume of the dissertation: The dissertation is written in A4 format, 332 pages, in Azerbaijani with "Times New Roman" 14 font and 1.5 line spacing, and the list of literature sources is written in Azerbaijani, Russian and English.

The dissertation consists of a table of contents, introduction, literature review, materials and methods chapter, analysis of the results obtained from the results presented in 8 chapters, conclusions, list of used literature sources and a list of abbreviated words.

The literature list includes 327 sources. 12 of them are literature written in Azerbaijani, 233 in Russian, and 82 in English.

The dissertation is illustrated with 51 tables and 50 graphs.

MAIN CONTENT OF THE WORK

Materials and methods of the study: The studies were carried out on 200 white rats weighing between 140-260 g, raised in vivarium conditions.

Due to the uncertainty in the results obtained, 65 white rats were excluded from the experiment, and the results obtained from 135 were statistically analyzed and a dissertation was written on its basis.

The experiments were carried out under pain-free conditions in accordance with the requirements of the European Bioethics Commission (Strasbourg 1986). For this purpose, 0.5 ml of calypsol solution was injected into the abdominal cavity.

In accordance with the goals and objectives set in the dissertation work, the white rats selected for the experiment were divided into 25 groups, each with 5 animals.

The experimental animals included in group 1 were examined in an intact state and the results obtained from them were accepted as the norm.

The experimental animals in group 2 were injected intraperitoneally at a dose of 0.04 mg/kg once a day for 7 days, and the experimental animals in group 3 were injected intraperitoneally at a dose of 0.02 mg/kg.

The experimental animals in group 4 were examined 10 days after the cessation of the intraperitoneal injection of 0.02 mg/kg for 7 days.

A hepatitis model was created in the experimental animals in group 5.

The experimental animals in group 6 were also injected intraperitoneally at a dose of 0.02 mg/kg for 3 days, and the experimental animals in group 7 were injected intraperitoneally at a dose of 0.02 mg/kg for 7 days.

The experimental animals in group 8 were injected intraperitoneally at a dose of 0.02 mg/kg for 7 days, and were decapitated 3 days after the last injection.

The development of the pathological process was monitored for 10 days after creating a drug hepatitis model in experimental

animals included in group 9.

A toxic hepatitis model was created in experimental animals included in group 10.

In experimental animals included in group 11, mexdazole was injected into the abdominal cavity of the experimental animals in which a toxic hepatitis model was created at a dose of 0.02 mg/kg per day for 3 days.

In group 12, mexdazole was injected into the abdominal cavity of the experimental animals in which a toxic hepatitis model was created at a dose of 0.02 mg/kg per day for 7 days.

In experimental animals included in group 13, mexdazole was injected into the abdominal cavity of the experimental animals in which a toxic hepatitis model was created at a dose of 0.02 mg/kg per day for 7 days and was decapitated 3 days after the last injection.

In experimental animals included in group 14, toxic hepatitis model was created at a dose of 0.02 mg/kg per day for 7 days and was decapitated 3 days after the injection of mexdazole into the abdominal cavity of the experimental animals in which a toxic hepatitis model was created at a dose of 0.02 mg/kg per day for 7 days.

In experimental animals included in group 15, examinations were performed 10 days after the toxic hepatitis model was created.

In white rats included in group 16, an alcoholic hepatitis model was created, and in group 17, the duration of the pathological process was monitored 10 days after its creation.

In experimental animals included in group 18, in which an alcoholic hepatitis model was created, mexdazole was injected into the abdominal cavity for 3 days.

In group 19, mexdazole was injected into the abdominal cavity for 7 days at a dose of 0.02 mg/kg.

In experimental animals included in group 20, in which an alcoholic hepatitis model was created, mexdazole was injected into the abdominal cavity for 7 days at a dose of 0.02 mg/kg.

In white rats included in group 21, they were irradiated with X-rays.

The duration of the pathological process was monitored 10 days after the cessation of X-ray irradiation in white rats included in

group 22.

After X-ray irradiation of experimental animals included in group 23, mexdazole was injected into their abdominal cavity at a dose of 0.02 mg/kg per day for 3 days, and in group 24, at a dose of 0.02 mg/kg per day for 7 days.

Cystplatin was injected intraperitoneally into the intact experimental animals included in group 25 for 3 days.

In group 1 of the white rats taken for the experiment, the enzymatic and non-enzymatic metabolism of the liver, the norms of markers of oxidative stress and antioxidant defense system were determined.

In white rats included in groups 2-4, the optimal dose of mexdazole on liver metabolism was selected.

After creating a drug hepatitis model in white rats included in groups 5-10, the changes in liver metabolism and the role of mexdazole in its recovery were clarified.

In experimental animals included in groups 10-15, a toxic hepatitis model was created, the changes in liver metabolism were studied, and the role of mexdazole in their recovery was investigated.

After creating a model of alcoholic hepatitis in white rats included in groups 16-20, the state of liver metabolism was determined and the role of mexdazole in its regulation was studied.

After irradiating experimental animals in groups 21-24 with X-rays, changes in liver metabolism were studied and the role of mexdazole in its recovery was clarified.

In experimental animals included in group 25, the effect of the drug cystplatin on liver metabolism was determined and the results obtained were analyzed in comparison with the effect of mexdazole.

To assess the functional state of the liver, the concentration of Alate aspartate transaminase (AsAT GOT Ş AcJ; Aspartate Aminotransferaze UJ 2.6.1.1), Alanine Aminotransferase (AlAT GRT 1 FsJ, Alanine Aminotransferaze EJ 2.6.1.2), Glutamine transferase, creatine phosphokinase (CPK), Lactate dehydrogenase (LDH), and Alkaline phosphatase was determined in the blood.

To assess the non-enzymatic metabolism of the liver, the amount of creatinine, urea, total bilirubin, residual nitrogen, and total

protein was determined in the blood.

The amount of the indicated markers in the blood was determined using reagent kits manufactured by Human Company on a fully automated Bio Skreen MS-2000 analyzer manufactured in the USA.

In the homogenate prepared from liver tissue, lipid free radical products and total ADS markers, which are the basis of oxidative stress, were determined.

The concentration of hydrogen peroxide (H2O2), the initial product of lipid free peroxidation, was determined by the method of Askava T., Matusushita S. (1980), the concentration of diene conjugates (DK), the intermediate product, was determined by the method developed by I.D.Stalnaya (1977), and the concentration of malondealdehyde (MDA), the final product, was determined by the method proposed by Uchiyama, Michara (1978).

In the homogenate prepared from liver tissue, the following markers of ADS of the organism, which are an integral part of oxidative stress, were determined.

The surface-located protein – SH group and the intrastructural protein – SH group, the concentration were determined by the method of Ellman (1957), the concentration of catalase and reduced glutathione (peroxidase) concentration were determined by Bergmeyer (1974), and the total antioxidant activity – (UAF) was determined by the method proposed by E.B.Spektor (1984).

The drug hepatitis model was created by giving paracetamol at the rate of 2500 mg per kg of weight. For this purpose, we crushed the paracetamol tablet in a porcelain bowl and first added 20 ml of water to obtain a homogeneous solution. Then, in order to dilute it, we added 30 ml of water again, collected it in a syringe and connected it to a thin Folu catheter. We inserted the other end into the esophagus of the white rats and carefully slowly injected the paracetamol solution into the stomach of the white rats. Repeating this procedure every other day, we transferred the liquid in which paracetamol was dissolved into the stomach of the white rats 5 times. We confirmed the creation of the model based on the increase in the concentration of biochemical markers in the blood. Manipulation was carried out under anesthesia.

The toxic hepatitis model was created using the method developed at the ETM (R.C. Karimova, 2016). For this purpose, a chamber developed by R.C. Karimova was used at the ETM on the recommendation of Professor Kh.I. Hasanov.

White rats selected for the experiment were placed in that chamber and exposed to exogenous intoxication by inhaling HCl acid vapor. Inhalation with acid vapor was continued for 9 days.

To create an alcoholic hepatitis model, 1 ml of alcohol was injected into the stomach of each white rat through a small-diameter probe once a day for 10 days. 20 minutes after the alcohol injection, the experimental animals were given water to drink, thereby facilitating the absorption of alcohol from the stomach. The model we used was developed by K.G. Garayeva and G.Yh. Hajiyeva (2012) at the Department of Pathological Process Modeling at the ETM.

The animals taken into the experiment were irradiated with X-rays using the "RUM-17" device within the following parameters.

– Intensity – 180 kV;
– Current intensity – 15 m;
– Filters – 0.5 mm Cu+1.0 mm Al;
– Focal length factor – 3
– Tubeless dose rate – 0.86 Gy/sec

During the irradiation of the experimental animals, taking into account the recommendation of A.U. Eminov (2014), a single dose of 4 Gy was taken and the experimental animals were irradiated for 5 days.

Statistical processing: The quantitative indicators obtained from the experiments were processed based on modern recommendations[10,11,12].

After determining the mean score (M), its standard error (m), and the minimum and maximum limits of the quantitative indicators obtained for each group, the reliability of the results was calculated by applying the Student's T-criterion and the Wilcoxon-Mann-Whitney non-parametric U-criterion.

Correlation analysis was performed using the Brave-Pearson method. In this case, the presence of a strong correlation was confirmed when $r>0.07$.

All calculations were performed in the MS Excel spreadsheet developed at the Department of Medical Physics and Informatics of the Azerbaijan Medical University.

In Chapter 3 of the dissertation, a brief characterization of the synthesis of a new complex based on palladium and mexidol is given. The structure of the newly synthesized complex compound, conditionally called "Mexidazole", was studied using an infrared spectrometer and photographed on a Varian-Cary-100 spectrophotometer.

The electrical conductivity of the aqueous solution of Mexidazole, the spatial arrangement of atoms, the distance between atoms, the angle and the X-ray structure of the coordination sphere coverage were determined on a Bruker KEL-1M2 conductometer at a temperature of 25ºC using the X 8 Apex apparatus.

It was determined that “Mexidazole” is well soluble in water (0.12.1 ml), physiological saline, acetic and HCl acid. It is thermally stable.

When studying the kinetic stability of the obtained complex, it was found that the mentioned 832 nm absorption band disappears after 50 minutes at room temperature. At this time, the intensity of the absorption band with a maximum of 358 nm increases over time. We associate the disappearance of the mentioned 832 nm absorption band with the spontaneous intramolecular deprotonation of the ligand – (HL)2[PdCl4] in the complex.

Chapter 4 presents the results of the study on the effect of mexidazole on liver metabolism in white rats in the Internet state. The concentrations of AST, ALT, glutamine transferase, LDH, KFK and alkaline phosphatase enzymes in the blood of experimental animals included in group 1, the amount of keratin, urea, total bilirubin, residual nitrogen and total protein were determined and accepted as a norm for comparison with the results obtained from future groups.

In the homogenate prepared from liver tissue, the concentration of H_2O_2, diene conjugates, MDA, surface and intrastructural protein-SH groups, peroxidase and UAF were determined, thereby evaluating the free peroxidation of lipids in the liver tissue and the state of the general antioxidant defense system.

White rats included in group 2 were injected intraperitoneally at a dose of 0.04 mg/kg daily for 7 days. It was found that the activity of enzymes and the amount of markers characterizing non-enzymatic metabolism in the blood of experimental animals increased sharply (Table 1).

Table 1.
Changes in hepatic metabolism in the blood depending on the dose of mexidol administered intraperitoneally

	Marker	Intact condition (group 1)	group 2	group 3
1	AST	29.4±1.50	38±2.30	36.2±2.13
2	ALT	35.2±1.85	49.8±2.48	47.2±2.35
3	Glutamine transferase	43.2±5.43	54.6±3.01	51.4±4.01
4	LDH	368±28.53	386±9.27	379±7.48
5	CPK	260.4±6.00	277±13.73	295.2±13.61
6	Alkaline phosphatase	234±27.13	276.4±21.32	271.2±23.74
7	Creatine	0.92±0.09	1.04±0.10	0,96±0.11
8	Urea	33±5.08	37±5.77	35.4±5.61
9	Total bilirubin	0.8±0.14	1.0±0.4	0.96±0.13
10	Residual nitrogen	12.2±2.06	13±1.61	12.2±1.69
11	Total protein	75.4±3.47	73±2.98	73.6±3.06

In the liver tissue, the intensification of free lipid peroxidation was moderately reduced. It was determined that, compared to the intact state, the average concentration of H2O2 decreased by 1.5%, the average concentration of diene conjugates by 13%, and the average concentration of MDA by 3.5%.

The concentration of antioxidant defense system markers increased significantly. Thus, an increase of 3% was recorded in the average concentration of surface protein-SH groups, 2% in the average concentration of intrastructural protein-SH groups, 4% in the average concentration of peroxidase, 1% in the average concentration of catalase, and 17% in the average concentration of UAF.

The results obtained in the 3rd group of experimental animals

showed that a 2-fold decrease in the dose of mexidazole injection into the abdominal cavity to 0.02 mg/kg had a more adequate effect on liver metabolism (table 1). In 40% of the white rats taken into the experiment, the concentration of the AST enzyme, in 80% of the glutamine transferase and alkaline phosphatase enzymes, in 100% of the LDH enzyme, and in 20% of the CPK enzyme remained at normal levels. However, the concentration of the ALT enzyme remained above normal.

Positive dynamics of markers characterizing non-enzymatic metabolism were also observed in the blood taken from the hepatic portal vein. Thus, compared to the 2nd group, the amount of creatinine in the blood of the 3rd group animals decreased by 8%, the amount of urea and total bilirubin by 4%, the amount of residual nitrogen by 6%, and the amount of total protein increased by 1%.

The administration of mexidazole at a dose of 0.02 mg/kg also had a positive effect on lipid peroxidation in the liver tissue and the antioxidant defense system. Thus, the concentrations of H2O2, diene conjugates and MDA in the blood taken from the liver decreased by 2%, 7% and 9%, respectively, compared to group 2. Accordingly, the concentrations of markers of the body's antioxidant defense system increased significantly. Compared to group 2, the concentration of surface protein-SH groups in the homogenate prepared from liver tissue increased by 3%, the concentration of intrastructural protein-SH groups by 1%, the concentration of peroxidase by 2%, the concentration of catalase by 7.5%, and the concentration of UAF by 8%.

This chapter also provides information on the duration of action of mexidazole after its administration to the body at a dose of 0.02 mg/kg. The continuation of the effect of mexidazole was confirmed in the blood taken from the portal vein of the liver and in the homogenate prepared from the lungs 10 days after the cessation of mexidazole administration into the abdominal cavity of experimental animals included in group 4.

In group 25, a comparative analysis of cystplatin and mexidazole, which are used in chemotherapy in oncology, was conducted. It was determined that mexidazole has a more adequate

effect on liver metabolism than cisplatin.

In chapter 5 of the dissertation, the effect of the drug hepatitis model on liver metabolism and the role of mexidazole in its regulation were clarified.

A drug hepatitis model was created by giving paracetamol to experimental animals included in group 5. It was proved that hepatitis developing after paracetamol intake disrupted the physiological course of liver enzyme metabolism and sharply increased the concentration of enzymes synthesized in the liver in the blood (table 2). Among these enzymes, glutamine transferase, CPK and alkaline phosphatase are more sensitive markers for drug hepatitis. The concentration of the mentioned enzymes increased to a level higher than normal in 100% of the animals taken for the experiment.

Table 2.
Effect of mexidazole on increased concentrations of markers characterizing liver metabolism in the blood of white rats in which a drug hepatitis model was created

	Marker	Group 1	Group 5	Group 6	Group 7
1	AST	29.4±1.50	58.6±5.34	47.2±5.05	36.6±4.40
2	ALT	35.2±1.85	63.4±4.56	55.6±2.46	42±4.56
3	Gamma glut. transferase	43.2±5.43	86.8±8.98	71.4±9.74	58.2±8.70
4	LDH	368±28.53	718±47.79	636±41.30	548±46.84
5	CPK	260.4±6.00	519±23.33	483.4±52.34	350±28.72
6	Alkaline phosphatase	234±27.13	526±37.89	446.2±30.27	384±28.74
7	Creatine	0.92±0.09	1.62±0.17	1,16±0.19	0,94±0.12
8	Urea	33±5.08	63±9.66	54.4±9.57	49.4±8.97
9	Total bilirubin	0.8±0.14	1.7±0.20	1.42±0.24	1.2±0.16
10	Residual nitrogen	12.2±2.06	21.8±3.44	16.8±3.54	13.8±3.44
11	Total protein	75.4±3.47	70±4.28	71.0±3.97	74.2±4.18

The concentration of markers characterizing non-enzymatic metabolism of the liver in the blood also increased sharply. Compared to the intact state, the amount of creatinine in the blood of animals of group 5 increased by 76%, the amount of urea by 91%, the amount of total bilirubin by 112.5%, and the amount of residual nitrogen by 79%. The amount of total protein decreased by 7% below normal. However, unlike enzymes, the amount of non-enzymatic metabolism markers remained normal in 20-60% of the animals tested. The amount of creatinine, urea, and total bilirubin did not go beyond the normal range in 20% of the animals tested, the amount of residual nitrogen by 40%, and the amount of total protein by 60%.

As a result of the determination of oxidative stress markers in the homogenate prepared from the liver, it was determined that the process of free radicalization of lipids in the liver of white rats with drug hepatitis was intensified. Thus, the concentration of the first product H_2O_2 formed during free radical oxidation of lipids in the homogenate increased by 79% compared to the intact state ($P<0.001$). The difference in the concentration of diene conjugates and MDA was 40% and 133%, respectively ($P<0.001$).

Despite the intensification of free peroxidation of lipids, the concentration of antioxidant defense system markers in the liver significantly decreased. This decrease was more pronounced in the concentration of the surface protein-SH group. Its average concentration decreased by 43% compared to the intact state ($P<0.001$).

The concentration of the intrastructural protein SH group decreased slightly compared to the surface protein SH group. The difference with the level in the intact state was 36% ($P<0.01$). The concentration of peroxidase was 34%, the concentration of catalase was 8.5%, and the UAF was 26%.

Thus, the results of our experiments showed that oxidative stress occurs in the liver of white rats in which a drug hepatitis model was created as a result of a disruption in the balance between the body's general antioxidant system and the process of lipid free radicalization. Due to the oxidative stress that occurred, the functional state of the liver is disrupted and, as a final result, the amount of

enzyme and non-enzyme markers characteristic of hepatitis in the blood increases.

After the drug hepatitis model was created in the experimental animals included in the 6th group, mexidazole was injected into their abdominal cavity at a dose of 0.02 mg/kg each time for 3 days. On the 4th day of the experiment, the concentration of the AST enzyme in the blood decreased by 19.5%, the concentration of the ALT enzyme by 12%, the concentration of the glutamine transferase enzyme by 18%, the concentration of the LDH enzyme by 11%, the concentration of the CPK enzyme by 7%, and the concentration of the alkaline phosphatase enzyme by 15% compared to the 5th group. The concentration of the remaining enzymes, with the exception of AST and glutamyl transferase, was higher than normal in 100% of the experimental animals.

Thus, mexidazole, injected intraperitoneally at a dose of 0.02 mg/kg for 3 days in experimental animals with a drug-induced hepatitis model, significantly reduced the elevated concentration of liver enzymes in the blood (table 2).

Mexidazole also caused significant changes in the amount of non-enzymatic markers of the liver (table 2). Creatinine decreased by 28%, urea by 14%, total bilirubin by 16.5%, and residual nitrogen by 23%. The amount of total protein tended to increase. The results of the experiments showed that mexidazole has hepatoprotective properties. Because, as a result of the effect of mexidazole, the increased levels of creatinine in 80% of the experimental animals, urea and total bilirubin in 40%, and residual nitrogen and total protein in 60% decreased to normal levels.

The regulation of oxidative stress in the liver tissue was also revealed due to the effect of mexidazole. The concentration of H_2O_2 decreased by 31% compared to group 5, the concentration of diene conjugates by 14%, and the concentration of MDA by 32%.

Positive changes occurred in the direction of restoring the disturbed balance between free lipid peroxidation and the body's antioxidant defense system. The concentration of surface protein-SH groups increased by 61%, the concentration of intrastructural protein-SH groups by 32%, the concentration of peroxidase by 14%, the

concentration of catalase by 20%, and the concentration of UAF by 56% confirm the above-mentioned idea.

The results of the experiments of group 7 showed that the effect of mexidazole increases as the duration of its administration to the body is prolonged (table 2).

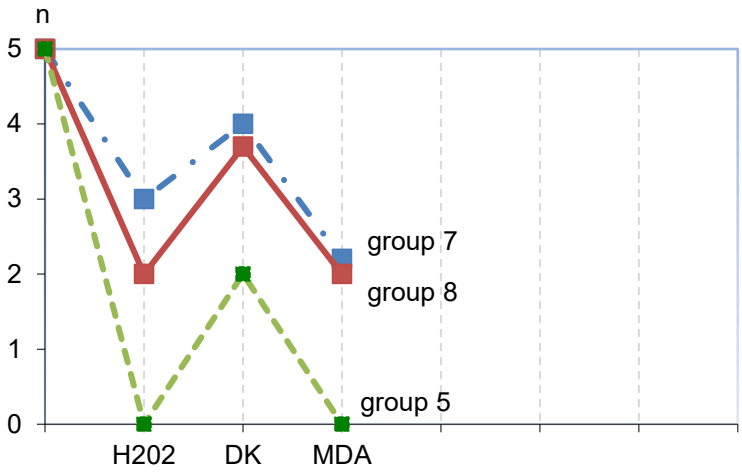
One of the tasks set was to investigate the effect of mexidazole after its administration to the body is stopped. To solve this task, we had to investigate the changes in liver metabolism in experimental animals included in group 8 3 days after the administration of mexidazole to the body is stopped. It was determined that the concentration of AST, ALT, glutamine transferase, LDH, CPK and alkaline phosphatase in the blood remained almost unchanged.

The determination of markers that assess non-enzymatic metabolism of the liver in the blood gave slightly different results. 3 days after stopping the administration of mexidazole, the amount of creatinine increased by 6%, and the amount of residual nitrogen by 4%. Other indicators remained at the level of group 7.

After stopping the administration of mexidazole, the concentration of the initial product of free lipid peroxidation in the liver tissue increased again. However, the concentration of intermediate and final products continued to decrease. This is due to the fact that mexidazole inhibits oxidative stress and prevents the completion of free lipid peroxidation. This idea is also confirmed by the increase in the number of experimental animals with normal levels of free lipid peroxidation products (graph 1). Thus, the concentration of H2O2 in 60% of experimental animals, diene conjugates in 80%, and MDA in 40% was at normal levels.

Along with the attenuation of free lipid peroxidation, the strengthening of the antioxidant system was also recorded.

The concentration of the protein-SH group located on the surface not only maintained the level of group 7, but also continued to increase, albeit weakly.



Graph 1. The dynamics of the number of animals with normal concentrations of free lipid peroxidation products in the liver tissue

Compared to group 7, the concentration of each of the other markers of the antioxidant system increased by 2%.

Thus, based on the results obtained from experimental animals included in group 8, we conclude that mexidazole stimulates the antioxidant defense system in the body and strengthens it. This property continues even after the drug is stopped being administered to the body.

The results of the experiments conducted on animals included in group 9 show that the drug hepatitis model created by administering paracetamol to white rats creates oxidative stress in the liver, as well as serious changes in its metabolism. These changes continue even 10 days after the model was created. Based on this, we explain the positive results obtained from experimental animals included in group 8 with the effect of mexidazole administered to the body.

Chapter 6 of the dissertation describes the changes in liver metabolism in white rats, in which a toxic hepatitis model was created, and the role of mexidazole in its regulation.

It was determined that the enzymatic metabolism of the liver

was more seriously impaired in white rats, in which a toxic hepatitis model was created. In the intact state, the concentration of AST and ALT enzymes in the blood increased by 152% and 139%, respectively, the concentration of glutamyl transferase enzyme by 137.5%, the concentration of LDH enzyme by 133%, the concentration of CPK enzyme by 142%, and the concentration of alkaline phosphatase enzyme by 198%.

It should be noted that the increase in the concentration of the enzymes we studied was observed in 100% of the animals taken for the experiment.

Analysis of the results obtained from both models showed that the enzymatic metabolism of the liver was more severely impaired in the toxic hepatitis model than in the drug hepatitis model. This was also reflected in the determination of markers characterizing non-enzymatic metabolism of the liver.

It was determined that the amount of creatinine in the blood increased by 172%, the amount of urea by 153%, the amount of total bilirubin by 210%, the amount of residual nitrogen by 157%, and the amount of total protein decreased by 12%. In the liver homogenate prepared from the intact state, the concentration of H_2O_2 increased by 98%, the concentration of diene conjugates by 70%, and the concentration of MDA by 168% compared to the intact state. The concentration of lipid peroxidation products in the liver tissue also increased significantly compared to animals modeled with drug hepatitis. Thus, the concentration of H_2O_2 in the liver homogenate prepared from animals of group 10 was 11% higher, the concentration of diene conjugates by 22%, and the concentration of MDA by 15% higher than in group 5.

Thus, the results of our experiments proved that in the liver of white rats, in which a toxic hepatitis model was created, free lipid peroxidation was sharply intensified.

With the exception of catalase, the concentration of antioxidant defense system markers decreased significantly. The decrease in the concentration of surface protein-SH groups and the concentration of UAF was more pronounced than the concentration of other markers.

When analyzing the results obtained from both protein–SH

groups, it becomes clear that the protein–SH group located on the surface has undergone a more profound change than the protein–SH group located inside the structure. Thus, compared to the intact state, the concentration of the protein–SH group located on the surface has decreased by 48% ($p<0.001$), and the concentration of the protein–SH group located inside the structure has decreased by 42% ($p<0.001$). This ratio was not observed in comparison with the results obtained from the drug hepatitis model. Compared to the 5th group, the concentration of the protein–SH group located on the surface has decreased by 9%, while the concentration of the protein–SH group located inside the structure has decreased by 10%.

Compared to the intact state, the concentration of peroxidase has decreased by 9%, and the concentration of UAF has decreased by 51%.

Thus, the results obtained from the 10th group animals prove that, as in the drug hepatitis model, the balance between the intensity of lipid peroxidation and the antioxidant defense system of the organism in the liver tissue of experimental animals in which the toxic hepatitis model was created is disrupted, and as a result, oxidative stress occurs.

In order to determine the role of mexidazole in regulating the impaired metabolism of the liver during toxic hepatitis, mexidazole was injected into the abdominal cavity of white rats in group 11 at a dose of 0.02 mg/kg daily for 3 days. It was determined that due to the effect of mexidazole, the concentration of AST and ALT in the blood of animals in group 11 decreased by 9% and 10.5%, respectively, compared to group 10. The concentration of the glutamine transferase enzyme decreased by 17.5%, the concentration of the LDH enzyme decreased by 6%, the concentration of the CPK enzyme decreased by 7%, and the concentration of the alkaline phosphatase enzyme decreased by 3%.

Thus, the injection of mexidazole into the abdominal cavity of white rats in which a toxic hepatitis model was created reduced the elevated levels of enzymes characterizing liver metabolism in the blood to a certain extent. The decrease in the concentration of glutamine transferase and ALT enzymes was higher than that of other

enzymes. The concentration of alkaline phosphatase enzyme changed very little.

When we examined the comparative effect of Mexidazole on drug-induced hepatitis and toxic hepatitis, we came to the following conclusion.

In the blood of experimental animals included in group 11, compared to the experimental animals injected with the aforementioned complex for drug hepatitis, the concentration of AST enzyme was 42% ($P<0.05$), the concentration of ALT enzyme was 35% ($P<0.01$), the concentration of glutamine transferase enzyme was 18.5%, the concentration of LDH enzyme was 26% ($P<0.05$), the concentration of KFK enzyme was 21%, and the concentration of alkaline phosphatase was 52% ($P<0.001$) higher. Based on the results obtained, we believe that Mexidazole has a better effect on the normalization of liver enzymes against the background of the drug hepatitis model.

Mexidazole also had a positive effect on non-enzymatic metabolism of the liver. Thus, after 3 days of intraperitoneal injection of mexidazole, the amount of creatinine in the blood decreased by 20%, the amount of total bilirubin by 23%, and the amount of residual nitrogen by 21%. The decrease in the amount of urea was relatively small and amounted to 6%.

However, despite this positive dynamics, the average amount of markers characterizing liver metabolism in the blood differed sharply from the intact state, with the exception of the amount of total protein. Thus, compared to the intact state, the amount of creatinine in the blood was 117% ($P<0.01$), the amount of urea by 138% ($P<0.001$), the amount of total bilirubin by 137.5% ($P<0.01$), and the amount of residual nitrogen by 103% ($P<0.01$). The amount of total protein, on the other hand, came closer to the level in the intact state. Thus, it decreased by only 6% from the level in the intact state.

In comparison with experimental animals in which a drug hepatitis model was created, it was determined that mexidazole significantly reduced the elevated concentration of enzymes, as well as the elevated concentration of non-enzymatic markers characteristic of liver metabolism in the blood, with the exception of urea.

Intraperitoneal injection of mexidazole for 3 days also gave significant results in regulating the disturbed balance between free lipid peroxidation and the antioxidant defense system in the liver tissue. The concentration of H_2O_2 decreased by 20% compared to the level in group 10, the concentration of diene conjugates by 7%, and the concentration of MDA by 10%.

At the same time, from the analysis of the results obtained, it became clear that mexidazole has a more effective effect on drug hepatitis.

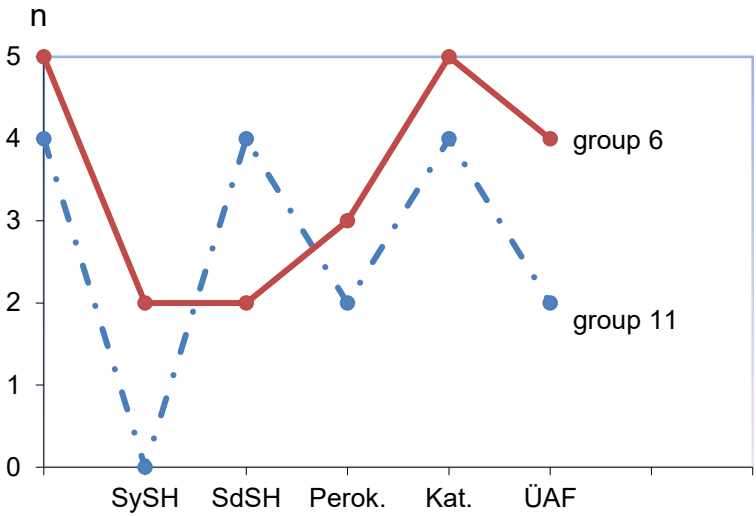
Thus, while the concentration of lipid peroxidation products in the liver of 100% of experimental animals included in group 11 was higher than normal, the concentration of H2O2 in 60% of experimental animals included in group 6, DK in 40% and MDA in 20% decreased to normal levels.

Thus, the injection of mexidazole into the abdominal cavity during toxic hepatitis partially suppresses the intensity of lipid peroxidation in the liver tissue.

Mexidazole also had a positive effect on the body's antioxidant defense system. Compared to group 10, the concentration of surface-located protein-SH groups increased by 52%, the concentration of intrastructural protein-SH groups by 78%, the concentration of peroxidase by 33%, the concentration of catalase by 7%, and the concentration of UAF by 70%.

Mexidazole had a better effect on drug-induced hepatitis (group 6) than on toxic hepatitis (graph 2).

Group 6 also prevailed in terms of the number of experimental animals whose concentrations of the markers we studied reached normal levels. Thus, in 40% of the experimental animals included in group 6, the concentration of surface-located and intrastructural protein-SH groups decreased to normal levels, the concentration of peroxidase by 60%, the concentration of catalase by 100%, and the concentration of UAF by 80%.



Graph 2. Number of experimental animals in groups 6 and 11 whose concentration of antioxidant defense system markers reached normal levels

In order to determine the degree of recovery of impaired liver metabolism as a result of toxic hepatitis depending on the duration of mexidazole administration, we conducted experiments on white rats included in group 12. We injected mexidazole into their abdominal cavity for 7 days. In the blood of experimental animals included in this group, the concentration of enzymes synthesized in the liver decreased more than in group 10. Thus, the decrease in the concentration of AST enzyme in the blood was 36%, the decrease in the concentration of ALT enzyme was 27%, the decrease in the concentration of glutamine transferase enzyme was 15.5%, the decrease in the concentration of LDH enzyme was 11%, the decrease in the concentration of CPK enzyme was 15%, and the decrease in the concentration of alkaline phosphatase enzyme was 12%.

Positive changes were recorded in the amount of markers characterizing non-enzymatic metabolism of the liver in the blood taken from experimental animals included in group 12. Compared to group 10, the amount of creatinine in the blood decreased by 44%, the

amount of urea by 23%, the amount of total bilirubin by 52%, and the amount of residual nitrogen by 43%, approaching the norm. The amount of total protein increased by 9%.

Analysis of the results obtained from groups 11 and 12 showed that, as in the drug hepatitis model, the effect of mexidazole in experimental animals in which the toxic hepatitis model was created is directly proportional to the duration of its introduction into the body.

However, despite this positive dynamics, the amount of creatinine in the blood remained at a high level of 52%, the amount of urea by 96%, the amount of total bilirubin by 50%, and the amount of residual nitrogen by 46% compared to the intact state. The amount of total protein was 4% lower.

When comparing the results obtained from groups 7 and 12, it becomes clear that mexidazole has a more effective effect on the drug hepatitis model.

A positive change was also observed in the dynamics of oxidative stress in the liver of white rats, in which a toxic hepatitis model was created due to the effect of mexidazole. The results obtained from groups 11 and 12 in the liver homogenate showed that the administration of mexidazole to the body for 7 days had a more effective effect on extinguishing oxidative stress. The concentration of H_2O_2 in the homogenate decreased by 33%, the concentration of DK by 5%, and the concentration of MDA by 25%. At the same time, the concentration of H_2O_2 in 60% of the experimental animals, and the concentration of diene conjugates and MDA in 20% of the experimental animals decreased to normal levels.

The concentration of general antioxidant defense system markers, which was below normal, approached normal levels.

Compared to group 11, the concentration of the surface protein-SH group increased by 61%, the concentration of the intrastructural protein-SH group by 90%, the concentration of peroxidase by 64%, the concentration of catalase by 20%, and the concentration of UAF by 70%.

Thus, the results of our experiments showed that as the duration of mexidazole administration to the body is prolonged, its effect coefficient also increases.

The positive effect of mexidazole continued even after the administration of mexidazole to the abdominal cavity of white rats in which a toxic hepatitis model was created was stopped. To prove this, when comparing the results obtained 3 days after stopping the administration of mexidazole (group 13) with the results obtained on the 10th day of the model creation in experimental animals with toxic hepatitis (group 14), we determined that the concentration of the AST enzyme in the blood decreased by 52%, the concentration of the ALT enzyme by 41%, the concentration of the glutamine transferase enzyme by 41%, the concentration of the LDH enzyme by 17%, the concentration of the CPK enzyme by 29%, and the concentration of the alkaline phosphatase enzyme by 22%.

3 days after stopping the administration of mexidazole, the non-enzymatic metabolism of the liver also maintained its positive dynamics.

Compared to group 13, the amount of creatinine in the blood decreased by 3%, the amount of urea by 5%, the amount of total bilirubin by 8%, and the amount of residual nitrogen by 3%. The amount of total protein increased by 2.8%. The results obtained show that despite the cessation of the administration of mexidazole to the body, its effect continues. In the homogenate prepared from liver tissue, the concentration of H_2O_2 decreased by 57%, the concentration of diene conjugates by 20%, and the concentration of MDA by 42%.

The concentration of the surface protein-SH group increased by 11%, the concentration of the intrastructural protein-SH group by 2%, and the concentration of peroxidase increased by 27%. However, the concentration of catalase decreased by 2%, and the activity of UAF decreased by 7%.

Thus, in experimental animals in which a toxic hepatitis model was created, mexidazole plays an important role in the regulation of impaired liver metabolism, as in animals in which a drug hepatitis model was created. Thanks to its administration to the body, the increased amount of enzymes and markers representing non-enzymatic metabolism of the liver in the blood tends to normalize. The disturbed balance between lipid peroxidation in liver tissue and the body's antioxidant defense system is moving towards at least partial

restoration.

In Chapter 7 of the dissertation, the role of mexidazole in the regulation of liver metabolism in white rats in which an alcoholic hepatitis model was created and its role were explained.

In accordance with the method shown in Chapter II of the dissertation, we created an alcoholic hepatitis model on experimental animals included in the 16th group. As a result of the examinations conducted on the same experimental animals, we determined that alcoholic hepatitis also has a negative effect on liver metabolism. However, compared to other models, the enzymatic and non-enzymatic metabolism of the liver was relatively less disturbed (Table 3). Compared to the intact state, the concentration of the AST enzyme in the blood increased by 56%, the concentration of the ALT enzyme by 61%, the concentration of the glutamine transferase enzyme by 80%, the concentration of the LDH enzyme by 66%, the concentration of the CPK enzyme by 123%, and the concentration of the alkaline phosphatase enzyme by 88%.

At the same time, the amount of markers reflecting the non-enzymatic metabolism of the liver in the blood also increased. This increase was 65.2% for creatinine, 83% for urea, 102.5% for total bilirubin, and 67.2% for residual nitrogen. The amount of total protein decreased by 6% compared to the intact state.

The following results were obtained from the examination of the homogenate prepared from the liver. It was determined that the concentration of H_2O_2 was 80% higher than the level in the intact state, the concentration of diene conjugates was 26% higher, and the concentration of MDA was 126%. Based on the results obtained, we conclude that free lipid peroxidation in the liver tissue was intensified under the influence of alcohol. Despite this, inactivity was observed in the general antioxidant defense system of the body.

Table 3.
Changes in liver metabolism in white rats, in which a hepatitis model was created depending on the etiological factors

	Markers	Drug hepatitis model	Toxic hepatitis model	Alcohol hepatitis model
1	AST	58.6±5.34	74.2±4.32	45.8±4.88
2	ALT	63.4±4.56	84±4.30	56.6±3.33
3	Glutamine transf.	86.8±8.98	102.6±5.64	72±10.68
4	LDH	718±47.79	856±50.36	610±43.93
5	CPK	519±23.33	629±23.58	581±31.85
6	Alkaline phosphatase	526±37.89	698±28.71	440±32.71
7	Creatine	1.62±0.17	2.5±0.22	1.52±0.15
8	Urea	63±9.66	83.6±4.30	60.4±8.93
9	Total bilirubin	1.7±0.20	2.48±0.19	1.62±0.17
10	Residual nitrogen	21.8±3.44	31.4±2.06	20.4±2.71
11	Total protein	70±4.28	66.4±4.34	70.8±4.26

Compared to the intact state, the concentration of surface protein – SH group decreased by 39%, the concentration of intrastructural protein – SH group decreased by 30%, the concentration of peroxidase decreased by 16%, the concentration of catalase decreased by 11%, and the concentration of UAF decreased by 44%.

The changes that occurred in the blood and liver tissue of white rats with alcoholic hepatitis were somewhat milder compared to drug and toxic hepatitis (table 3).

In the blood taken 10 days after stopping alcohol intake (group 17), both enzymatic and non-enzymatic liver metabolism indicators remained at a higher level than in the intact state. However, compared to the first days of the hepatitis model, the concentration of AST enzyme decreased by 1%, the concentration of glutamine transferase

enzyme decreased by 6%, and the concentration of alkaline phosphatase decreased by 1%. The concentration of ALT, LDH, and CPK enzymes remained at their previous levels.

Thus, the results of our experiments showed that despite the fact that 10 days had passed since the creation of the alcoholic hepatitis model, the enzymatic metabolism of the liver continued to be impaired in the blood.

The amount of markers representing the non-enzymatic metabolism of the liver remained at a high level in the blood of experimental animals included in group 17 (table 3). Compared with group 16, the amount of creatinine in the blood decreased by 4%, the amount of urea by 2%, and the amount of total bilirubin and residual nitrogen by 6%. Thus, the results of our experiments showed that in white rats, in which the alcoholic hepatitis model was created, the non-enzymatic metabolism of the liver is less stable than the enzymatic metabolism. Thus, on the 10th day of the creation of the model, the increased amount of markers of non-enzymatic metabolism tended to decrease.

The concentration of H_2O_2 in the homogenate prepared from the liver decreased by 1%, and the concentration of diene conjugates by 2%. The concentration of MDA did not differ from the level in animals of group 16.

Thus, although the free peroxidation of lipids in the liver of white rats in which the alcoholic hepatitis model was created was at a high intensity, it was slightly weakened compared to the first days of the model creation.

Despite the fact that 10 days had passed since the creation of the model in white rats in which the alcoholic hepatitis model was created, the overall antioxidant defense system of the liver tissue still remained at a low level.

In the homogenate, the concentration of the protein-SH group located on the surface increased by 40% compared to the intact state, the concentration of the protein-SH group within the structure increased by 30.5%, the concentration of peroxidase increased by 17.5%, the concentration of the catalase enzyme increased by 13.5%, and the concentration of UAF increased by 48%. However, in

addition, the concentration of the antioxidant defense system markers increased slightly compared to group 16.

Thus, the results of our experiments allow us to conclude that as a result of the influence of alcohol, liver metabolism is disrupted, an imbalance occurs between lipid peroxidation in hepatocytes and the general antioxidant defense system, and this situation persists even 10 days after stopping alcohol administration.

Group 18 animals, in which alcoholic hepatitis was induced, were injected intraperitoneally with mexidazole at a dose of 0.02 mg/kg per day for 3 days.

It was determined that under the influence of mexidazole, the concentration of the AST enzyme in the blood decreased by 7%, the concentration of the ALT enzyme and alkaline phosphatase enzyme by 8%, the concentration of the glutamine transferase enzyme by 13%, and the concentration of LDH and CPK by 5%.

Positive dynamics were also observed in the blood of the experimental animals included in this group in the non-enzymatic metabolism of the liver.

Compared to group 16, the amount of creatinine in the blood decreased by 17%, the amount of urea by 13%, the amount of total bilirubin by 26%, and the amount of residual nitrogen by 11%. The amount of total protein increased by 2%. However, the amount of markers representing non-enzymatic metabolism of the liver in the blood was still higher than the level in the intact state.

The intensity of oxidative stress in the liver was also significantly attenuated by the effect of mexidazole. As an example, the concentration of diene conjugates of H_2O_2 and MDA decreased by 13%, 12%, and 12%, respectively. Accordingly, the concentration of protein-SH groups located on the surface increased by 21%, the concentration of protein-SH groups within the structure by 28%, the concentration of peroxidase by 63%, the concentration of catalase enzyme by 20%, and the concentration of UAF by 25%.

Thus, the results of our experiments on white rats included in group 18 showed that as a result of the creation of alcoholic hepatitis, the enzymatic and non-enzymatic metabolism of the liver is disrupted. Oxidative stress occurs as a result of the imbalance between free

peroxidation of lipids in the liver tissue and the general antioxidant defense system of the body. As a result of the daily injection of mexidazole into the abdominal cavity for 3 days at a dose of 0.02 mg/kg, the impaired liver functions are regulated and come closer to normal compared to other models.

Group 19 white rats were injected intraperitoneally with mexidazole for 7 days. The main goal here was to determine whether the effect of mexidazole on liver metabolism depends on the duration of its administration. The results obtained from the experiments proved that the therapeutic effect of extending the duration of mexidazole administration is more effective (Table 4).

It was determined that the longer the duration of mexidazole administration, the more effective it is in inhibiting oxidative stress in the liver caused by alcohol.

Table 4.
Changes in liver metabolism in white rats in which a hepatitis model was created depending on etiological factors

	Markers	group 16	group 18	group 19
1	AST	45.8±4.88	42.8±4.65	37.6±3.91
2	ALT	56.6±3.33	52.0±2.59	45±2.59
3	Glutamine transf.	72.0±10.68	62.8±9.04	54.8±8.56
4	LDH	610±43.93	580±47.85	550±48.06
5	CPK	581±31.85	547.4±37.47	518±32.99
6	Alkaline phosphatase	440±32.71	404±20.40	384±23.79
7	Creatine	1.52±0.15	1.26±0.12	1.02±0.11
8	Urea	60.4±8.93	52.6±8.96	46.4±7.62
9	Total bilirubin	1.62±0.17	1.2±0.14	1.04±0.09
10	Residual nitrogen	20.4±2.71	18.2±2.85	15.6±2.73
11	Total protein	70.8±4.26	78.4±3.85	73.6±3.50

In the liver homogenate, the concentration of H_2O_2 decreased by 19%, the concentration of diene conjugates by 27%, and the concentration of MDA by 23% compared to group 18.

The concentration of markers of the body's general antioxidant defense system also increased significantly in the homogenate. Thus, the concentration of the surface protein-SH group was 15% higher than in group 18, the concentration of the intrastructural protein-SH group was 21% higher, the concentration of peroxidase was 35% higher, the concentration of catalase was 11% higher, and the average concentration of UAF was 45%.

The amount of markers we studied in the blood and liver homogenate taken from white rats in group 20 for 7 days after mexidazole was injected into the abdominal cavity and stopped 3 days later did not differ much from group 19.

The concentration of AST enzyme in the blood decreased by 8.5%, ALT enzyme by 3%, glutamine transferase enzyme by 12%, LDH enzyme by 7%, CPK enzyme by 6%, and alkaline phosphatase by 18.2%. However, despite this difference, it was still close to normal levels. From this we can conclude that even after stopping the intraperitoneal injection of mexidazole, its therapeutic effect continued.

The therapeutic effect of mexidazole was revealed in the determination of markers of non-enzymatic metabolism of the liver. Thus, although the amount of creatinine in the blood taken from the hepatic vein decreased by 12% compared to group 19, its amount remained within the normal range in 100% of the experimental animals.

Although the amount of urea decreased by 23%, it was 8% higher than the normal range.

The amount of total bilirubin decreased by 15%, and the amount of residual nitrogen decreased by 23%. However, in 100% of the experimental animals, the amount of total bilirubin and in 80% of the residual nitrogen remained at normal levels.

The amount of total protein increased by 3% and was at normal levels in 100% of the experimental animals.

The effect of mexidazole is also clearly visible in the liver

tissue. During the examination of the homogenate prepared from the tissue, it was found that 3 days after stopping the administration of mexidazole, free lipid peroxidation intensified.

Compared to animals in group 19, the intensity of H_2O_2 decreased by 33.3%, the concentration of MDA decreased by 12.5%. The concentration of diene conjugates remained stable.

The concentration of the surface protein-SH group increased by 24%, the concentration of the intrastructural protein-SH group increased by 16%, and the concentration of peroxidase increased by 3%. The concentration of UAF decreased by 6.2% compared to the level in animals in group 19. However, in 60% of the animals tested, the concentration of UFA in the liver tissue was higher than normal, in 20% it was normal, and in the same number it was lower than normal.

Thus, the results of our experiments prove that mexidazole restores the impaired metabolism of the liver of white rats with alcoholic hepatitis.

Group 21 of experimental animals was irradiated with X-rays. Under the influence of X-rays, the concentration of the AST enzyme in the blood increased by 27%, the concentration of the ALT enzyme by 30%, the concentration of the glutamine transferase enzyme by 17%, the concentration of the LDH enzyme by 31%, the concentration of the CPK enzyme by 52%, and the concentration of alkaline phosphatase by 29% compared to the level in the intact state. From this it is clear that as a result of the influence of X-rays, the enzymatic metabolism of the liver is disrupted.

Changes characteristic of the disruption of non-enzymatic metabolism occurred in the liver of white rats exposed to X-rays. The amount of creatinine in the blood increased by 43.5% compared to the level in the intact state, the amount of urea by 72%, the amount of total bilirubin by 70%, the amount of residual nitrogen by 45%. The amount of total protein decreased by 7% compared to the intact state.

X-rays disturbed the balance between lipid free radicalization and the body's antioxidant defense system in the liver tissue, leading to oxidative stress. As a result, the concentration of H_2O_2 in the blood increased by 87.5% compared to the intact state, the concentration of

diene conjugates by 61.5%, and the concentration of malondealdehyde by 158%.

Accordingly, the concentration of markers of the body's antioxidant defense system decreased. Compared to the intact state, this difference was 45% for the surface protein-SH group, 42% for the intrastructural protein-SH group, 29% for the concentration of peroxidase, 80% for the concentration of catalase, and 55% for the concentration of UAF.

Thus, the results of our experiments showed that the effect of X-rays disrupts the balance between enzymatic and non-enzymatic metabolism of the liver, as well as free lipid peroxidation and the antioxidant defense system.

The results of the experiments conducted in group 22 showed that the effects of X-rays permanently disrupt the functions of the liver. However, unlike other models of hepatitis, the disruption of enzymatic and non-enzymatic metabolism of the liver in group 22 animals was relatively mild.

In order to clarify the role of mexidazole in restoring impaired liver function, we conducted experiments on white rats included in group 23. We found that intraperitoneal injection of mexidazole at a dose of 0.02 mg/kg for 3 days plays an important role in restoring enzymatic metabolism of the liver. Thus, after stopping the injection of mexidazole, the concentration of AST enzyme in the blood decreased by 10%, ALT enzyme by 11%, glutamine transferase enzyme by 14%, LDH enzyme by 12%, CPK enzyme by 8%, and alkaline phosphatase enzyme by 10% compared to group 21.

Thus, based on the results obtained, it can be concluded that X-rays disrupt the enzyme synthesis function of the liver. The injection of mexidazole significantly reduces the hyperenzymemia that occurred in the blood. This once again confirms that mexidazole has hepatoprotective properties. In addition to reducing hyperenzymemia, mexidazole injected into the abdominal cavity partially corrected the impaired detoxification function of the liver.

It was determined that compared to group 21, the amount of creatinine in the blood decreased by 29%, the amount of urea by 33.5%, the amount of total bilirubin by 26.%%, and the amount of

residual nitrogen by 33%. An increase of 3% was observed in the amount of total protein.

Mexidazole also corrected the oxidative stress developed in the liver tissue to some extent. The concentration of H_2O_2 in the homogenate decreased by 51%, the concentration of diene conjugates by 16%, and the concentration of MDA by 32%. Despite this, the concentration of the surface protein-SH group increased by 32%, the concentration of the intrastructural protein-SH group by 54%, the concentration of peroxidase by 89%, the concentration of catalase by 17%, and the concentration of UAF by 65%. This once again confirms that mexidazole has antioxidant properties in addition to its hepatoprotective properties. As in the previous experimental groups, the results of the experiments conducted on group 24 animals showed that the administration of mexidazole at a dose of 0.02 mg/kg for 7 days produced a more prolonged and acute effect.

The concentration of AST enzyme in the blood decreased by 12% compared to group 23, the concentration of ALT enzyme and LDH enzyme decreased by 4%, and the concentration of alkaline phosphatase enzyme decreased by 12%. Accordingly, the number of experimental animals with normal concentrations of liver enzymes in the blood increased compared to other groups.

As a result of 7-day administration of mexidazole, the amount of markers characteristic of non-enzymatic metabolism of the liver reached normal levels. The same situation was observed in the concentration of markers representing oxidative stress.

Thus, summing up the experiments we conducted, we believe that oxidative stress, which develops due to the imbalance between free lipid peroxidation and the general antioxidant defense system of the body during hepatitis, regardless of its etiological factors, plays an important role in the disruption of enzymatic and non-enzymatic metabolism of the liver. At this time, the fact that mexidazole administered to the body acts with hepatoprotective and antioxidant properties through two mechanisms, partially restoring the impaired metabolism of the liver, once again confirms the role of oxidative stress in the disruption of liver metabolism in hepatitis of non-viral origin.

RESULTS

1. In the blood of intact white rats, the concentration of AST enzyme is 25-33 u/l, the concentration of ALT enzyme is 30-40 u/l, the concentration of glutathione transferase enzyme is 28-58 u/l, the concentration of LDH enzyme is 270-440 u/l, the concentration of CPK enzyme is 243-275 u/l, the concentration of QF enzyme is 150-300 u/l, the amount of creatinine is 0.7-1.2 mg/dl, the amount of urea is 16-45 mg/dl, the amount of total bilirubin is 0.3-1.1 mg/dl, the amount of residual nitrogen is 6-18 mg/dl, and the amount of total protein is 66-85 g/l [5].

2. In the liver of intact white rats, the concentration of the initial product of free lipid peroxidation (H2O2), which is a marker of oxidative stress, is 1.6-2.3 ppm, the concentration of DK is 1.1-1.8 mg/dl, the concentration of MDA is 0.9-1.4 mg/dl. The concentration of the surface protein-SH group, which is a marker of the antioxidant defense system, is 29.8-32.4 nmol/mg, the concentration of peroxidase is 10.0-12.4 nmol/mg, the concentration of catalase is 210.4-280.7 Mkat/l, and the concentration of UAF is 37.45-43.20% [6].

3. The optimal dose of mexidazole for the effect on liver metabolism is 0.02 mg/kg. In the blood of white rats receiving biologically active substance at this dose for 7 days, the average concentration of AST increased by 23%, the average concentration of ALT by 34%, the average concentration of glutamine transferase by 19%, the average concentration of LDH by 3%, the average concentration of CPK by 16%, the average amount of creatinine by 4%, the average amount of urea by 7%, and the average amount of total bilirubin by 20%. The average amount of residual nitrogen remained at the level of the intact state, while the amount of total protein decreased by 2% [15].

4. The administration of mexidazole at a dose of 0.02 mg/kg for 7 days showed a strong antioxidant effect, reducing the concentration of H2O2 in the liver tissue by 4%, the concentration of DK by 19%, and the concentration of MDA by 12%. The concentration of surface protein-SH group increased by 5.5%, the concentration of intrastructural protein-SH group increased by 3%, the

concentration of peroxidase increased by 6%, the concentration of catalase increased by 9%, and the concentration of UAF increased by 26%.

5. Parasitomol, which was administered orally to white rats for 10 days, affected the enzyme synthesizing function of the liver and increased the amount of AST, ALT, and glutamine transferase enzymes in the blood by 99%, 81, and 104%, respectively, and the concentration of LDH, KFK, and alkaline phosphatase enzymes by 97%, 103%, and 126% [17].

6. As a result of the disruption of non-enzymatic metabolism of the liver as a result of paracetamol intake, the amount of creatinine, urea, total bilirubin and residual nitrogen in the blood increased by 76%, 91%, 112.5% and 79%, respectively, compared to the intact state, and the amount of total protein decreased by 7%.

7. Regardless of the etiological factors, free lipid peroxidation in the liver tissue of white rats in which a hepatitis model was created is intensified, and the antioxidant defense system is weakened, and the imbalance between them leads to oxidative stress, and the developing oxidative stress seriously disrupts the enzymatic and non-enzymatic metabolism of the liver [20].

8. The oxidative stress developing in the liver tissue of white rats in which a toxic hepatitis model was created seriously disrupts the liver metabolism. Although the intraperitoneal injection of mexidazole, which has antioxidant properties, at a dose of 0.02 mg/kg for 3 days brought the amount of markers characterizing the liver metabolism of experimental animals in which a drug hepatitis model was created to the norm, it could not restore the metabolism disrupted in toxic hepatitis [21].

9. The oxidative stress developing in the liver of white rats irradiated with X-rays significantly disrupts the liver metabolism, and as a result, the level of markers of enzymatic and non-enzymatic metabolism in the blood increases. However, this increase is somewhat milder than in hepatitis of other etiologies.

10. Mexidazole has radioprotective properties and regulates the impaired metabolism of the liver due to the action of X-rays more effectively than in hepatitis of drug, toxic and alcoholic origin.

11. The restoration of impaired metabolism of the liver in white rats, in which a hepatitis model was created, depends on the duration of mexidazole administration.

12. Cisplatin injected into the abdominal cavity of intact white rats disrupts liver metabolism more seriously than mexidazole.

LIST OF PUBLICATIONS ON THE TOPIC OF THE DISSERTATION

1. Багиров И.М., Касумов Ш.Г., Ахундов Р.А., Гасанов Х.И. Биологически активные комплексы палладия (II) с 3-окси-6-метил-2-этилпиридином. //Материалы XXIII Международной науч. конф. «Онкология – XXI век» 29 апреля – 5 мая 2019.
2. Bağırov İ.M., Qarayeva G.Q., Həsənov X.İ. Meksidolun palladiumla koordinasion birləşmələrinin "Meksidazol"un alınması və tədqiqi //Sağlamlıq 2020, № 1, c. 157-167.
3. Багиров И.М., Касумов Ш.Г., Гасанов Х.И. Процесс этапного гидролиза комплекса палладия с мексидолом //Azərbaycan Tibb Universitetinin 90 illik yubileyinə həsr olunmuş Beynəlxalq elmi-praktik konfransın materialları. 19-20 dekabr 2020. Bakı. Səh.461.
4. Bağırov İ.M. Palladium və meksidol əsasında yeni sintez olunan kompleks birləşmənin qaraciyərin ferment sintezedici funksiyasına təsiri // Sağlamlıq.az. 2021. Cild 27, № 2, s.151-157.
5. Bağırov İ.M., Kərimova R.C. Cinsi xətti bəlli olmayan ağ siçovulların qanında qaraciyər metabolizmini səciyyələndirən markerlərin dəyişmə intervalının təyininin nəticələri //Azərbaycan təbabətinin müasir nailiyyətləri. 2021, № 3, s.168-170.
6. Багиров И.М., Кулиева С.В. Влияние комплексного соединения, синтезируемого на основе палладия и мексидола на развившийся оксидативный стресс в печени белых крыс на модели лекарственного гепатита //Медицинский Альманах 2022, № 3, (72), с. 38-43.
7. Bağırov İ.M. Dərman hepatiti modelləşdirilmiş ağ siçovullarda qaraciyər zədələnmələrinin patobiokimyəvi əlamətləri // Azərbaycan Tibb Jurnalı 2022, № 3, s.94-100.
8. Bağırov İ.M. Dkordinasion birləşmələr və onların dərman maddələrinin sintezində rolu // Azərbaycan təbabətinin müasir nailiyyətləri. 2022, № 4, s.156-161.
9. Багиров И.М., Кулиева С.В. Регуляция системы антиоксидантной защиты в печени белых крыс на фоне лекарственного гепатита //Фармация 2023,Т.72, № 1, с.47-55.

10. Bagirov I.M. The effect of x-rays on the enzymatic function of the liver. /IV international Liverity interdisciplinar studies conference, Avqust 2-4, 2023, New-York, P.82-83.
11. Bagirov I.M. The modern conception of etiological factors, diaqnosis and treatment of druginduced hepatitis //Transactions of the institute of Molecular Biology Biotechnologies MSE AP, vol. 7, № 1, P.121-126, 2023.
12. Багіров И.М. Окислиювальний стресс у тканинах пегінки при алкогольному гепатиті та його корекція комплексною ополукою, синтезованою на основі паладію і мексидолу. //Світ медицини ма біології. 2023, № 3 (84), с.180-185.
13. Багіров И.М. Вплив Рентгенівських променів на метаболизм пегінки //Світ медицини ма біології. 2023, № 3 (85), с.21-25.
14. Burak Tüzün, Rana Jafarovaç İsmail Bagirov, Nigar Magerramova, Tofa Nasibova. Mathematical Modeling of the Biological Activity of a New Complex Compound Based on Palladium and Mexidol. // J. Biochem Technol, 2023, 14 (1), P.40-44.
15. Bagirov I.M. The effect of Mexidolon recovery of Liver Metabolic Disorder induced bu x – RAYs. //Khazar Journal of Seicncc and Technology volume 7 2023, P.5-10.
16. Гулиева С.В., Багиров И.М., Исмаилова А.Т., Алекберова М.Г. Развитие оксидативного стресса на фоне лекарственного гепатита в эксперименте. // XXXII international Multidisciplinary Conference Prospects and key tendencies of Science in contemporary world. Madrid, Spain 2023, C.60-65.
17. Bagirov I.M. Oxidative stress in Liver Tissue and the Role of x-rays in ITS etiology /VIII – International European conference on interdisciplinar Scientific research. July 13-15, 2023 (Rome, Italy), p. 96-99.
18. Гулиева С.В., Ахундов Р.А., Багиров И.М., Алиев А.Н. Влияние комплексного соединения на основе палладия и мексидола на показатели оксидативного стресса в печени белых крыс на модели лекарственного гепатита. Ümumilli Lider Heydər Əliyevin 100 illiyinə həsr olunmuş "Çağdaş təbabət: yeniliklər və müasir yanaşmalar" mövzusunda Beynəlxalq elmi-

praktik konfransın tezisləri. Bakı – 2023, s. 200-201.
19. I.M.Baghirov, S.G.Garayeva. EFFECT OF X-RAYS ON LIVER METABOLISM. Scientific Research Center of Azerbaijan Medical University. mamed 2016 @list.ru // Journal of Radiation Researches, vol.ll, No.l, 2024, Baku Effect of X-rays on liver metabolism pp. 17-22. PACS: 87.57.un
20. Bagirov Ismayil Mammad. BIOCHEMICAL CHANGES IN LIVER METABOLISM CAUSED BY X-RAY EXPOSURE. Azerbaijan Medical University, Scientific Research Center ORCID: 0000-0003-0145-8390 Turkiye. 2025.
21. Bagirov Ismayil Mammad. LEVELS OF OXIDATIVE STRESS MARKERS IN THE LIVER OF WHITE RATS WITH AN ALCOHOLIC HEPATITIS MODEL. Azerbaijan Medical University, Scientific Research Center,Ph.D in Pharmacy ORC1D: https://orcid.org/0000-0003-0145-8390 Turkiye. 2025

LIST OF ABBREVIATION

1. Aspartate aminotransferase – AST
2. Alanine aminotransferase – ALT
3. Creatine phosphokinase – CPK
4. Lactate dehydrogenase – LDH
5. Hydrogen peroxidase – H2O2
6. Diene conjugates – DK
7. Malondealdehyde – MDA
8. Total antioxidant activity – TAA

The defense will be held on October 31, 2025 at 14^{00} at the meeting of the Dissertation council BED 4.33 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Azerbaijan Medical University.

Address: AZ 1022, Baku city, Anvar Gasimzadeh street 14, meeting hall of the Azerbaijan Medical University.

Dissertation is accessible at the library of the Azerbaijan Medical University.

Electronic version of the abstract is available on the official website of the official website of the Azerbaijan Medical University.

Abstract was sent to the required addresses on ___ _____ 2025.

Signed for print:
Paper format: 60x84 1/16
Volume: 71580 characters
Number of hard copies: 30