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The effect of carnitine, vitamins E and B_{12}, methionine, selenium, and zinc as part of a complex preparation on the antioxidant status of rats under conditions of toxic liver injury

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The relevance of this study stems from the fact that toxic liver injury is accompanied by the development of oxidative stress, which leads to structural and functional damage to hepatocytes, as well as disruption of the activity of key antioxidant defense enzymes. The study aimed to investigate the effect of Devivit Carnitine on lipid peroxidation parameters and the state of the glutathione antioxidant defense system in rats under conditions of carbon tetrachloride intoxication. The experiment was conducted on three groups of animals: a control group, an experimental group with carbon tetrachloride-induced liver injury, and an experimental group that received Devivit Carnitine in addition to carbon tetrachloride intoxication. Devivit Carnitine is a multicomponent preparation containing carnitine hydrochloride, vitamins E and B_{12}, methionine, selenium, and zinc. The levels of lipid hydroperoxides, TBA-active products, glutathione peroxidase activity, and reduced glutathione content in the blood of rats were assessed on days 2, 5, 10, and 14 of the experiment. Carbon tetrachloride intoxication caused a marked increase in lipid hydroperoxides and TBA-active products in the blood, along with inhibition of glutathione peroxidase activity and decreased glutathione content. Administration of Devivit Carnitine under these conditions significantly reduced lipid hydroperoxide and TBA-active product levels and normalized glutathione system parameters. By day 14, lipid hydroperoxide levels in animals of this group were close to physiological values, while glutathione peroxidase activity and reduced glutathione content reached control levels. The results confirm that Devivit Carnitine demonstrates pronounced antioxidant properties, manifested through inhibition of free radical oxidation processes and activation of both enzymatic and non-enzymatic components of antioxidant defense. The preparation may be a promising therapeutic agent in the complex treatment of toxic hepatoses, particularly those associated with oxidative stress, helping preserve the structural and functional integrity of the liver.

Keywords: carbon tetrachloride; oxidative stress; lipid hydroperoxides; TBA-active products; glutathione peroxidase.

Introduction

Diseases of the hepatobiliary system occupy one of the leading positions in the structure of internal diseases in humans and animals (Donkin, 2021; Gaul et al., 2021; Wallace, 2022). They are characterized by high prevalence, prolonged course, and significant economic losses in animal husbandry due to reduced productivity, impaired reproductive function, and increased culling rates (Vlizlo et al., 2023).

Over the past decades, global environmental changes driven by the intensive development of industry, agricultural production, and scientific and technological progress have substantially increased pollution levels of atmospheric air, water, soil, and food products. This, in turn, has caused a noticeable rise in the incidence of so-called chemical hepatoses-liver diseases associated with the accumulation of various xenobiotics in the body (Vlizlo et al., 2024).

The liver is the central organ responsible for detoxifying and metabolizing toxic substances, performing a barrier function (Khaleghipour et al., 2019; Gutyj et al., 2022; Gross, 2023). Here, xenobiotics undergo biotransformation through enzymatic processes of oxidation, reduction, hydrolysis, and conjugation, followed by the excretion of metabolic products with bile or urine. However, in cases of excessive toxin intake or prolonged exposure, the liver becomes a target organ, as the concentration of harmful substances in its tissues can reach a critical level, leading to structural and functional impairments (Chernushkin et al., 2020; Gillessen & Schmidt, 2020). Xenobiotics capable of causing liver damage include industrial toxins (solvents, heavy metals, petroleum products); agricultural pesticides and herbicides; carcinogenic substances of both natural and synthetic origin; synthetic pharmaceuticals (in particular, hepatotoxic antibiotics, antiparasitic agents, cytostatics); and household chemical products (detergents, paints, solvents) (Gutyj et al., 2017; Slivinska et al., 2019). In addition to chemical factors, liver damage of infectious etiology remains a relevant concern. In particular, viral hepatitis continues to be a significant problem in both human and veterinary medicine, while bacterial and parasitic infections can cause hepatobiliary disorders of both primary and secondary origin (Pisano et al., 2021; Odenwald & Paul, 2022).

Thus, the increasing toxic load on the body, combined with the action of infectious agents, creates conditions for a higher incidence of liver pathologies. This necessitates an in-depth study of the mechanisms of their development, improvement of early diagnostic methods, and the development of effective preventive and therapeutic measures, especially with the use of hepatoprotectors and antioxidants capable of enhancing the resistance of hepatocytes to damaging factors (Slivinska et al., 2021).

Numerous studies indicate that the activation of free radical oxidation processes is one of the key pathogenetic mechanisms in developing many liver diseases (Slivinska et al., 2022). The formation of

oxidative stress may vary in terms of its frequency, the involvement of specific components of lipid peroxidation (LPO) and protein free radical oxidation, as well as in the degree of reduction in antioxidant enzyme activity and the severity of these changes (Tokar et al., 2024; Fedorovych & Slivinska, 2025).

Lipid peroxidation damages the phospholipid layer of cellular and subcellular membranes of hepatocytes, resulting in increased membrane permeability, disruption of ionic homeostasis, and activation of cellular degradation processes. Protein free radical oxidation, in turn, is accompanied by alterations in their spatial structure and loss of biological activity, which adversely affects the functioning of enzymatic systems and structural components of the cytoskeleton (Usenko et al., 2020).

A decrease in the activity of antioxidant enzymes, particularly superoxide dismutase, catalase, and glutathione peroxidase, exacerbates the imbalance between the formation of reactive oxygen species and the body's capacity to neutralize them, thereby intensifying the destructive impact on liver cells (Stoyanovskyy et al., 2020). Collectively, these changes lead to persistent disruption of the structural and functional integrity of hepatocytes and contribute to the progression of the pathological process.

This study aimed to investigate the effect of carnitine, vitamins E and B_{12}, methionine, selenium, and zinc, as part of the complex preparation Devivit Carnitine, on the antioxidant status of rats under conditions of carbon tetrachloride–induced toxic liver injury.

Materials and methods

The study was conducted in compliance with the principles of bioethics, legislative norms, and requirements by the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and the General Ethical Principles for Animal Experiments adopted by the First National Congress on Bioethics (Kyiv, 2001).

The experiments were carried out on white, sexually mature young male Wistar rats weighing 180–200 g, which were housed in the institutional vivarium of the State Scientific Research Control Institute of Veterinary Medicinal Products and Feed Additives. Throughout the experiment, the rats were fed a balanced diet containing all necessary nutrients and had ad libitum access to drinking water from 0.2-liter glass drinkers.

The animals were divided into three groups of 10 rats: a control group composed of intact animals, and two experimental groups with carbon tetrachloride–induced liver injury. The second experimental group additionally received Devivit Carnitine. Toxic liver injury was induced by intramuscular injection of a 50% oil solution of carbon tetrachloride at a dose of 0.25 mL per 100 g of body weight on the first and third days of the study. In addition, the animals of the second experimental group were administered Devivit Carnitine at a dose of 0.1 mL/kg of body weight for five days. This preparation contains the following components: carnitine hydrochloride, vitamins E and B_{12}, methionine, selenium, and zinc.

Blood samples for biochemical and hematological studies were collected from the jugular vein under ether anesthesia on days 2, 5, 10, and 14 of the experiment.

The reaction with ammonium thiocyanate determined the content of lipid hydroperoxides in blood plasma according to the L. A. Romanova and I. D. Stalnoy method. The color intensity was measured colorimetrically at a wavelength of 480 nm. The concentration of lipid hydroperoxides was expressed in extinction units per 1 mL of blood plasma (Vlizlo et al., 2012).

The content of TBA-active products in blood plasma was determined using a method based on the reaction between malondialdehyde and thiobarbituric acid. The color intensity of the resulting trimethine complex was measured colorimetrically at wavelengths of 535 and 580 nm. Double measurement of absorbance made it possible to exclude the absorption of colored TBA complexes by non-lipid substances. The concentration of TBA-active products was expressed in nmol of malondialdehyde per ml of blood plasma (Vlizlo et al., 2012).

Glutathione peroxidase activity (EC 1.11.1.9) in blood plasma was determined by the rate of oxidation of the reduced form of glutathione in the presence of tert-butyl hydroperoxide in a color reaction with 5,5′-dithiobis-2-nitrobenzoic acid, measuring the absorbance at 412 nm (Vlizlo et al., 2012).

The reduced glutathione content in erythrocyte hemolysate was determined according to the method of E. Butler using Ellman's reagent, with spectrophotometric measurement at 412 nm (Vlizlo et al., 2012).

The obtained data were analyzed using Statistica 6.0 software (StatSoft Inc., USA). The tables present the results as $x \pm SD$ (mean ± standard deviation). Differences between the values in the control and experimental groups were assessed using ANOVA, with differences considered statistically significant at $P < 0.05$ (with Bonferroni correction).

Results

The investigation of lipid hydroperoxide levels in rat blood plasma showed that in the control group, the values of this parameter ranged from 0.242 to 0.244 ext. units/ml. Under oxidative stress conditions, in the blood of rats from the first experimental group, a significant 3.4-fold increase ($P < 0.001$) in lipid hydroperoxide levels was recorded on day 2 of the experiment compared to the control group. On days 5 and 10, the lipid hydroperoxide level in the first experimental group was 0.758 ± 0.004 and 0.652 ± 0.004 ext. units/mL, respectively, which was 3.1 and 2.7 times higher than the control values. By day 14 of the experiment, this indicator remained 2.9 times higher than in the control group ($P < 0.001$).

In rats of the second experimental group receiving Devivit Carnitine, a 1.98-fold increase in lipid hydroperoxide levels was observed on day 2 compared to the control. On days 5 and 10, the levels gradually decreased compared to the previous sampling days; however, they remained elevated relative to the control group. Specifically, on day 5, the lipid hydroperoxide level was higher by 80% ($P < 0.001$), and on day 10, by 38.3% ($P < 0.001$) compared to the control. The lowest value in this group was recorded on day 14, amounting to 0.261 ± 0.004 ext. units/mL, whereas in the control group it was 0.244 ± 0.001 ext. units/mL, and in the first experimental group it reached 0.719 ± 0.004 ext. units/mL.

When examining the end products of lipid peroxidation, it was found that the lowest level was recorded in the blood plasma of rats from the control group. The highest level of TBA-active products was observed in the blood of rats in the first experimental group, which underwent carbon tetrachloride loading. On day 2 of the experiment, the plasma level of TBA-active products in the first experimental group increased by 87%, and on day 5, it doubled compared to the control group at the corresponding time points. This parameter was slightly lower on day 10, amounting to 7.90 ± 0.036 nmol/mL ($P < 0.001$). By day 14, the plasma level of TBA-active products in the first experimental group was 93.5% higher than in the control group.

In the second experimental group, which received Devivit Carnitine under carbon tetrachloride loading, an increase in TBA-active product level by 51.2% compared to the control was observed on day 2 of the experiment. Subsequently, a gradual decrease in this parameter was recorded compared to the previous sampling days. However, relative to the control group, the level of TBA-active products in the second experimental group remained elevated by 40.5% on day 5 and by 20.7% on day 10. By day 14, the parameter had decreased to physiological values, amounting to 4.42 ± 0.008 nmol/mL, whereas in the first experimental group it remained high at 8.05 ± 0.022 nmol/mL.

Thus, Devivit Carnitine administered to rats during the development of oxidative stress inhibited the formation of lipid oxidation products, as evidenced by the low levels of lipid hydroperoxides and TBA-active products in the blood of the second experimental group. This effect is likely due to specific antioxidants in its composition.

An important indicator in assessing the antioxidant status of animals is the glutathione system, which includes reduced glutathione and several enzymes, including glutathione peroxidase. Based on the results obtained, the activity of glutathione peroxidase in the blood se-

rum of the control group rats ranged from 0.288 ± 0.003 to 0.295 ± 0.002 nmol GSH/min×mg protein.

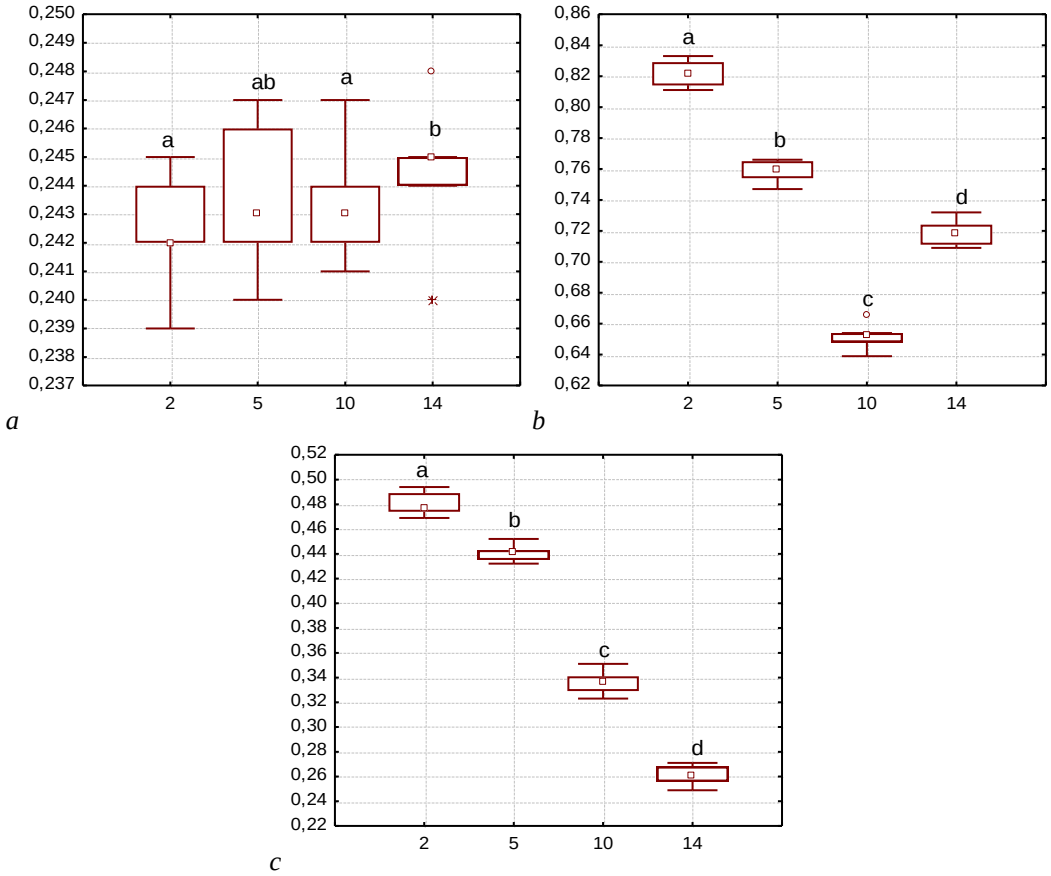

Fig. 1. Effect of Devivit Carnitine on the level of lipid hydroperoxides in rat blood plasma under oxidative stress: *a* – control group; *b* – first experimental group; *c* – second experimental group (extinction units/mL)

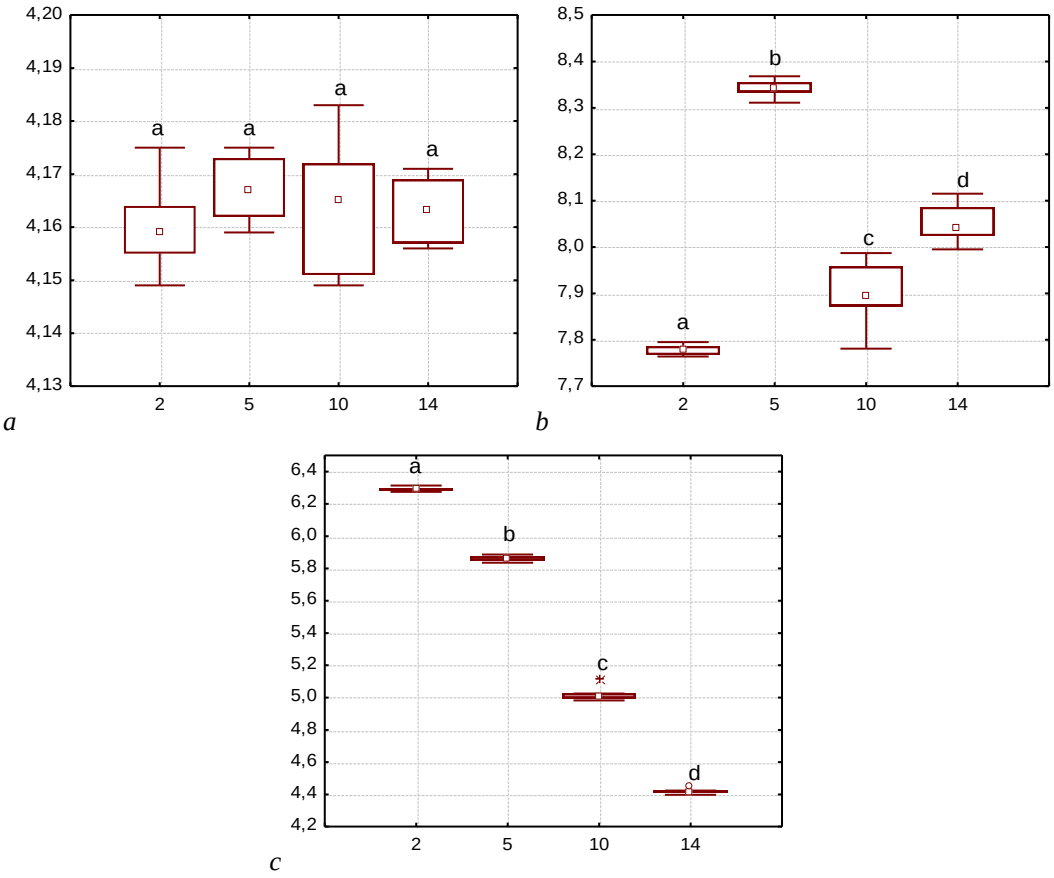

Fig. 2. Effect of Devivit Carnitine on the level of TBA-active products in rat blood plasma under oxidative stress: *a* – control group; *b* – first experimental group; *c* – second experimental group (nmol/mL)

Under conditions of carbon tetrachloride poisoning, glutathione peroxidase activity in the blood serum of the first experimental group decreased by 56.3% on day 2 of the experiment and by 53.4% on day 5 compared to the control group values. During these periods, the enzyme activity in the blood serum of the second experimental group ranged from 0.283 ± 0.004 to 0.280 ± 0.004 nmol GSH/min×mg protein.

On day 10 of the experiment, glutathione peroxidase activity was the lowest in the first experimental group, amounting to 0.143 ± 0.003 nmol GSH/min×mg protein; it was slightly higher in the second experimental group (0.286 ± 0.003 nmol GSH/min×mg protein) and the highest in the control group (0.294 ± 0.004 nmol GSH/min×mg protein). By day 14, glutathione peroxidase activity in the first experimental group was 47.8% lower than in the control. In the second experimental group, the enzyme activity remained within the range of the control group values – 0.299 ± 0.004 and 0.295 ± 0.002 nmol GSH/min×mg protein, respectively.

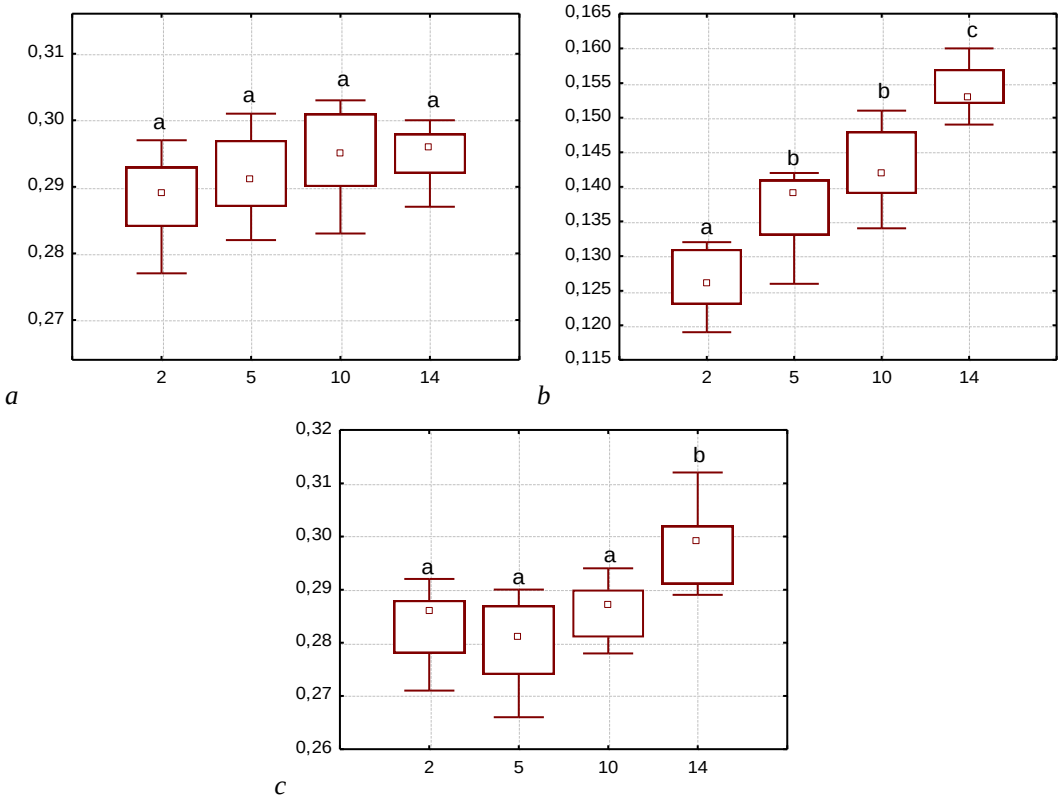

Fig. 3. Effect of Devivit Carnitine on glutathione peroxidase activity in the blood serum of rats under oxidative stress: *a* – control group; *b* – first experimental group; *c* – second experimental group (nmol GSH/min×mg protein)

Under conditions of carbon tetrachloride intoxication, on day 2 of the experiment, the level of reduced glutathione in the blood of rats from the first experimental group had decreased by 48.1% compared to the control group. The lowest value of this parameter was observed on day 5 in the first experimental group, amounting to 0.266 ± 0.002 μmol/mL, whereas in the control group it was 0.528 ± 0.004 μmol/ml. On days 10 and 14, the reduced glutathione level in the first experimental group remained lower than in the control group by 45.7% and 46.8%, respectively. In the experimental group of rats receiving Devivit Carnitine, an increase in reduced glutathione levels was observed throughout the entire experiment. On day 2, the level of reduced glutathione in the second experimental group was 15.6% higher, and on day 5, 18.6% higher compared to the control group. The highest values of this parameter in the second experimental group were recorded on days 10 and 14, amounting to 0.654 ± 0.003 and 0.649 ± 0.002 μmol/mL, respectively.

Thus, Devivit Carnitine promotes the activation of the antioxidant defense system in rats under conditions of carbon tetrachloride intoxication, as evidenced by the high levels of reduced glutathione and glutathione peroxidase activity.

Discussion

Among the most common pathologies that develop under the influence of toxic agents, chemical liver injuries occupy a leading position. The scientific literature contains a significant number of publications devoted to the effects of toxic factors on the liver; however, certain aspects of the biochemical mechanisms of hepatocyte damage, as well as issues of prevention and therapy of such lesions, remain insufficiently elucidated and require further comprehensive investigation (Kulyaba et al., 2019; Vlizlo et al., 2023).

Carbon tetrachloride belongs to the group of xenobiotics with high selectivity for damaging liver tissue (Xue et al., 2022; Cohen et al., 2023). The specific features of its molecular action on the subcellular membranes of hepatocytes–particularly microsomal activation and the initiation of lipid peroxidation (LPO) processes–allow the use of intoxication with this compound as a model of molecular pathology of membrane structures (Gutyj et al., 2017). Upon entering the body, carbon tetrachloride causes two main types of damage: disruption of the structural and functional integrity of the liver and alterations in enzyme system activity (Unsal et al., 2020; Zhang et al., 2023). Its toxic effects are realized through the intensification of lipid peroxidation and the direct covalent binding of radicals to proteins of membrane structures and cytosolic enzymes (Gutyj et al., 2017; Fareed et al., 2024).

The main morphological manifestations of toxic damage include fatty and protein dystrophy of hepatocytes, extensive necrotic changes, marked suppression of regenerative processes, and the development of cholestasis. On the part of the stroma, focal inflammatory infiltration, uneven vascular engorgement, decreased Kupffer cell activity, and simultaneous activation of Ito cells are observed (Gutyj et al., 2017; Ivankiv et al., 2019). Among the numerous functions of the liver, its detoxification role is particularly important. Impairment of this function is one of the key causes of the development of endogenous intoxi-

cation syndrome (Khaleghipour et al., 2019; Stoyanovskyy et al., 2020). Within the spectrum of diseases caused by toxic factors, chemical liver injuries occupy a prominent place, which underscores the relevance of finding effective treatment methods for toxic hepatoses as one of the important areas of modern veterinary medicine.

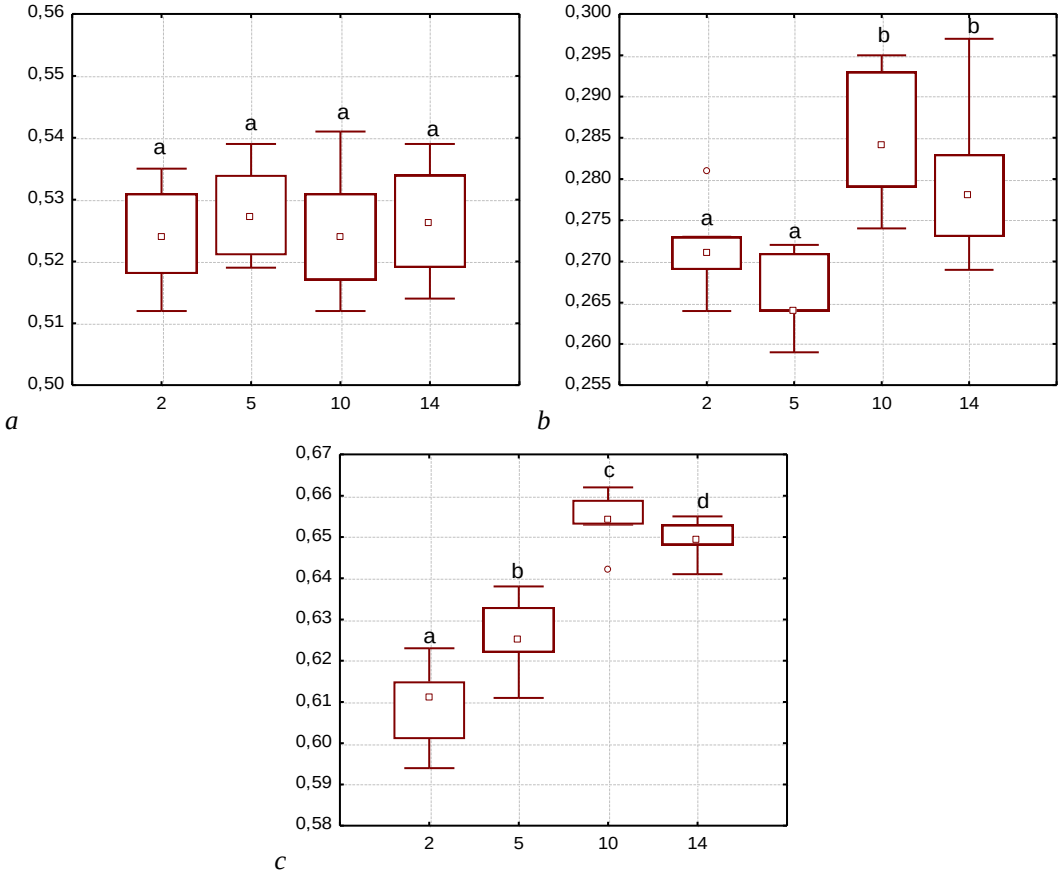

Fig. 4. a b c d Effect of Devivit Carnitine on the content of reduced glutathione in the blood of rats under oxidative stress: *a* – control group; *b* – first experimental group; *c* – second experimental group (μmol/mL)

Currently, the correction of toxic liver injuries is mainly carried out in two primary directions. The first, based on the theory of the pro-oxidant mechanism of toxin action, involves the wide use of antioxidants in complex therapy to inhibit free radical processes (Gutyj et al., 2021). The second approach, aimed at detoxification, relies on the use of enterosorption, which has become widespread due to the development of high-quality sorbents with high sorption capacity, selectivity, absence of side effects, inability to be absorbed, and safety for the intestinal mucosa (Slivinska et al., 2022).

The results indicate that the pharmacological action of Devivit Carnitine has a pronounced hepatoprotective effect, which is important in treating animals with toxic liver injury.

Carnitine hydrochloride optimizes lipid metabolism in the liver by facilitating the transport of long-chain fatty acids into the mitochondria for β-oxidation. This reduces triglyceride accumulation and prevents the development of fatty liver dystrophy. Furthermore, enhanced efficiency of energy metabolism helps maintain the protein-synthesizing function of hepatocytes, which is crucial for synthesizing albumin and blood clotting factors (Vus et al., 2025).

Vitamin E (tocopherol), due to its antioxidant properties, protects hepatocyte cell membranes from damage by free radicals formed during oxidative stress (Romanovych et al., 2019). Reducing the intensity of lipid peroxidation prevents membrane destabilization, improves the functional integrity of liver tissue, and promotes hepatocyte regeneration (Galli et al., 2022).

Vitamin B_{12} (cyanocobalamin) synthesizes methionine and S-adenosylmethionine, which play a key role in liver detoxification processes. It supports the synthesis of nucleic acids and proteins necessary for hepatocyte repair, as well as erythropoiesis, which indirectly improves oxygenation of liver tissue (Green & Miller, 2022; Temova Rakuša et al., 2022).

Methionine is an essential donor of methyl groups in transmethylation reactions, which are important for the biosynthesis of phospholipids in hepatocyte cell membranes. It also serves as a precursor of glutathione, a key intracellular antioxidant that neutralizes toxins and reduces oxidative stress in the liver. Using methionine helps decrease fatty infiltration and accelerates the regeneration of liver tissue (Li et al., 2020; Tassinari et al., 2024; Vus et al., 2025).

Selenium, as a component of glutathione peroxidase, enhances the liver's antioxidant defense and prevents hepatocyte damage by peroxidative compounds. It also regulates immune processes, which may reduce the severity of inflammatory changes in the hepatic parenchyma (Sobolev et al., 2018; Mojadadi et al., 2021).

Zinc is a cofactor of antioxidant enzymes (particularly superoxide dismutase) and synthesizes proteins and nucleic acids required for liver tissue regeneration. In addition, zinc stabilizes cell membranes and reduces the permeability of hepatocytes to toxic substances (Schoofs et al., 2024; Vus et al., 2025).

Overall, the synergistic action of the components of Devivit Carnitine is aimed at restoring and protecting the liver from metabolic and oxidative damage, which not only improves the functional state of this organ but also indirectly supports the cardiovascular system. Enhancement of the protein-synthesizing, detoxifying, and energy-producing functions of the liver creates favorable conditions for faster rehabilitation of animals and increased productivity.

The results of the conducted studies indicate that carbon tetrachloride-induced liver injury in rats is accompanied by the development of pronounced oxidative stress, as evidenced by a significant increase in lipid hydroperoxides and TBA-active products in blood plasma. In the first experimental group, a sharp rise in lipid peroxidation markers was observed on day 2 and persisted throughout the entire experiment, although with a tendency toward partial reduction at later stages. This dynamic reflects the intense formation of lipid

peroxidation products under toxic exposure, accompanied by suppression of the natural antioxidant defense mechanisms.

Administration of Devivit Carnitine to rats in the second experimental group under carbon tetrachloride loading led to a marked reduction in the intensity of lipid peroxidation processes. Although in the early stages of the experiment the levels of lipid hydroperoxides and TBA-active products remained elevated relative to the control, a gradual decrease was noted from day 5 onward, and by day 14 these values approached physiological levels. This indicates the ability of Devivit Carnitine to limit free radical formation and stabilize cell membranes, likely due to the presence of active antioxidant components in its composition.

An important complement to these results is assessing the glutathione system, one of the key components of endogenous antioxidant defense. Under conditions of carbon tetrachloride intoxication, rats in the first experimental group showed a significant decrease in glutathione peroxidase activity. They reduced glutathione levels, indicating depletion of the body's protective reserves and an inability to neutralize excess peroxidative compounds effectively. In contrast, in rats administered Devivit Carnitine, glutathione peroxidase activity and reduced glutathione levels remained at control values or even exceeded them at certain experiment stages. This suggests that the preparation reduces the intensity of lipid peroxidation and promotes the restoration and maintenance of the enzymatic component of the antioxidant system, ensuring more effective neutralization of free radicals.

Thus, the obtained data confirm the pronounced antioxidant properties of Devivit Carnitine, which are realized through the reduction of lipid peroxidation product accumulation and activation of the glutathione system. This makes the preparation a promising agent for correcting oxidative stress and preventing cell membrane damage in toxic liver injuries.

Conclusions

The conducted studies demonstrated that carbon tetrachloride intoxication in rats is accompanied by the development of pronounced oxidative stress, manifested by a significant increase in lipid hydroperoxide and TBA-active product levels in the blood, as well as by the suppression of glutathione peroxidase activity and a decrease in reduced glutathione content.

Administration of Devivit Carnitine under conditions of toxic liver injury contributed to a substantial reduction in the intensity of lipid peroxidation processes and the restoration of antioxidant system activity, as evidenced by a decrease in lipid peroxidation products and an increase in reduced glutathione content and glutathione peroxidase activity to values close to the control.

The obtained results indicate the pronounced antioxidant properties of Devivit Carnitine and its potential for use in the complex therapy of toxic liver injuries aimed at correcting oxidative stress and preserving the functional integrity of cells.

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The authors declare no conflict of interest.

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