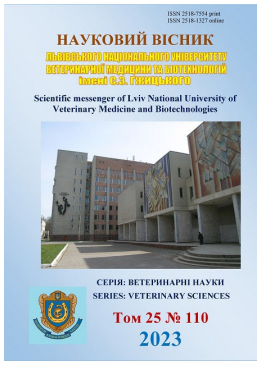

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The state of the immune system of rats under conditions of oxidative stress and the influence of the feed additive "Sylimevit"

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The immune system plays a crucial role in maintaining the body's homeostasis, determining the state of health of animals and their ability to adapt. The work aimed to investigate the effect of a feed additive based on milk thistle fruits, selenium, metiphene, and vitamins A, E, and C on rats' immune status under experimental tetrachloromethane poisoning conditions. The study was conducted on young white male Wistar laboratory rats. Intragastric administration of tetrachloromethane twice (with an interval of 48 hours) in a dose of 0.1 ml per 100 g of body weight in a 50 % oil solution was used for the experimental intoxication of rats. The animals of the second experimental group were fed the feed additive "Sylimevit" for 30 days together with feed at a dose of 0.1 g per 100 g of body weight. The introduction of tetrachloromethane in experimental groups of rats led to the development of oxidative stress, which occurs due to specific chemical processes in the body of experimental animals. It was found that the development of oxidative stress caused by tetrachloromethane leads to suppression of the humoral and nonspecific link of the immune system of rats. This is manifested in a decrease in the bactericidal and lysozyme activity of the blood serum, a decrease in the phagocytic index, and the phagocytic activity of neutrophils. In addition, an increase in the number of circulating immune complexes was observed. It was also established that feeding the feed additive "Sylimevit" strengthens the immune defense of the body of rats poisoned with tetrachloromethane. This feed additive helps to strengthen the body's defense mechanisms, increasing the immune response and helping to resist the toxic effects of tetrachloromethane.

***Keywords**: milk thistle, oxidative stress, immune system, tetrachloromethane.*

Introduction

The homeostasis of the internal environment of the animal body depends on the interrelationship of individual links of metabolic processes and the ability of the components that participate in the overall system (Gutyj et al., 2022; 2023). Blood, as one of the body's biological fluids, responds with quantitative and qualitative changes in its composition to any exogenous or endogenous influences. Therefore, it is a biomarker that allows for determining the general state of organs and systems and assessing the course of the main metabolic processes (Zhang et al., 2021; Lesyk et al., 2022; Kushnir et al., 2023). Therefore, studying morphological and biochemical indicators of blood is one informative method that allows for establishing the transition from the body's physiological state to the pathological one (Kisera et al., 2021; Kuljaba et 2022).

The problem of the influence of adverse environmental factors on the immune system has gained particular importance since it plays a leading role in maintaining health and is recognized as one of the most sensitive factors, even in relatively low concentrations (Khariv et al., 2017; Krempa et al., 2021; Varkholiak et al., 2021).

The immune system is one of the essential homeostatic systems of the body, which determines the degree of health of animals and their adaptive capabilities (Müller et al., 2019; Wang et al., 2021; Radzykhovskyi et al., 2022). As an indicator of the body's physiological state, it reacts to changes in environmental conditions. Violation of its function is considered one of the pathogenetic mechanisms of the pathological process (Netea et al., 2020; Place & Kanneganti, 2020; Daëron, 2022). Immunotoxicity is defined as the property of a toxicant to cause impairment of the function of the immune system, which is manifested by inadequate immune reactions. Immunotoxicity is considered in two aspects: the direct damaging effect of the substance on the immune system and the participation of the immune system in the implementation of the mechanisms of their toxic action (McComb et al., 2013; 2019; Hillion et al., 2020).

To improve the immune and antioxidant status of animals with toxic liver damage, new drugs and feed additives based on plant raw materials have been widely used in recent years.

The intensive development of animal husbandry at the current stage requires new approaches to the organization of feeding farm animals and the introduction of modern feed additives, which are usually not used in their pure form as feed but are purposefully added to feed or water to improve their quality, increase productivity and well-being of animals (Martyshuk et al., 2020; 2021; Martyshuk & Hutyi, 2021).

The aim of the research

The work aimed to investigate the effect of the feed additive “Sylimevit” on the state of the immune system of rats under the conditions of tetrachloromethane poisoning

Materials and methods

The study was conducted on young white laboratory rats of the Wistar line with a body weight of 180 to 200 g. These rats were kept in standard conditions of the vivarium of the State Research Control Institute of Veterinary Medicines and Feed Additives. The rats were fed a balanced diet throughout the experiment containing all the necessary components. Animals had unlimited access to drinking water. The animals were divided into three groups of 20 individuals each: 1st group (C) intact animals; 2nd group (R1) – rats affected by tetrachloromethane; The 3rd group (R2) – rats affected by tetrachloromethane, which were fed with the feed additive “Sylimevit”.

Intragastric administration of tetrachloromethane twice (with an interval of 48 hours) in a dose of 0.1 ml per 100 g of body weight in a 50 % oil solution was used for the experimental intoxication of rats. The animals of the second experimental group were fed the feed additive “Sylimevit” for 30 days together with feed at a dose of 0.1 g per 100 g of body weight. This supplement contained milk thistle fruits, selenium, methiphene, and vitamins A, E, and C.

Using ether anesthesia, blood for biochemical and hematological studies in rats was collected from the jugular vein on the experiment's fifth, tenth, twentieth, twenty-fifth, and thirtieth days.

Lysozyme activity of blood serum was determined using a daily culture of Micrococcus lysodeicticus strain VKM-109 as a test microbe by the nephelometric method; optical density was measured at a wavelength of 540 nm. Bactericidal activity in blood serum samples was studied according to this method by Yu. M. Markov (1968) using a daily culture of E. coli strain VKM-125. Photocolorimetry was performed before and after a 3-hour incubation.

Determination of the content of circulating immune complexes in blood serum was carried out using a borate buffer. Selective precipitation of antigen-antibody complexes occurred under the influence of high molecular weight PEG with a mass of 6000 Da. The results were calculated by photocolorimetry of the density of the precipitate at a wavelength of 450 nm.

The phagocytic reaction of blood neutrophils was assessed by PhA and phagocytic index (PhI) according to the method of V. S. Gostev (1950). Stabilized blood was incubated with a daily culture of E. coli strain VKM-125. Smears were examined under a microscope in an immersion system. PhA was determined by the number of active neutrophils from 100 counted cells and PhI – by the number of phagocytosed microbial bodies by one active neutrophil.

Housing, feeding, care, and all manipulations with animals were carried out following the European Convention “On the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes” (Strasbourg, 1986) and “General Ethical Principles of Animal Experiments”, adopted by the First National Congress on bioethics (Kyiv, 2001). The experiments were carried out in compliance with the principles of humanity outlined in the directive of the European Community.

Results and discussion

When evaluating the activity of the immune system in the animal body, it is essential to consider that immunological parameters are subject to significant fluctuations both in the presence of oxidative stress and under the influence of the Silimevit feed additive. The reaction of the immune system is the first to receive toxic substances. Through a general assessment of the indicators of the immune system and the antioxidant protection system of the animal body, it is possible to develop an optimal scheme for the prevention of the development of oxidative stress.

When studying the antimicrobial activity of the blood serum of rats under the conditions of experimental development of oxidative stress, it was established that on the 5th and 10th day of the experiment, there was a slight increase in the activity of lysozyme and bactericidal activity of the cow. In particular, the lysozyme activity of the blood serum of the rats of the first experimental group increased by 6.2 % and 5.8 %, respectively (Table 1), and the bactericidal activity of the blood serum increased by 2.81 % and 2.23 % (Table 2). compared to the control group. Subsequently, a decrease in both lysozyme and bactericidal activity of blood serum was established in the rats of the first experimental group. Thus, on the 20th day of the experiment, LABS decreased by 7.6 % and BABS – by 5.69 % compared to the tenth day.

A decrease in the bactericidal and lysozyme activity of blood serum indicates inhibition of the functioning of the humoral link of immunity. The lowest values of bactericidal activity (BABS) and lysozyme activity (LABS) were found in rats of the first experimental group on the 25th day of the experiment, where BABS was 25.41 ± 0.75 %, and LABS was 31.2 ± 0.63 %, respectively.

In the rats of the second experimental group fed with the feed additive “Sylimevit”, a probable increase in the lysozyme activity of the blood serum was established throughout the experiment. Thus, on the 5th and 10th day of the experiment, LABS increased by 7.3 and 7.8 % compared to the control group. It is worth noting that the highest lysozyme activity of blood serum was on the second experimental group's 10th day of the experiment. On the 25th and 30th day of the experiment, the lysozyme activity of the blood serum of the second experimental group of rats increased by 6.8 and 6.2 % compared to the control.

Table 1

Lysozyme activity of blood serum of rats under conditions of oxidative stress and action of Sylimevit, % (M ± m; n = 5)

Day of Research	Group of animals		
	Control	Research 1	Research 2
Fifth	35.4 ± 0.76	41.6 ± 1.06**	42.7 ± 0.68***
Tenth		40.9 ± 0.85**	43.2 ± 0.67***
Twentieth		33.3 ± 1.00	42.7 ± 0.84***
Twenty-fifth		31.2 ± 0.63*	42.2 ± 0.99***
Thirtieth		31.3 ± 0.95	41.6 ± 0.63***

Table 2

Bactericidal activity of blood serum of rats under conditions of oxidative stress and action of Sylimevit, % (M ± m; n = 5)

Day of Research	Group of animals		
	Control	Research 1	Research 2
Fifth	30.74 ± 1.22	33.55 ± 0.84	37.68 ± 1.21**
Tenth		32.97 ± 1.11	39.21 ± 0.88**
Twentieth		27.28 ± 0.98	41.54 ± 0.76**
Twenty-fifth		25.41 ± 0.75*	42.36 ± 1.15***
Thirtieth		25.37 ± 1.18	41.14 ± 1.22**

During experimental tetrachloromethane intoxication in rats of the second research group, feeding Sylimevit increased the bactericidal activity of blood serum. A probable increase in this indicator was observed from the fifth day, when it increased by 6.94 % compared to the control group. Subsequently, a gradual increase in the bactericidal activity of blood serum was observed, where it increased by 8.47 % on the 10th day of the experiment and by 10.8 % on the 20th day, relative to the control group. It is worth noting that the bactericidal activity of blood serum in rats of the second experimental group was the highest on the 25th day of the experiment.

Under physiological conditions, the formation and presence of circulating immune complexes in fluids is a manifestation of the immune response of the animal body to the penetration of antigens. Circulating immune complexes trigger successive chains of pathological changes since the long-term circulation of even a tiny amount of these complexes in body fluids can lead to their accumulation in tissues.

With the development of oxidative stress caused by the introduction of tetrachloromethane in the rats of the first experimental group, the number of circulating immune complexes probably increased from the fifth day of the experiment. Thus, on the 5th and 10th day of the experiment, the number of circulating immune complexes in the blood of the first experimental group increased by 59.7 % and 73.2 %, respectively, compared to the number in the control group of rats. The highest number of circu-

lating immune complexes was observed on the 25th and 30th day of the experiment (Table 3).

Detection of a high number of circulating immune complexes in the blood serum of rats of the first research group indicates suppression of the body's immunoreactive system. This results from binding specific antibodies to metabolic products in tetrachloromethane poisoning.

Feeding the feed additive "Sylimevit" to rats of the second experimental group during experimental tetrachloromethane poisoning contributed to a decrease in the level of circulating immune complexes in their blood compared to sick rats not fed the feed additive. The level of circulating immune complexes in the blood of the second experimental group of rats was lower than that of the first experimental group throughout the experiment. However, compared to the control group of animals, the level of the studied indicator in the blood of the second experimental group of rats remained high, where on the 5th and 10th day of the experiment, it increased by 41.4 and 30.7 %, respectively. On the 25th and 30th day of the experiment, the level of circulating immune complexes in the blood of rats of the second experimental group decreased to 52.39 ± 1.99 and 51.68 ± 1.24 %. At the same time, this indicator was significantly higher in the first experimental group.

Table 3

Circulating immune complexes in the blood of rats under conditions of oxidative stress and the effect of the feed additive "Sylimevit", mmol/l (M ± m; n = 5)

Day of Research	Group of animals		
	Control	Research 1	Research 2
Fifth		67.58 ± 2.19*	59.81 ± 1.35***
Tenth		73.26 ± 3.19***	55.31 ± 1.57**
Twentieth	42.31±1.14	73.89 ± 2.18***	53.47 ± 1.92**
Twenty-fifth		74.67 ± 2.27***	52.39 ± 1.99**
Thirtieth		74.55 ± 2.11***	51.68 ± 1.24***

In sick rats of the first research group, in addition to a decrease in the activity of the immune system's humoral link, suppression of the immune system and the nonspecific link of the immune system were also detected. This is manifested in a decrease in the phagocytic activity of neutrophils and a decrease in the phagocytic index (tables 4 and 5).

It was established that in rats experimentally induced to develop oxidative stress, the phagocytic activity of neutrophils probably decreased on the 25th and 30th day of the experiment. Compared with the indicators of the control group, the phagocytic activity of neutrophils in the blood of the first experimental group decreased by 7.7 and 7.4 %, respectively.

When feeding the feed additive "Sylimevit" to the rats of the second experimental group, an increase in the phagocytic activity of neutrophils was established, where, accordingly, on the 20th day of the experiment, this indicator increased by 4.2 %, and on the 25th day – by 7.2 % compared to the first experimental group.

Table 4

Phagocytic activity of neutrophils in the blood of rats under conditions of oxidative stress and the effect of the feed additive "Sylimevit", % (M ± m; n = 5)

Day of Research	Group of animals		
	Control	Research 1	Research 2
Fifth		19.1 ± 1.75	19.4 ±1.95
Tenth		17.1 ± 1.50	19.6 ± 2.15
Twentieth	20.4 ± 1.56	15.2 ± 0.87	19.4 ± 1.27
Twenty-fifth		12.7 ± 1.31*	19.9 ± 1.40
Thirtieth		13.0 ± 0.87*	19.9 ± 1.34

Table 5

The phagocytic index of the blood of rats under conditions of oxidative stress and the effect of the feed additive "Sylimevit", units (M ± m; n = 5)

Day of Research	Group of animals		
	Control	Research 1	Research 2
Fifth		9.2 ± 1.35	10.1 ± 1.12
Tenth		8.4 ± 1.76	9.8 ± 1.81
Twentieth	10.5 ± 1.49	7.2 ± 1.62	9.4 ± 0.81
Twenty-fifth		6.5 ± 0.95	9.9 ± 0.78
Thirtieth		6.8 ± 0.71	10.3 ± 0.56

When examining the phagocytic index in experimental rats injected with tetrachloromethane, a decrease of 20 and 31.4 % compared to the control group was established on the 10th and 20th day of the experiment. The lowest phagocytic index was in the blood of rats of the first experimental group on the 25th and 30th day of the experiment, where relative to the control group, it decreased by 38.1 and 35.2 % (Table 5).

When rats were fed Sylimevit under conditions of oxidative stress, a slight decrease in the phagocytic index was established on the 20th and 25th days of the experiment. On the 30th day of the experiment, PhI in the blood of rats of the second experimental group reached physiological limits.

Conclusion

The introduction of tetrachloromethane in experimental groups of rats led to the development of oxidative stress caused by specific chemical processes occurring in the body. During the development of oxidative stress in rats caused by the introduction of carbon tetrachloride, suppression of the humoral and nonspecific links of the immune system was established, which indicates a decrease in the bactericidal and lysozyme activity of blood serum, the phagocytic index, and the phagocytic activity of neutrophils. At the same time, an increase in the number of circulating immune complexes was observed.

In addition, it was established that the feeding of the feed additive "Sylimevit" led to the strengthening of the immune defense of the body of rats that were poisoned with tetrachloromethane. "Sylimevit" feed additive contributed to the increase of the body's immune response, helping to strengthen the protective mechanisms against tetrachloromethane poisoning.

Conflict of interest

The authors declare that there is no conflict of interest.

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