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Indicators of Immunity in Associated Mycotoxicosis of Cows

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Abstract. The issue of cattle reproduction was and still is one of the main tasks in cattle breeding. Losses of farms from infertility of cows are quite significant and range within 3.19-5.41 per 1 day of infertility. Mycotoxins produced by fungi of the *Fusarium* family, namely deoxynivalenol (DON) and zearalenone (ZEN) adversely affect not only the functioning of all organs and systems of the cow's body, but also produce an immunosedative effect. The purpose of this study was to establish the effect of the DON and ZEN complex on the main indicators of the immune response of cows and its correction in a comparative aspect using a feed additive based on zeolite and organic acids and recombinant α-, g-interferons. The study material was the blood of cows (serum and stabilized) sick with mycotoxicosis caused by the association of DON and ZEN. Methods used: photonephelometric using *E. coli* test culture, spontaneous rosette formation with sheep red blood cells according to M. Jondal, modified method of rosette formation according to M. Wansbrough-Jones, R. Limatibul's method, simple radial immunodiffusion in gel according to G. Mancini, precipitation in a polyethylene glycol solution according to M. Digeon. Experimental studies were performed on black-spotted cows in farms of the Sumy Oblast. The dynamics of the immune indicators of cows during the development of mycotoxicosis and upon treatment with products zeolite-based, organic acids, and an aqueous solution of recombinant α-, g-interferons were studied. It was found that the indicator of bactericidal, lysozyme, complementary, and phagocytic activity of cow blood serum under treatment increased to the indicator inherent in healthy animals. The dynamics of immunoglobulins in the treatment with zeolite and organic acids and recombinant α-, g-interferons was investigated, and an increase to the level of intact cows was established. It was proved that the indicators of the immune response of cows upon using a feed additive based on zeolite and organic acids at a dose of 2.5 kg per tonne of fodder and a preparation based on an aqueous solution of recombinant α-, g-interferons at a dose of 3 ml per animal were significantly higher

Keywords: cows, mycotoxicosis, zearalenone, deoxynivalenol, cow immunity, feed additives

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INTRODUCTION

Animal husbandry is currently facing such a phenomenon as mycotoxin damage to fodder in many regions of Ukraine. The economic losses suffered by milk production farms are quite significant and, according to the American method of determining the economic effect, range within $3.19-5.41 per day (Kibar *et al*., 2018). Improving existing and developing new methods for intensifying the reproductive capacity of cows is an urgent issue. It is known that mycotoxins, which are produced by fungi of the *Fusarium* family, such as deoxynivalenol and zearalenone, have a toxic effect on the body of cows (Gupta *et al*., 2022). These toxins are described by destructive changes in the intestine and suppress the body's immune reactions (Bulgaru *et al*., 2021). However, the effect on the organs of the immune system is insufficiently described.

The phenomenon is quite widespread in the world and scientists (Kemboi *et al*., 2020; Santos Pereira *et al*., 2019) are inclined to believe that the damage to feed by mycotoxins ranges within 42-65%. Nevertheless, the author (Bailey *et al*., 2019) points out damage to wheat and barley, but damage to feed mixture made from maize is not covered in this study. In the production of livestock products, it is mycotoxins that cause considerable economic losses, which can include reduced productivity of cows, insufficient production of offspring (Faisal *et al*., 2018) and premature culling of cows (Nichea *et al*., 2015). However, the research of the above-mentioned authors was conducted on Simmental and red-spotted cows, and other breeds of cows in other climatic zones can have quite substantial features of the course of mycotoxicosis. Researchers (Wang *et al*., 2019) developed a method for detecting mycotoxins in fodder and food products, which is based on the use of specific extremely sensitive monoclonal antibodies and solid-phase enzyme immunoassay. In addition, the studies (Wang *et al*., 2022; Wang *et al*., 2021) developed an express analysis based on two parallel specific immunochromatographic tests for the simultaneous detection of aflatoxin B1 (AFB1) and zearalenone (ZEN) in fodder.

Therewith, researchers (Clin *et al*., 2016; Barański *et al*., 2021) indicate that under the action of mycotoxins, the overall resistance of the body decreases, which leads to a violation of the reproductive ability of the body and infertility. Several *Fusarium* mycotoxins can alter various intestinal defence mechanisms, such as epithelial integrity, cell proliferation, mucus layer, immunoglobulin uptake, and cytokine production. Recently, the emergence of new and disguised *Fusarium* mycotoxins in farm animals has been of concern, which may contribute to toxic health effects (Ekwomadu *et al*., 2021), although the metabolic fate of mycotoxins is still a matter of scientific debate.

Acute aflatoxicosis leads to the death of the animal, while chronic aflatoxicosis leads to immune suppression and other chronic pathologies of internal organs and pathological conditions (Zahran *et al*., 2019). However, the authors cite data related to deoxynivalenol damage in animals, and the effect of assimilated exposure to mycotoxins still requires further investigation. It was found that aflatoxins temporarily reduced the phagocytic activity of leukocytes in cows. Furthermore, the ability to induce T-cell proliferation in mycotoxicosis decreased (Toutounchi *et al*., 2021). Therewith, the observation described by the authors was over 60 days of age and requires clarification of the generation of these cells directly in the thymus.

Under the action of deoxynivalenol, the regulation of antigen-presenting ability is disrupted, which may explain the immunotoxicity of this mycotoxin (Toutounchi *et al*., 2021). However, the author focuses on the formation of antigen-receptor bonds but does not describe exactly how mycotoxins affect the synthesis of distinct types of lymphocytes.

Immune responses are variable. Aflatoxin B1-induced immunosuppression has been demonstrated in various livestock species (e.g., turkeys, chickens, and pigs) and in laboratory animals (mice, guinea pigs, and rabbits). The response of bovine lymphocytes to aflatoxin in vitro is similar to that of other laboratory animals. Trichothecenes are powerful immunosuppressants that directly affect immune cells, as well as alter immune responses because of tissue damage elsewhere. Sheep and calves treated with *fusarium* T-2 toxin develop leukopenia and the functioning of peripheral lymphocytes decreases. Immunosuppressive effects of ochratoxin A, rubratoxin B, and patulin have been reported. Citrinine caused lymphopenia, but stimulated responses against antigens (Sun *et al*., 2022). Antibodies against mycotoxins conjugated with proteins are formed for analytical purposes. Therewith, it is necessary to clarify the mechanism of action of zearalenone on the immune response.

The studies of Roberts *et al.* (2021) described that a considerable increase in the percentage of CD4-CD8+ T-cells was observed in bulls treated for 2 weeks and characterized by a decrease in the ratio of CD4:CD8 T-cells ($p \leq 0.10$). Cattle at the final stage of fattening are susceptible to immunotoxic and inhibitory transcripts of the effects of deoxynivalenol and fumonisins. However, the coverage of similar mechanisms in dairy cows requires attention.

Considering the above, *the purpose of this study* was to figure out the dynamics of changes in immunity indicators in the dynamics under the action of mycotoxins according to the classical scheme of prevention of mycotoxicosis and compare with experimental treatment.

MATERIALS AND METHODS

The study was conducted in the conditions of farms of LLC "Marivske" and LLC "Vitchyzna" of the Sumy Oblast on cows of black-spotted breed. The animals were aged

from 3 to 5 years, weighing 550-580 kg. Therewith, cows were divided into 4 groups according to the analogue method. Animals of Group 1 (n=25) – healthy cows that have not been diagnosed with mycotoxisosis. Animals of Groups 2-4 were fed fodder containing zearalenone and deoxynivalenol at concentrations above 0.5 mg/kg. Cows of Group 2 (n=27) were not tested during the experimental period. Animals of Group 3 were given a feed additive based on zeolite and organic acids at a dose of 2.5 kg per tonne of fodder. Cows of Group 4 were given a feed additive based on zeolite and organic acids at a dose of 2.5 kg per tonne of fodder and a preparation based on an aqueous solution of recombinant α–, g-interferons at a dose of 3 ml per animal.

The presence of mycotoxins in concentrated fodder was found. European standards EN 15891:2011 (SIST 1) and EN 15850:2010 (SIST EN 15850:2010…, 2010) were used for this.

Research material: cow blood taken from the tail vein in an amount of 12 ml on Day 0, 10, 30, 60, and 125 of the research, in sterile polystyrene syringes. After sampling, the blood was divided into 2 parts, one part was placed in the refrigerator for 1.5 hours at 3°C to form blood serum, while the other was stabilized according to the EDTA method.

Bactericidal and lysozyme activity was found in blood serum by photonephelometric method using the *E. coli* test culture. Neutrophil phagocytic activity was found in stabilized blood using the *E. coli* test culture.

The number of T-lymphocytes was found according to the "rosette formation" method. The total number of T-lymphocytes was found according to M. Jondal's method of spontaneous rosette formation with sheep red blood cells (Jondal *et al.*, 1993). The content of early lymphocytes was investigated according to M. Wansbrough-Jones's modified method of rosette formation (Wansbrough-Jones *et al.*, 1979). The number of theophylline-sensitive and theophylline-resistant T-cells was found according to S. Limatibul's method (Limatibul *et al.*, 1978). The immunoregulatory index was calculated as the ratio of T-helper cells to T-suppressors. The number of B-lymphocytes was found according to N.F. Mendes (Mendes *et al.*, 1973).

Immunoglobulins of the main classes (A, M, G) in blood serum were investigated according to G. Mancini's method of simple radial immunodiffusion in a gel (Mancini *et al.*, 1965). The total level of circulating immune complexes (CEC) and their fractional composition by molecular weight were investigated according to M. Digeon's method of precipitation in a polyethylene glycol solution (Digeon *et al.*, 1977).

Statistical data were processed according to the Student's t-test of variational statistics for research in biology. The data are presented as an average value for groups with a square deviation error (M±m), the critical significance level was 0.05 (P). When calculating statistical data, the authors of this study used the Statistica 7.0 software.

All experimental studies were conducted per the corresponding requirements and standards that meet the requirements of DSTU ISO/IEC 17025:2005, IDT. Animal husbandry and all manipulations were performed according to the provisions of the Procedure for conducting tests and experiments on animals by scientific institutions (Law of Ukraine No. 249, 2012) of the European Convention for the protection of vertebrates used for experimental and other scientific purposes (European Convention…, 1986).

RESULTS AND DISCUSSION

Natural resistance and its correction in cows with mycotoxicosis. The bactericidal activity of blood serum of healthy animals during the 125-day experimental period ranged within 44.9±1.31-47.1%. The results of the study of cow blood serum are presented in Table 1.

Table 1. *Change dynamics in the bactericidal activity of cow blood serum, %*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Experimental period, day	0	46.8±1.14	33.65±1.03 *	34.36±1.1 *	33.3±1.26 *
	10	47.1±1.22	33.64±1.29 *	37.94±1.26*	37.1±1.36 *
	30	44.9±1.31	29.36±1.62 *	38.91±1.31 *	41.4±1.35
	60	46.2±1.83	29.67±1.33 *	39.64±1.26 *	44.3±1.39
	125	46.3±1.76	27.35±1.06 *	41.29±1.98	46.7±1.97

Note: **P⩽0.05*
Source: *compiled by the authors*

The indicator of bactericidal activity (BA) in sick cows (with mycotoxicosis) was reduced by 1.4-1.6 times. The value of BA in the blood serum of animals of Group 2 during the studies was 1.4 times lower than the control values by Day 10 of the experiment, by Day 30 – by 1.5 times, by Day 60 – by 1.6 times, by Day 125 – by 1.70 times.

The bactericidal activity of blood serum of animals of Groups 3 and 4 during the experiment changed upwards, but at contrasting times and in separate groups

this indicator did not change equally. The greatest value of bactericidal activity was achieved in the blood serum of animals of these groups by Day 125 of experiments. At that time, this indicator increased in Group 3 by 1.2 times, and in Group 4 – by 1.4 times. Therewith, the bactericidal activity of the blood serum of cows of Group 3 was 1.15 times lower than that of healthy animals, and in Group 4 it practically did not differ from that of healthy animals.

Dynamics of lysozyme activity in cow blood serum. Lysozyme plays an important function as a biomarker produced by the cow's body (Chia *et al.*, 2019). The lysozyme activity (LA) of the blood serum of cows of the control Group 1 practically did not alter during the experiment period – 21.0-22.5%. LA of the blood serum of sick animals at the beginning of the experiment was lower than in healthy animals and amounted to 14.9±1.24%, 15.3±0.95% in cows of Group 3, 14.95±0.98% in cows of Group 4.

Analysing the dynamics of this indicator, it is worth pointing out that unreliable fluctuations were observed in healthy cows during the entire research period. The authors of this paper believe that this is explained by the influence of external factors, such as high ambient temperature, crowded housing. This is confirmed by the study (Toutounchi *et al.*, 2021).

Lysozyme activity in cows with mycotoxicosis was reduced during the entire follow-up period and not significantly ranged within 13.8±1.67–15.1±1.28%. The decrease in this indicator is conditioned upon the effect of mycotoxins on the body of cows, which leads to a decrease in the activity of white blood cells. Comparable results were obtained by researchers (Zahran *et al.*, 2021; Cheng *et al.*, 2016). The results of the study of lysozyme activity of cow blood serum are presented in Table 2.

Table 2*. Change dynamics in the lysozyme activity of cow blood serum, %*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Experimental period, days	0	21.3±1.25	14.9±1.24*	15.3±0.95*	14.95±0.98*
	10	22.1±1.27	15.1±1.28*	17.64±0.65*	18.82±0.65*
	30	21.95±1.62	14.95±1.39*	20.6±0.78	20.94±0.94
	60	21.76±0.95	13.9±1.25*	21.4±1.32	21.22±0.84
	125	22.01±0.97	13.8±1.67*	21.75±1.22	22.47±0.93

Note: **P⩽0.05*
Source: *compiled by the authors*

The dynamics of lysozyme activity in the blood serum of cows of Group 3 began to increase on Day 10 of research, and on Day 30 – did not differ from a similar indicator of healthy animals. The best result was obtained in Group 4, where a significant increase in lysozyme activity was recorded on Day 10 of the study.

Dynamics of complementary activity of cow blood serum. The complementary activity of the blood serum of cows of the control Group 1, for 125 days of experiments, practically did not change and was within 22.86±1.28–23.96±1.35. Data from the study of the dynamics of complementary activity of cow blood serum are presented in Table 3.

Table 3*. Change dynamics in the complementary activity of cow blood serum, units*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Number of animals		25	27	20	20
Experimental period, days	0	23.31±1.04	12.92±1.86*	13.4±0.44*	13.39±0.35*
	10	23.56±1.09	13.27±0.25*	15.82±0.4*	16.6±0.65*
	30	23.98±1.35	13.81±0.36*	17.27±0.27*	18±1.91*
	60	23.96±0.36	13.37±0.51*	19.98±0.46*	19.48±0.95*
	125	23.32±0.92	14.14±1.66*	20.25±0.57	21.02±1.2

Note: **P⩽0.05*
Source: *compiled by the authors*

The complementary level in the blood serum of cows with mycotoxicosis was 1.17-1.28 times lower than the physiological norm before the start of experiments. The same indicator in the blood serum of cows of Group 2 was even lower compared to the background and control values by 1.2 times by Day 30 of the experiment, by Day 60 – by 1.4 times, and by Day 125 – by 2.3 times.

Complementary activity in the blood serum of cows of Groups 3 and 4 increased significantly before the end of the experiments, and, depending on the group, changed differently: in Group 3 in relation to Day 0, on Day 10 – by 1.09 times, on Day 30 – by 1.22 times, on Day 60 – by 1.20 times, on Day 125 – by 1.15 times. However, the animals of the control group were 1.20, 1.15, 1.14, and 1.15 times inferior in this indicator, respectively. The same indicator of blood serum of cows of Group 4 increased by 1.08, 1.17, 1.15, and 1.20 times, respectively, compared to the initial value on Days 10, 30, 60, and 125 of the experiment. However, it was respectively 1.12, 1.10, 1.20, and 1.10 times lower than control in the same experimental periods.

Phagocytosis and its correction in cows with mycotoxicosis. The initial value of phagocytic activity in the blood of animals of Groups 2-4 was lower by an average of 1.4-1.5 times (by 12.5-16.0%) (Table 4).

Table 4*. Change dynamics in the phagocytic activity of cow blood serum, %*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Experimental period, days	0	45.51±1.41	26.32±1.03*	24.21±1.18*	25.3±0.93*
	10	45.42±1.15	26.46±1.08*	28.55±1.11*	28.39±1.44*
	30	45.46±1.12	25.34±1.66*	30.21±1.12*	31.98±1.81*
	60	46.1±0.59	26.34±0.64*	32.33±0.78*	35.41±2.02*
	125	45.31±1.24	25.39±0.72*	34.53±1.38*	43.18±0.87

Note: **P⩽0.05*
Source: *compiled by the authors*

The phagocytic activity of leukocytes in the blood of cows of Groups 3-4 was reduced and amounted to 26.32±1.03% in Group 2; 24.21±1.18% in – Group 3, and 25.0±0.93% – in Group 4. Subsequently, in animals of Group 2, the indicator of phagocytic activity of leukocytes did not change significantly, and at the end of the studies was 26.14±1.06%.

A similar indicator in cows of Group 3 had substantial dynamics on Day 10 and amounted to 28.55±1.11%, on Day 30 – 30.21±1.12%, on Day 60 – 32.33±0.78%, and at the end of the experimental period was 34.53±1.38%, which is 1.4 times more than the initial value. However, this indicator in Group 3 stayed significantly lower (P<0.01) compared to the same indicator in healthy animals. The phagocytic activity of leukocytes of cows in Group 4 increased, starting from Day 10, and at the end of studies amounted to 43.18±0.87%, which did not significantly differ from healthy cows.

In case of mycotoxicosis of cows caused by zearalenone and deoxynivalenol from *Fusarim* and *Aspergillus fumigatus* toxin, all elements of the natural resistance system are suppressed, which is manifested in a decrease in the bactericidal, lysozyme, and complement activity of blood serum (Knutsen *et al*., 2017).

Indicators of T- and B-immune systems and their correction in cows with mycotoxicosis. The results of studies of the dynamics of the content of T-E-ROC lymphocytes in the blood of cows are presented in Table 5.

Table 5*. Content dynamics of T-E-ROC lymphocytes in the blood of cows, %*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Experimental period, days	0	42.02±1.14	26.15±0.74*	25.95±0.55*	27.03±1.15*
	10	42.35±1.41	26.44±0.42*	27.67±0.8*	30.18±1.03*
	30	42.37±1.6	26.56±0.11*	30.97±1.12*	36.17±1.17*
	60	41.64±1.01	26.04±1.05*	33.72±0.62*	39.54±1.82*
	125	42.12±1.07	25.88±0.38*	37.34±0.7*	40.34±1.45

Note: **P⩽0.05*
Source: *compiled by the authors*

The content of T-lymphocytes in the blood of cows that received balanced mineral composition had a value at the level of 41.87±1.34 - 42.37±1.6%. The level of T-E-ROC lymphocytes in the blood of cows of Groups 2-4 at the beginning of the experiment was 1.55-1.62 times less than in healthy cows. In cows of Group 2, no increase in the values of this indicator was noted throughout the experiment. The indicator of blood T-cells of cows of this group on Day 10 of the experiment tended to increase, but they were 1.53 times lower than the same indicator in healthy animals. On Day 30, this ratio was 1.37, on Day 60 – 1.23, and on Day 125 – 1.13 times.

The level of T-cells in the blood of Group 4 in relation to the indicator of healthy animals was 1.55 times lower on Day 0, 1.14 times lower on Day 10, and 1.17 times lower on Day 30. However, starting from Day 60 of the experiment, this indicator did not significantly differ from that in healthy cows.

Content dynamics of T-helpers in the blood of cows. The blood of cows of Group 1 contained 20.51-21.67% of T-helpers. This indicator in the blood of cows of Groups 2-4 was 1.5 times lower before the start of experiments than in Group 1. Data from the study of the dynamics of T-helpers in the blood of cows are presented in Table 6.

Table 6. *Dynamics of T-helpers in the blood of cows, %*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Experimental period, days	0	21.67±1.14	14.19±0.1*	14.37±0.88*	14.49±0.93*
	10	20.51±1.39	13.49±0.53*	15.78±1.29*	18.32±0.35*
	30	21.15±0.51	13.77±1.21*	17.26±0.19*	19.06±0.65*
	60	20.97±1.11	13.86±1.29*	18.65±0.06*	19.52±0.54
	125	21.45±0.06	14.06±0.95*	18.61±0.42*	20.59±0.6

Note: **P⩽0.05*
Source: *compiled by the authors*

The level of T-helpers in the blood of Group 2 cows was stable throughout the experiment. The content of T-helpers in the blood of cows of Group 3 slightly increased compared to the background: up to Day 10, on Days 30, 60, and 125 – by 1.09, 1.20, 1.3, and 1.27 times, respectively, and was inferior to the control values. The indicator of T-helpers in the blood of cows of Group 4 increased by 1.29 times by Day 10 of the experiment, by 1.3 times – by Day 30, by 1.35 times – by Day 60, by 1.42 times – by Day 125, not significantly differing from the same indicator in healthy cows.

Content dynamics of T-suppressors in the blood of cows. The results of the study of the dynamics of T-suppressors in the blood of cows are presented in Table 7.

Table 7. *Content dynamics of T-suppressors in the blood of cows, %*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Experimental period, days	0	18.06±0.57	23.51±1.39*	23.39±0.6*	23.4±1.84*
	10	18.56±0.2	23.19±0.87*	22.13±1.15*	22.39±0.33*
	30	19.05±1.38	22.37±1.05*	21.46±0.47*	18.32±0.55
	60	18.75±0.72	22.76±1.52*	20.01±0.33*	18.02±1.29
	125	18.42±0.86	22.57±1.28*	20.01±0.35*	18.12±1.61

Note: **P⩽0.05*
Source: *compiled by the authors*

Normalization of suppressor reactions was noted in cows of Group 4, since the level of T-suppressors almost corresponded to physiological standards by Day 10 of the experiments. The number of T-suppressors in the blood of cows of Group 1 (control) was stable – 17.9-18.8%. Background indicator of T-suppressors in the blood of cows of Groups 2-4 had greater values (1.18-1.18 times), which was higher by 2.4-3.4%. This trend in cows of Group 2 persisted throughout the experiment. The number of T-suppressors increased by Day 10 compared to the background and control by 1.10 and 1.24 times, by Day 30 – by 1.14 and 1.26 times, by Day 60 – by 1.15 and 1.3 times, by Day 125 – by 1.16 and 1.33 times. The reaction of T-suppressors in the blood of cows of Groups 3 and 4 during the experiment significantly decreased but did not occur in the same way.

The level of T-suppressors in the blood of animals of Group 3 decreased in comparison with the background values: by Day 10, on Days 30, 60, and 125, respectively – by 1.07 times, 1.0 times, 1.06 times, 1.08 times, while exceeding the control figures by 1.10; 1.05; 1.07, and 1.20 times. The maximum decrease in T-suppressors was observed in the blood of cows of Group 4.

The level of T-suppressors was 1.60 times lower than the background by Day 10 of the experiment, 1.10 times lower – by Day 30, 1.09 times lower – by Day 60, and 1.10 times lower by Day 125, which practically corresponded to the control data. Zearalenone is thought to affect the immune response considerably, which is the main defence mechanism against pathogens, toxins, and other antigens in all mammals, with immunostimulating or immunosuppressive results (Bulgaru *et al.*, 2021).

Immunoglobulins and their correction in cows with mycotoxicosis. Studies of the blood serum of cows of Group 1 on IgG in real time showed that their level was within 26.5-28.0 g/l (Table 8).

Table 8. *Dynamics of T-helpers in the blood of cows, %*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Experimental period, days	0	27.12±0.86	17.3±0.53*	17.36±1.16*	17.29±1.1*
	10	27.2±1.07	16.47±0.01*	18.74±0.19*	19.36±0.57*
	30	27.24±0.64	15.72±0.82*	19.44±0.98*	23.23±0.83*
	60	27.16±0.78	14.07±1.9*	19.62±1.51*	24.94±0.71*
	125	27.0±1.13	13.84±0.43*	19.96±1.16*	26.87±0.11*

Note: **P⩽0.05*
Source: *compiled by the authors*

Immunoglobulins are an indispensable indicator, as they indicate the level of antibodies, which generally characterizes the possibility of an immune response to the action of a pathogenic agent (Nagahata *et al*., 2020).

At the same time, under the toxic compounds, namely mycotoxins, a decrease in this indicator was observed, which may indicate a decrease in the synthesizing function of lymphatic cells (Rahman *et al*., 2021). The level of IgG in the blood serum of animals of Group 2 decreased, and during the experiment and up to Day 10 of research, compared to the background indicator, was 1.05 times lower, up to Day 30 – 1.1 times, up to Day 60 – 1.23 times, up to Day 125 – 1.25 times.

The IgG content in the blood serum of cows of Groups 3 and 4 during studies on Day 10 was higher than the initial (background value) by 1.08; and 1.12 times, by Day 30 – by 1.12 and 1.36 times, by Day 60 – by 1.13 and 1.44 times, by Day 125 – by 1.15 and 1.55 times, respectively. This indicates a more effective increase in immunoglobulins when using recombinant α-, g-interferons compared to the use of a feed additive based on zeolite and organic acids through the activation of immunocompetent organs of the body. Similar data were obtained by the authors in a study on calves (Tang *et al*., 2022)

Dynamics of IgA content in cow blood serum. The level of IgA in the blood serum of healthy cows (Group 1) ranged within 2.25-3.11 g/l. This indicator in the blood serum of cows of Groups 2-4 was reduced by 1.4-1.5 times before the start of experiments. The level of serum IgA in cows of Group 2 dynamically decreased, yielding to the background and control levels on Day 10 of the experiment by 1.04 times, on Day 30 – by 1.08 times, on Day 60 – by 1.15 times, on Day 125 – by 1.17 times. The same indicator in the blood serum of cows of Group 3 increased compared to the beginning of the experiment and on Day 10 was 1.6 times higher, on Day 30 – 1.56, on Day 60 – 1.88, and on Day 125 – 1.81 times higher, respectively. In the blood serum of cows of Group 4, the IgA content increased by 1.7, 1.59, 1.6, and 2.45 times, respectively, starting from Day 10. Data on the dynamics of IgA in blood serum of cows are presented in Table 9.

Table 9. *Dynamics of IgA in blood serum of cows, g/l*

Group of cows		Control – healthy Group 1	Control – sick with mycotoxicosis Group 2	Experimental Group 3	Experimental Group 4
Experimental period, days	0	2.91±0.28	1.25±0.16*	1.14±0.61	1.29±0.14
	10	2.63±0.43	1.20±0.57*	1.87±0.17	2.24±0.19
	30	3.11±0.9	1.15±0.23*	1.78±0.06	2.06±0.17
	60	2.61±0.61	1.09±0.23*	2.15±0.26	2.09±0.57
	125	2.25±0.38	1.07±0.35*	2.06±0.38	3.16±0.91

Note: **P⩽0.05*
Source: *compiled by the authors*

The authors also report that the innate immune response is triggered by receptors that recognize the pathogen and activate several signalling pathways that control the immune response. Neutrophils, monocytes/macrophages, and dendritic cells that mediate interaction with pathogens are components of the innate immune system that can form networks, playing a key role in the initial immune response to infection and tissue damage. These are phagocytic cells that, upon stimulation, can produce reactive oxygen species that are important for cell signalling and homeostasis. The indicator of bactericidal activity of blood characterizes

the ability of blood serum complexes to destroy 99.9% of bacteria (Zaghi *et al*., 2020). The data obtained confirm the statement of most studies that under toxic substances, in this case mycotoxins, it leads to a decrease in non-specific immune factors due to inhibition of the work of immunocompetent organs. Rivera notes that a decrease in the bactericidal activity occurs due to the action on the body of exogenous and endogenous microflora that produces toxins (Rivera *et al*., 2020). It is important that mycotoxins exert a negative effect complexly and in a lower concentration, while microorganisms in the early process act in the overwhelming majority in the zone of the inflammatory reaction.

The use of a feed additive (experimental Group 3) in the diets of cows at a dose of 2.5 kg per tonne of fodder contributed to an increase in bactericidal activity due to a decrease in toxic substances in the blood of experimental cows. The mechanism of action of the supplement is based on a synergistic combination of mechanical (adsorption) and detoxification action of organic acids. Organic acids, namely acetic acids, increase the acidity to pH 6.3-6.5 when feeding the additive, which adversely affects the growth and development of microscopic fungi, while not suppressing the viability of scar microflora. Comparable results were obtained by other scientists who investigated the pig livestock, but in their studies more attention was paid to studying the effect of sorbents on the gastrointestinal tract of monogastric animals. Therewith, the level of acidity displacement had only a lower limit sufficient for the destruction of fungi (Dąbrowski *et al*., 2016; Bailey *et al*., 2019).

Furthermore, the toxic effect on the liver and the decrease in the synthesis of immunomodulating proteins is also indicated by Iori *et al*. (2022) who noted transcriptomic changes that showed differences in the expression of genes involved in the inflammatory response, oxidative stress, drug metabolism, apoptosis, and cancer. Cell death associated with necrosis rather than apoptosis was noted. As for the mechanism of toxicity, a molecular pathway linking the inflammatory response and oxidative stress has been postulated. Activation of Toll-Like Receptor 2 (TLR2) by AFB1 triggers an intracellular signalling cascade involving a kinase (p38β MAPK), which enables the nuclear translocation of activator protein-1 (AP-1) and NF-κB, ultimately leading to the release of pro-inflammatory cytokines.

P. Ferraboschi (2021) points out the need to use synthesized lysozyme to protect animal feed from the effects of microscopic fungi and bacteria. The author notes that this increases the level of lysozyme in the blood and positively affects the immunity of animals. This statement correlates with the authors' studies that the action of immunostimulants increases lysozyme activity, but the authors do not agree that exogenous lysozyme can support a high immune response for a long time.

The use of an immunomodulator based on recombinant α- and g-interferons (experimental Group 4) gave the best result. The increase in the bactericidal activity of the blood was caused by the immune system stimulation, based on an increase in the formation of cytokines and blocking of lymphocyte receptors, which is confirmed by the results of studies by Malvandi *et al*. (2022).

R. Falkauskas *et al*. (2022) reported a significant negative correlation (r=−0.540) between urinary beta-zearalenol and beta-zearalanol concentrations and a positive correlation (r=0.826) between serum beta-zearalenol and alpha-zearalanol concentrations ($p<0.05$). During the study, it was found that feeding cows for two weeks with feed without mycotoxins can reduce the concentration of alpha- and beta-zearalenol in body fluids and can reduce the concentration of ZEN in milk but does not reduce the concentration of zearalenone. This is consistent with the results of the present study, although this paper also suggests using sorbent-and interferon-based agents to reduce mycotoxin levels.

An imbalance between the formation of reactive oxygen species and their inefficient elimination leads to a sharp increase in them, which causes cell damage known as oxidative stress (Solhaug *et al*., 2016). Wang *et al*. (2019) reported that zearalenone (5, 10, 20 μm) increases the formation of reactive oxygen species in bovine neutrophils and reduces the activity of antioxidant enzymes, followed by the formation of extracellular neutrophil traps, a network of extracellular DNA fibres that help neutrophil cells kill extracellular pathogens.

However, F.A. Uzal (2016) states that locally generated and systemically circulating Ig can have an effect when vascular permeability and inflammation occur due to its ability to fix complement, promote antibody-dependent cell-mediated cytotoxicity, and opsonize. In most species, IgE-producing plasma cells are present in the lamina propria in small numbers. Its significance may lie in the IgE-dependent cytotoxicity of eosinophils, mast cells and basophils, as well as in mediating immediate type (Type I) hypersensitivity reactions in the intestinal mucosa, which confirms changes in the production of immunoglobulins in toxic conditions, but the author draws attention to IgE, and the dynamics of IgA and IgG stays out of the researcher's attention.

CONCLUSIONS

It was found that the presence of associated forms of mycotoxins in the diet of cows, produced by fungi of the genus *Fusarium*, has an immunosuppressive effect and causes a decrease in the bactericidal activity of blood serum from 23.47% to 29.9%, the lysozyme activity of blood serum of cows from 28.17% to 32 .58%, complement activity of serum from 44.12% to 56.52%, phagocytic activity of serum from 45.12% to 47.48%, blood T-E-ROC lymphocytes from 35.09% to 38.72%, T-helpers from 32.23% to 34.52%, immunoglobulins from 42.23% to 44.52% and an increase in T-suppressors from 16.63% to 23.18%.

The use of a zeolite-based feed additive and organic acids had an effect on the restoration of indicators, namely: bactericidal activity of blood serum – by 16.78%, lysozyme activity of blood serum of cows – by 29.66%, complementary activity of serum – by 37.62%, phagocytic serum activity – by 29.89%, T-E-ROC blood

lymphocytes – by 30.50%, T-helpers – by 22.78%, immunoglobulins – by 51.48%, and T-suppressors – by 14.79%.

The use of a zeolite-based feed additive and organic acids and a product based on an aqueous solution of recombinant α-, g-interferons affected the recovery of indicators, namely: bactericidal activity of blood serum – by 28.69%, lysozyme activity of blood serum of cows – by 20.12%, complementary activity of serum – by 41.52%, phagocytic activity of serum – by 41.41%, T-E-ROC blood lymphocytes – by 32.99%, T-helpers – by 29.63%, immunoglobulins – by 51.48%, and T-suppressors – by 24.17%.

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Показники імунітету при асоційованому мікотоксикозі корів

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Анотація. Питання відтворення великої рогатої худоби було і залишається одним із найголовніших завдань у галузі скотарства. Збитки господарств від неплідності корів досить значні та становлять від 3,19 до 5,41 $ за 1 день неплідності. Мікотоксини, що виробляються грибами родини *Fusarium*, а саме деосиніваленол (DON) і зеараленон (ZEN) негативно впливають не тільки на роботу всіх органів і систем організму корови, а й справляють імуноседативний ефект. Метою досліджень було встановити вплив комплексу DON і ZEN на основні показники імунної відповіді корів та її корекції в порівняльному аспекті з використанням кормової добавки на основі цеоліту і органічних кислот та рекомбінантних α- g-інтерферонів. Матеріалом досліджень була кров корів (сироватка та стабілізована), хворих на мікотоксикоз, спричинений асоціацією деосиніваленолу та зеараленону. Використані методи: фотонефелометричний з використанням тест-культури *E. coli*, спонтанного розеткоутворення з еритроцитами барана за M. Jondal, модифікований метод розеткоутворення за M. Wansbrough-Jones, метод P. Limatibul, простої радіальної імунодифузії в гелі за G. Mancini, преципітації в розчині поліетиленгліколю за M. Digeon. Експериментальні дослідження були виконані на коровах чорно-рябої породи в господарствах Сумської області. Було досліджено динаміку показників імунітету корів при розвитку мікотоксикозу та при застосуванні лікування із застосуванням засобів на основі целеоліту, органічних кислот та водного розчину рекомбінантних α- g-інтерферонів. Встановлено, що показник бактерицидної, лізоцимної, комплементарної та фагоцитарної активності сироватки крові корів під дією проведеного лікування підвищувався до показника у здорових тварин, Було досліджено динаміку імуноглобулінів в процесі лікування при застосуванні цеоліту та органічних кислот і рекомбінантних α- g-інтерферонів, встановлено підвищення до рівня інтактних корів. Було доведено, що показники імунної відповіді корів при застосуванні кормової добавки на основі цеоліту та органічних кислот у дозі 2,5 кг на тону корму та препарату на основі водного розчину рекомбінантних α- g-інтерферонів у дозі 3 мл на тварину були достовірно вищими

Ключові слова: корови, мікотоксикози, зеараленон, деосиніваленол, імунітет корів, кормові добавки