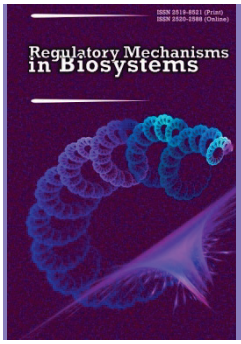

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Efficacy of hepatoprotectors in prophylaxis of hepatosis of laying hens

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Hepatoses of laying hens are quite common in poultry farms as a result of improper practices of poultry maintenance consisting in excessive number of protein feeds for provision of high productivity. The objective of the study was preventive efficacy of Gep-A-Stress hepatoprotectors (carnitine hydrochloride, D L methionine, sorbitol, choline chloride, magnesium sulfate heptahydrate) and Hepasan VS (L-carnitine hydrochloride, sorbitol, choline chloride, magnesium sulfate hepahydrate, betaine hydrochloride, L-arginin) against hepatosis of laying hens. To determine the efficacy of Hep-A-Stres and Hepasan-VS hepatoprotectors during production tests (n = 4,500), we monitored the parameters of survival rate (the final number of individuals as percentage of the initial number) and egg productivity of laying hens. We determined that after 30 days of using the hepatoprotectors, the content of overall protein in blood serum of laying hens of the first and the second experimental groups decreased by 21.4% and 18.9% compared with the parameters prior to providing the hepatoprotectors and by 26.3% and 23.3% compared with the control group after receiving the drug. The urea contents in blood serum increased by 19.0% and 10.5%. Compared with the control, the activity of alanine aminotransferase decreased by 43.7% and 24.1% in the first experimental group and by 23.4% and 14.9% in the second. The activity of aspartate aminotransferase in blood serum of the experimental groups decreased by 10.7%. The cholesterol concentration decreased by 50% and 58.3%. The content of triaglycerols decreased by 24.1% and 8.9% respectively. The concentrations of high-density lipoproteins after 30 days of the experiment decreased by 33.3% and 77.8% respectively, the content of low-density lipoproteins decreased by 61.3% and 40.4% and 42.3%. Population maintenance equaled respectively 97.1%, 98.3% and 98.1%. At the end of the experiment, the egg productivity of laying hens of the first and second groups increased by 4% and 3.6% compared with the control. Therefore, intake of the hepaprotectors by laying hens stimulated their metabolism, positively influenced the blood parameters, survival and egg productivity. The conducted studies confirm the benefits of using hepatoprotectors for the prohylaxis of hepatosis of hens.

Keywords: metabolism; liver; blood serum; productivity; poultry survival; enzymes; proteins.

Introduction

The liver is known as a central organ of chemical homeostasis of the organism which creates the single metabolic energy pool for metabolism of proteins, lipids and carbohydrates (Jarosz, 2019; Karpenko et al., 2022). It performs a number of important functions oriented at support of homeostasis of the entire organism, including the antigenic functions its structures (Zaefarian et al., 2019). Moreover, the liver of birds generates yolk material (vitellogenin) for the production of egg yolk in the ovary (Shini et al., 2019). The liver is a barrier preventing toxic substances from entering the organism, since it performs metabolism and detoxification of xenobiotics. This particular circumstance makes it a target during the action of chemical substances. Negative effect of toxic substances on the liver causes a broad range of pathogenic changes at various levels of its organization. Liver disease is one of the most common types of pathology in the clinical picture of internal diseases (Surai et al., 2018; Tao et al., 2020; Gao et al., 2021).

The liver plays an active part in metabolism, particularly in relation to fats. The liver is where they are broken down with energy release (Xu et al., 2019). However, not only do liver cells take part in metabolism of fats, but also in their accumulation, causing development of fatty hepatosis. Improper maintenance practices, high-calory feeding for obtaining highest parameters of productivity of poultry, and also deficiency of methionine is an etiological factor of emergence of liver pathologies (Tilbrook & Fisher, 2020). The constantly increasing morbidity rate of liver disease and inefficiency of the treatment makes it necessary to seek for new safe and highly effective medicinal drugs for the treatment of this pathology (Mel'nyk, 2017; Yan et al., 2019). Taking into account that during the liver disease, the membranes of hepatocytes are seen to be damaged and that a significant role of the processes of lipid peroxidation was noted, it is important to prescribe hepatoprotectors. Studies by a number of authors indicate the efficiency of using hepatoprotectory drugs that contain vitamin E, methionine, carnitine (El-Katcha et al., 2019).

Veterinary practice quite often uses complex drugs that contain several main active components (Karpenko et al., 2022). Vitamins B_4, B_{12}, E, methyonine, selenium mutually support each other when used in combinations, thereby strengthening the protective functions of the liver (Levchenko et al., 2017; Gutyj et al., 2019; Ostapyuk et al., 2021). An important peculiarity of contemporary drugs is their ability to exert a broad range of pharmacological activity, which in turn is measured by dynamic changes in the organism (Gu et al., 2021; Underwood et al., 2021).

Solving the problem of normalization of metabolic processes in the organism and morphofunctional conditions of the liver using hepatoprotectory drugs is potentially of vital importance for increasing the productivity of poultry farming and production of poultry goods.

Therefore, we consider the use of novel hepatoprotectors a relevant direction of improvement of the technology of poultry farming. This, in turn, would allow not only the treatment and prophylaxis of hepatosis of laying hens, but also the increases in their survival and productivity.

The purpose of our research was determining the hepatoprotective effect of drugs Hep-A-Stress and Hepasan-VS on the body of laying hens for treatment of hepatosis.

Material and methods

When performing the experimental studies on laying hens, we followed all the bioethics norms regarding the requirements of the Law of

Ukraine No. 3447-4 "On Protection of Animals Against Abuse", position of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasburg, 1986) and the positions on using vertebrate animals for experimental and other scientific purposes developed in the Lviv Gzhytskyi National University of Veterinary Medicine and Biotechnologies.

To carry out the study, in Ltc Agrofirm Zahaii of Kamianka-Bug district of Lviv Oblast, we formed three groups of 224 days-old laying hens (control and two experimental) of Loman Braun cross breed (n = 1500). In this farm, poultry are kept in a typical room, equipped by 3-story batteries with feeders and water reservoirs, the density equaling 5 individuals per cage. Laying hens of all the groups were kept on the main diet (MD) according to the technological card of using this croossbreed. The laying hens of the first experimental group were additionaly given Hep-A-Stres hepatoprotector (carnitine hydrochloride, D, L, methionine, sorbitol, choline chloride, magnesium sulfate heptahydrate) in the dose of 1 mL/L of drinking water for 10 days, and the second experimental group was given Hepasan VS hepatoprotector (L-carnitine hydrochloride, sorbitol, choline chloride, magnesium sulfate hepahydrate, betaine hydrochloride, L-arginin) in the dose of 1 mL/L of drinking water for 10 days, using a dispencer. Hep-A-Stres drug is produced by O.L.KAR-Agrozoovet-Service Enterprise (Ukraine), certified, registered. Hepasan-VS drug is produced by Vetsynthez LLC, Kharkiv, Ukraine. The ratios of the contents of active substances in 1 mL of Hep-A-Stres and Hepasan-VS drugs are given in Figure 1.

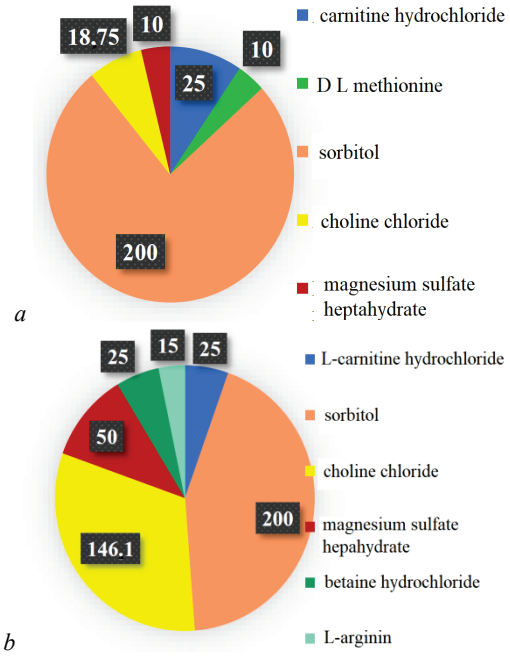

Fig. 1. Proportions of active agents (mg/mL of drug): *a* – Hep-A-Stres; *b* – Hapasam VS

Blood of laying hens was drawn from the basilic vein prior to giving the drugs (224 days), after 10 days and after 30 days from the start of giving the birds the hepatoprotectors. Biochemical studies of blood serum were carried out on 30 chickens of each group. In the blood serum, we determined the total protein and contents of its fractions, activity of aspartate (AST) and alanine (ALT) aminotransferases, cholesterol level, concentration of urea and uric acid, parameters of lipidogram (cholesterol, triacylglycerols, high-density lipoproteins, low-density lipoproteins, lipoproteins of very low density). The level of overall protein was determined using an IRF-22 refractometer. Fractional composition of blood serum proteins was determined using the method of electrophoresis on cellulose acetate with devices for microzonal electrophoresis Scan Power 300 and Scanion Lira 400, Hospitex Diagnostics. Pathanatomic study was performed on 10 laying hens from each experimental group in prosectorium of the Department of Normal and Pathological Morphology and Forensic Veterinary. The autopsy of the birds was carried out using the method developed by H. V. Shor.

To determine the efficiency of the experimental hepatoprotectors during a production experiment, we determined the parameters of survival rate and egg productivity of laying hens according to the generally accepted methods.

The study results were analyzed using Statistica 6.0 software (StatSoft Inc., USA). To compare the differences between the average parameters of the control and experimental groups, we used the Tukey test, where the differences were considered statistically significant at $P < 0.05$.

Results

The concentration of total protein in blood serum decreased by 6% in laying hens of the first experimental group on day 10 of the experiment, and by 5.4% in the second compared with the control (Fig. 2a). On the 30th day of intake of the drugs, this parameter in blood serum of laying hens of the first and the second experimental groups was down by 21.4% and 18.9% ($P < 0.001$) compared with the parameters prior to the experiments and by 26.3% and 23.3% ($P < 0.001$) compared with the control group. Increase in the total protein in blood serum of laying hens of the control group on the 10th day of the studies indicates the development of hepatodystrophy resulting from impaired synthesis of proteins.

In the blood serum of laying hens of the experimental groups, the decrease in the level of overall protein was caused by increase in the level of albumin fractions and decrease in globulins (Fig. 2). By day 10 of the experiment, the concentration of albumins in the blood serum of laying hens of the first experimental group had increased by 3.7% compared with the control and by 4% compared with the start of the experiment. By the 30th day of the experiment, the concentrations of albumins in the blood serum of laying hens of the experimental groups had increased by 5.7% and 3% compared with the parameters at the beginning of the intake of the drugs. The level of α_1 globulins in the blood of experimental group birds had significantly increased by the 10th day of the experiment. However, on the 30th day of the intake of Hep-A-Stres drug, we determined a 27% decrease in α_1 globulins compared with the control group for the indicated period of the experiment (Fig. 2c).

When studying the concentration of α_2 globulins, we determined that in the first experimental group, this parameter droped by 25% ($P < 0.001$) compared with the control group (Fig. 2d). Concentration of β globulins in blood serum from the first experimental group was the highest throughout all the study periods (Fig. 1e). Concentration of γ globulins in the blood serum of hens of the first experimental group at the beginning of the experiment was 49% lower ($P < 0.001$) compared with the control (Fig. 2f).

Concentration of urea in the blood serum of laying hens of the first experimental group after 10 days of the experiment increased by 15.8% ($P < 0.001$) compared with the control group (Fig. 3a). This parameter in the blood serum of laying hens of the second experimental group did not change. We determined that by day 30 of the experiment, urea content in the blood serum of laying hens of the first and the second groups increased by 19% ($P < 0.001$) and 10.5% ($P < 0.05$) respectively. Furthermore, this parameter increased in the blood serum of laying hens by 25% ($P < 0.001$), compared with the control, indicating renewal of urea formation in the liver.

We determined that prior to the experiment, the content of uric acid in blood serum of laying hens of the control group had increased. By days 10 and 30 of the experiment, there were 4.3% and 13.7% increases in this parameter respectively (Fig. 3b). By day 10, the intake of the drugs caused 5.6% decrease in the concentration of uric acid in the blood compared with the beginning of the experiment. In laying hens of the second experimental group, this parameter was 11.3% lower ($P < 0.05$) compared with the beginning of the experiment.

Functional condition of the liver was evaluated according to the parameters of the activity of hepatospecific enzymes of the blood serum (alanine- and aspartate aminotrasferases). We determined a 32% increase in the activity of alanine aminotransferase in the blood of experimental groups after 10 days of the intake of hepatoprotectors, compared with the control values (Fig. 3c). On the 30th day of the experiment, we determined a 19.4% decrease in the first experimental group, and 13% decrease in the second experimental group, compared with the control.

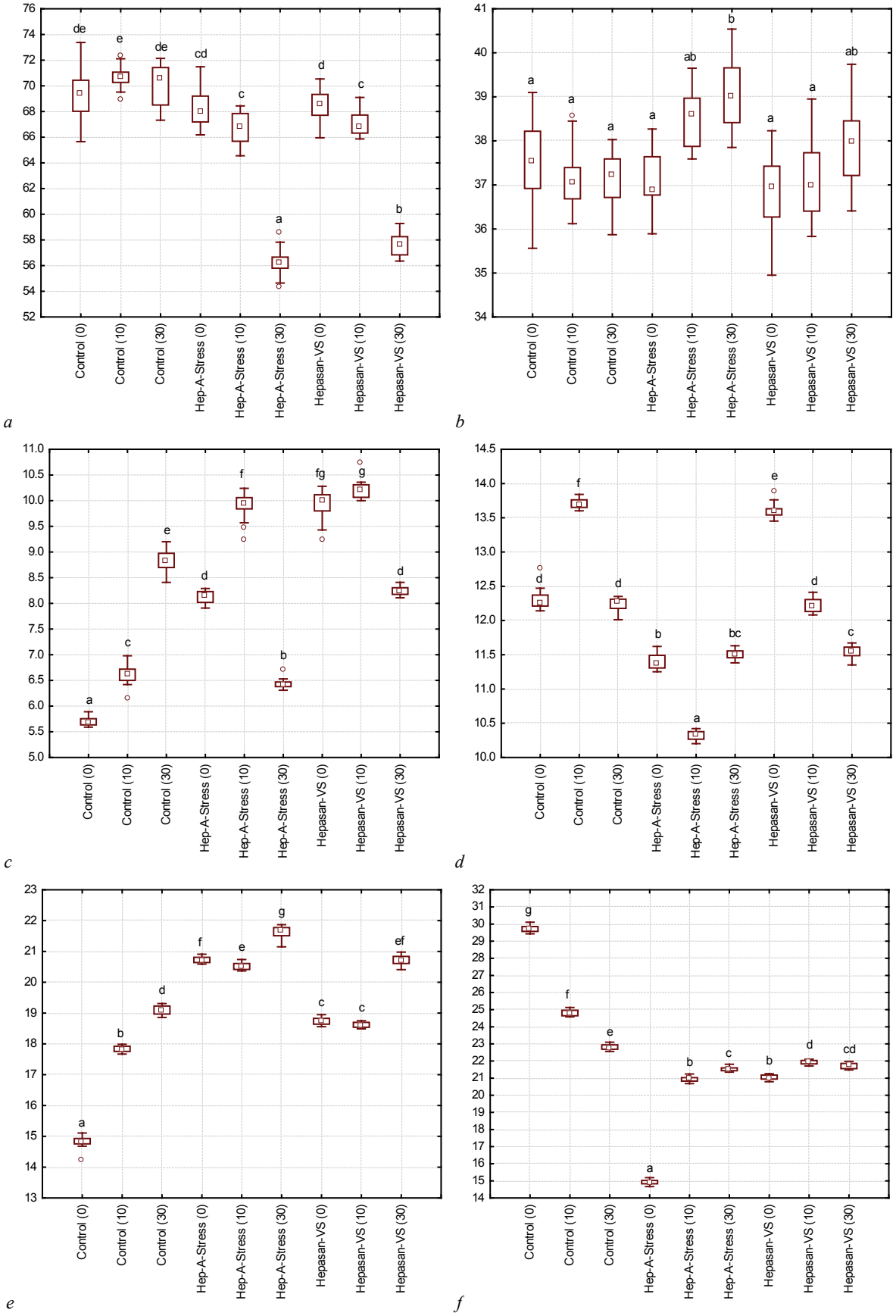

Fig. 2. Protein-synthesizing function of the liver of laying hens: *a* – total protein (g/L), *b* – albumins (%), *c* – α_1 globulins (%), *d* – α_2 globulins (%), *e* – β globulins (%), *f* – γ globulins (%); n = 20

Activity of the other enzyme, aspartate aminotransferase, had a similar tendency (Fig. 3d). In particular, activity of this enzyme in the blood serum of laying hens of the control group insignificantly increased ($P < 0.01$) after the experiment. In the first and second experimental groups, the activity of aspartate aminotransferase by the 10th day of the intake of the drug had increased by 4.1% and 2.2% compared with the beginning of the

experiment and by 2.7% and 2.1% compared with the control. After 30 days of the experiment, the activity of the enzyme decreased respectively by 10.7% and 11.9% compared with the control. Decrease in the activity of alanine aminotransferase and aspartate aminotransferase in the serum of laying hens of the experimental groups indicates the stabilization of mitochondrial and cytosol structures of hepatocytes.

The status of lipid metabolism was determined according to the concentration of total cholesterol in the blood serum of laying hens (Fig. 4a). On the 10th day of the experiment, the concentration of overall cholesterol in the blood serum of laying hens of the first and second experimental groups was 10% ($P < 0.001$) and 18.8% lower compared with the control group and 14.9% ($P < 0.001$) and 10.4% ($P < 0.05$) compared with the beginning of the consumption of the hepatoprotectors. On the 30th day of the experiment, the concentration of the overall cholesterol in the blood serum of laying hens of the first experimental group had decreased by 50% ($P < 0.001$) compared with the beginning of the experiment and by 58.3% ($P < 0.001$) compared with the control. In the second experimental group, it decreased respectively by 51.4% and 62.9% ($P < 0.001$).

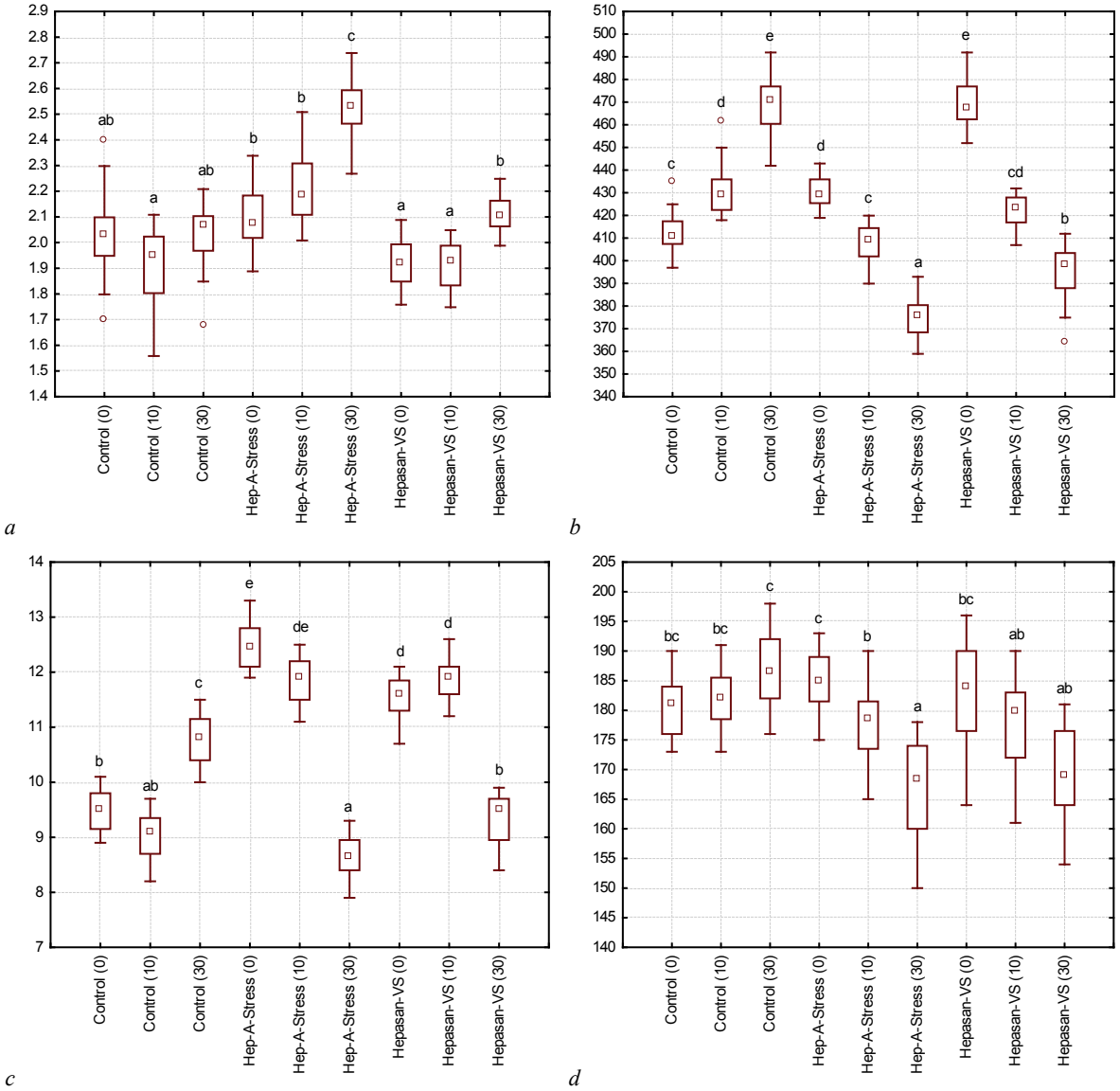

Fig. 3. Biochemical parameters of blood of hens: *a* – content of urea (mmol/L), *b* – uric acid concentration (mmol/L), *c* – activity of alanine aminotransferase (U/L), *d* – activity of aspartate aminotransferase (U/L); n = 28

We determined decrease in the concentration of triacylglycerols in the blood serum of laying hens of the experimental groups on days 10 and 30 of the intake of hepatoprotectors (Fig. 4b). Concentration of triacylglycerols in the blood serum of laying hens of the experimental groups was gradually decreasing after 10 and 30 days after the start of the intake of drugs. In particular, after 10 days of the intake of the hepatoprotectors, there was a 4.4% ($P < 0.05$) decrease in the first experimental group, and after 30 days – 24.1% decrease ($P < 0.001$) compared with the beginning of the experiment. In hens of the second experimental group, the changes were less expressed, though the concentration of triacylglycerols in the first and second experimental groups decreased by 27.1% and 11.8% after 30 days of intake of the hepatoprotectors. We observed a positive effect of the hepatoprotectors during the assay of lipoproteins in the blood serum. Specifically, we observed a 34.4% increase in the concentration of high-density lipoproteins in the blood serum of laying hens of the control group after 10 days and 50% ($P < 0.001$) increase after 30 days. In the experimental groups, the changes in hens were opposite. In the first experimental group, the concentration of high-density lipoproteins decreased by 10.8% ($P < 0.01$) on the 10th day, and by 57.7% ($P < 0.001$) and 16.2% and 84.6% ($P < 0.001$) after 30 days, compared with the control group (Fig. 4c). In the second experimental group, it decreased by 12.5% ($P < 0.001$) and 33.3% ($P < 0.01$) and by 34.4% ($P < 0.001$) and 77.8% ($P < 0.001$) respectively. After 10-day intake of the hepatoprotectors, concentration of low-density lipoproteins in the blood serum of laying hens decreased in the first and the second experimental groups by 4.4% and 2.8% compared with the beginning of the experiment and by 11.8% ($P < 0.01$) and 7% ($P < 0.05$) compared with the control (Fig. 4d). After 30 days of the experiment, the decreases accounted for 61.3% and 68.2% in the first experimental group and 40.4% and 42.3% in the second respectively.

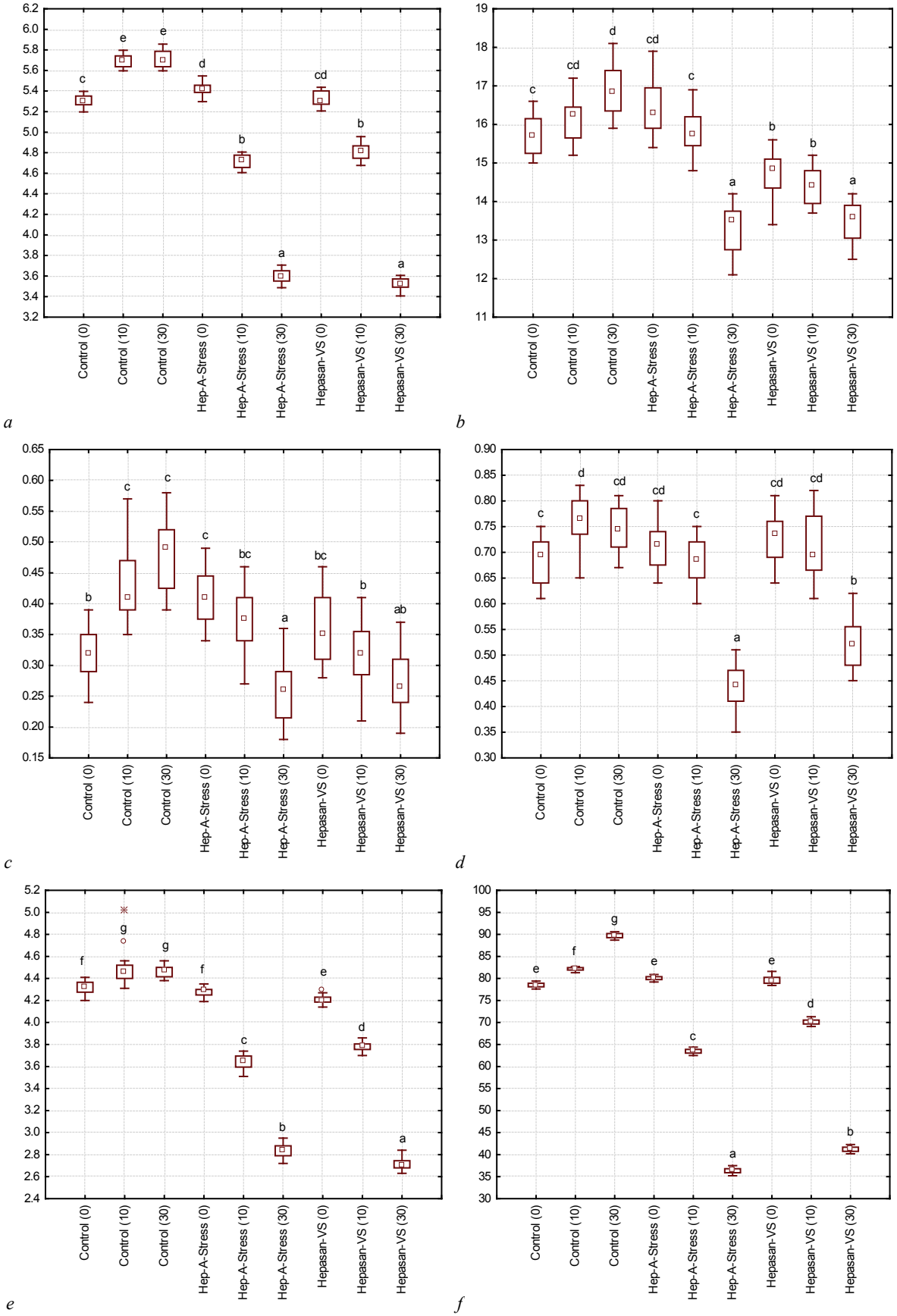

Fig. 4. Biochemical parameters of blood plasma of hens: *a* – content of overall cholesterol (mmol/L), *b* – concentraton of triacylglycerols (mmol/L), *c* – concentration of high-density lipoproteins (mmol/L), *d* – concentration of low-density lipoproteins (mmol/L), *e* – concentration of very-low-density lipoproteins (mmol/L), *f* – concentration of uric acids (mmol/L); n = 28

In the liver, synthesis of triacyglycerols, phospholipids and cholesterol takes place. These form very-low-density lipoproteins and transport them to the tissues outside the liver, which are the main transport forms of endogenous lipids. We determined that on the 10th and 30th days of the intake of the hepatoprotectors, the concentrations of very-low-density lipoproteins in laying hens of the experimental groups were 17.6% (P <

0.001) and 11.4% ($P < 0.05$) and 49.7% ($P < 0.001$) and 55.4% ($P < 0.001$) lower than at the beginning of the experiment. Compared with the control group, this parameter decreased by 23.1% ($P < 0.001$) and 55.9% ($P < 0.001$) and 18.5% ($P < 0.01$) and 64.6% ($P < 0.001$) respectively.

The concentration of uric acids in the blood serum of laying hens in the first and the second experimental groups decreased by 0.8 and 1.1 times ($P < 0.001$) on the 10th day after the start of the experiment, and by 2.2 and 1.9 times respectively after 30 days (Fig. 3f). The changes were also significant compared with the control group, particularly 0.8 and 2.5 times decreases in the concentration of uric acids in the first experimental group, and 0.9 and 2.2 times decreases in the second group. Such changes, in our opinion, indicate recovery of the hepatic functions, specifically the secretion of uric acids.

Thus, we determined no significant changes in the functional condition in the liver and homeostasis of protein after consuming Hep-A-Stres and Hepasan-VS hematoprotectors on the 10th day of the experiment. However, on the 30th day of the experiment, the biochemical parameters in the blood of laying hens, namely the concentrations of total protein, lipid metabolism and activity of enzymes, indicate the preventive efficacy of the applied drugs and their slow action in relation to the poulry organisms.

Discussion

The physiological vital activity of the organisms of animals and birds requires supporting the conditions of the internal environment, which is significantly different from the ambient conditions (Pu et al., 2020; Dong et al., 2021; Liu et al., 2021). Important preconditions of successful poultry farming is maximal fulfillment of biological needs of poultry and prevention of diseases, the etiology of which are various stress factors (Zhao et al., 2020; Liu et al., 2021).

The domestic poultry farming of Ukraine is one of the most important spheres of agricultural farming. In order to increase the production of poultry farming, it is necessary to provide the poultry with highly-active feeds, appropriate maintenance conditions, and also a high level of veterinary service (Gu et al., 2020).

Poultry, compared with productive livestock, differ by greater energy of growth and intense metabolism. This causes its high sensitivity to nutrition. That is why the fodders need to be balanced according to protein, mineral and vitamin compositions. Consumption of fodders that are nutrient-imbalanced causes impairments in metabolism of poultry and development of liver diseases (Levchenko et al., 2017; Ostapyuk et al., 2021).

Complex polyfunctional drugs may be the solution to the problem. Therefore, it would be scientifically and practically significant to improve the existing drugs and develop novel drugs for increasing the resistance of the birds' organism, and also stimulation of the reparative and regenerative proceses in liver hepatocytes (Laptjeva, 2012; Levchenko et al., 2017; Ostapyuk & Gutyj, 2019).

Some of the commonest medicinal drugs in cases of liver pathology in poutry are hepatoprotective drugs. They improve metabolism in the liver, providing the intense growth, development and high productivity of poultry (Yaremchuk & Slivinska, 2020). Studies by a number of authors suggest a positive effect of hepatoprotectory drugs that contain methyonine, vitamin E and carnitine (Avdosjeva et al., 2013, 2014).

In the analysis of protein metabolism, an important role belongs to the identification of concentrations of total protein and its fraction in the blood (Chowdhury et al., 2021). According to the data (Bashchenko et al., 2021; Brezvyn et al., 2021; Mylostyvyi et al., 2021), the concentrations of the overall protein during various pathological conditions of the liver may increase, decrease or remain in the norm. Based on the performed studies, we determined that consumption of Hep-A-Stres and Hepasan-VS drugs by poultry of the experimental groups promoted a significant increase in the content of albumins in the blood. This increase in albumins indicates positive effect of hepatoprotectors on the formation of synthesis of proteins in the liver of poultry of the experimental groups.

The study of impairments of protein metabolism in the organism of highly-productive poultry (Milroy, 1993), increase or decrease in concentration of uric acid indicates impairment of protein metabolism and, combined with changes in other laboratory parameters, indicates changes in the functional condition of the liver. Disorders in the functional condition of the birds' livers are also determined by aminotransferase activity in the blood. Because the pathological process in the organism of poultry is accompanied by increase in permeability of cellular membranes or cellular lysis and release of aminotransferases into the blood, the activity of those enzymes in blood serum increases (Kaneko et al., 1997). According to the study (Dhawale, 2007), during pathological conditions of the liver, alanine and aspartate aminotrasferases are released into the blood in large amounts, and increase in their activity is a feature of destructive processes in the liver itself. In those conditions, there is also observed hypoglycemia, which affects the mobilization of fat from the fat "depot" and its influx into the liver. Hypercholesterolemia promotes this process as well (Melnyk, 2017). According to the study (Mohamed et al., 2019), liver diseases that are related to the impairment of the processes of the formation of uric acids and urination are characterized by increased concentration of cholesterol. Hypercholesterolemia is observed during hyperlipidemia, and also in the conditions of increase of triacylglycerols in blood serum (Levchenko et al., 2017). According to the data (Nishhemenko et al., 2013), increase in alkaline phosphatase is seen during cholestasis and impairment of mineral metabolism. Increase in activity in this enzyme was also recorded during egg production and oviposition (Shcherbatyy & Slivinska, 2021).

By analyzing the survival rate during the experiment, we determined that by the 10th day since the start, it had decreased in the control, first and second experimental groups by 0.9%, 0.5% and 0.7%. By the 30th day of the experiment, the number of poultry had decreased by 3.0%, 1.7% and 1.9% respectively. The survival rates of laying hens at the end of the experiment were 97.1%, 98.3% and 98.1%. This parameter was 1.2% higher in the first experimental group, and 1% in the second, compared with the control.

Furthermore, over 30 days of the intake, every day we were determining the parameter of egg yield in all the groups of laying hens. We determined that the difference in the number of eggs in the first and second experimental groups was 4.0% and 3.6% compared with the control. Therefore, the intake of Hep-A-Stres and Hepasan-VS hepatoprotectors by laying hens in the period of intense oviposition promotes the survival, continuation of the period of using poultry and increase in their productivity.

Conclusion

Hep-A-Stres and Hepasan-VS hepatoprotectors stimulate the metabolism in poultry and have positive effects on the blood parameters. We determined preventive effect of the experimental drugs after 30 days of their intake. In the blood of poultry that received those drugs, we determined a decrease in concentrations of total protein, uric acid, with simultaneous increase in albumin fraction and urea in blood. The stabilization of cellular structures of hepatocytes was indicated by decrease in the activity of aminotransferases in the blood serum. Decrease in concentration of uric acids suggests normalization of secretion of uric acids by hepatocytes and recovery of the functional ability of the liver. The positive effect of Hep-A-Stres and Hepasan-VS is also indicated by decrease in the level of lipidogram parameters of blood serum of the experimental groups: concentration of the overall cholesterol, triacylglycerols, high-density lipoproteins, low-density lipoproteins and very-low-density lipoproteins. Intake of the hepatoprotectors by laying hens in the period of intense egg-laying promoted better survival, prolongation of the period of using poultry and increase in their productivity.

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