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Effect of the Feed Additive Butaselmevit-Plus on the Antioxidant Status of the Rat Body Due to Cadmium and Lead Intoxication

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Abstract. The relevance of the study subject is due to the need to create effective methods for preventing the poisoning of animals with heavy metals because lead and cadmium are among the environmental pollutants that negatively affect agriculture and are potentially dangerous to animal and human health. The purpose of the study was to establish the effect of the feed additive Butaselmevit-Plus on the antioxidant protection of the rat body under the chronic action of cadmium and lead. Experimental studies were performed on 2 groups of male rats, 6 animals each. In the control and experimental groups, rats were given a 16.6% aqueous solution of lead acetate at a dose of 100 mg/kg (0.6 ml/kg) of body weight and 0.029% aqueous solution of cadmium chloride at a dose of 2.0 mg/kg (6.9 ml/kg) of body weight. In the experimental group, the rats were additionally provided with food containing the feed additive Butaselmevit-Plus in the amount of 0.1 g per 100 g of body weight. Experimental lead-cadmium toxicosis in the blood serum of rats demonstrated a substantial decrease in the indicators of the antioxidant protection system (reduced glutathione – by 38.4%, superoxide dismutase – by 27.6%, catalase – by 22.7%). On the fourteenth day of the experiment, the lowest activity of the antioxidant protection system indicators in the blood of control rats was observed with the combined administration of heavy metals. Under the experimental load of lead and cadmium, the feed additive Butaselmevit-Plus demonstrated antioxidant properties, which is due to its chemical composition (milk thistle, selenium, methionine, and vitamins). The introduction of the feed additive Butaselmevit-Plus to the rats of the experimental group contributed to an increase in the activity of superoxide dismutase and catalase in the blood serum by 22.7 and 20.7%, respectively. When providing this feed additive to rats of the experimental group, an increase in the level of reduced glutathione was also identified, which reached its maximum value on the 28th day of the experiment. Thus, the results of the study confirm the effectiveness of using the supplement Butaselmevit-Plus to improve the antioxidant status of animals in conditions of chronic intoxication of the rat body with lead and cadmium. The practical value of the results obtained is to substantiate the feasibility of using the feed additive Butaselmevit-Plus in animal husbandry to prevent the negative impact of heavy metals on the animal body

Keywords: heavy metals, catalase, superoxide dismutase, reduced glutathione, milk thistle, vitamins, selenium

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Introduction

In the conditions of substantial man-made or natural pollution of the environment with heavy metals, the issue of finding and creating modern methods and means to prevent the intoxication of the animal body with them becomes relevant. Compliance with sanitary and hygienic standards and requirements for the content of heavy metals in feed, water, and the air is an important step in the prevention of animal poisoning. However, farming involves the use of machinery, pesticides, and fertilisers of organic and inorganic origin, which creates prerequisites for the accumulation of heavy metals in the body of animals. Therefore, the use of drugs and feed additives that prevent the absorption of heavy metals into the blood from the digestive canal, promote their rapid elimination from the body or limit their pathogenic effect on the body becomes important in the prevention of heavy metal poisoning in animals.

Contamination of the environment with heavy metals as a result of anthropogenic activities has negative consequences for agricultural production [1; 2]. High concentrations of heavy metals in the soil can directly harm crops, limiting photosynthesis, damaging roots, reducing growth, and ultimately causing plant death [3]. The intake of heavy metals in products of plant or animal origin worsens their safety indicators and poses a threat to human health since the consumption of such products can cause diseases. Heavy metals, even in small amounts, negatively affect the body of animals. They do not take part in physiological metabolic processes, but, accumulating in organs and tissues, can cause acute or chronic poisoning. Heavy metals can become an etiological factor in the development of many pathological processes in the animal body. As a result of their toxic effects, the liver, kidneys, bones, and cardiovascular and nervous systems can be affected, blood disorders and various types of cancer occur [4].

Lead and cadmium are substantial environmental pollutants belonging to very toxic heavy metals [5]. Entering the body, these toxicants can accumulate in organs and tissues and cause deterioration of the health of animals and their productivity [6-8]. The reaction of animals to various toxicants and their concentrations is ambiguous and depends on the type and form of heavy metal, the route of its entry into the body, age, gender, and physiological state of the animal, feeding conditions, etc. [9-11]. Heavy metals will enter the body of productive animals mainly with contaminated feed and water, and, to a certain extent, with inhaled air containing metal particles. It is proved that due to environmental pollution with cadmium and lead, the manifestation of toxic effects on the animal's body is determined not only by the toxicity of each metal separately but also by their combined effect [12-14].

To date, it has been established that the occurrence and development of cadmium and lead poisoning causes an imbalance between the processes of free radical lipid peroxide oxidation and the antioxidant defence system of the body, which leads to the development of oxidative stress [15; 16]. As a result of the latter, first of all, changes occur in the membranes of liver cells – the lipid bilayer is delaminated, which substantially disrupts the functioning of membrane enzymes [17; 18]. Subsequently, changes occur in the plasma, mitochondrial, peroxisomal, lysosomal, endoplasmic, and core structural units of cells. There is swelling and lysis of mitochondria, microsomes, organelle dysfunction, polymerisation of proteins and rupture of their polypeptide chain, DNA destructures, cellular enzymes are inactivating, the level of intracellular calcium increases, which leads to cell necrosis [19; 20].

An antioxidant protection system, which consists of enzymatic and non-enzymatic mechanisms functions to maintain a balance between the formation and neutralisation of reactive oxygen species in the body of animals. As you know, reactive oxygen species in the animal body are formed not only as a result of the normal course of cellular metabolism but also as a result of harmful environmental factors (ionising radiation, toxins, heat stress). Therewith, the antioxidant protection system largely determines the adaptive resistance of animals to the influence of negative environmental factors [21; 22].

The functional usefulness and power of the antioxidant protection system largely determines the course of toxicosis and the possibility of full recovery of the body. Therefore, the study of this important biological aspect requires further and in-depth research. Considering the above, *the purpose of the study* consisted in the investigation of the effect of Butaselmevit-Plus on the indicators of the antioxidant protection system during chronic cadmium and lead loading of the rat body.

Literature Review

Various methods and means are used to prevent heavy metal intoxication and treat animals for their occurrence. Enterosorption is one of the safest and most effective methods of removing toxic substances, which is based on the oral use of drugs that can absorb various toxic substances in the lumen of the digestive canal without entering into chemical reactions with them [23]. For the treatment of animals for heavy metal poisoning, enterosorbents of various origins are used: carbon sorbents of natural and synthetic origin; natural polymers: polysaccharides and lignin; aluminosilicates and clays: zeolites, saponites; combined materials: mixtures, composites [24]. The most effective enterosorbents include Enterosgel [25]. Enterosorbents mainly have a non-selective effect and, if used for a long time, will help to remove useful micronutrients from the body. Therefore, their use is limited and appropriate for acute heavy metal poisoning.

Organic and inorganic chelators such as ethylenediaminetetraacetic acid (EDTA), 2,3-dimercaptoburshtic acid, unitiol, and penicillamine are also used to neutralise and remove heavy metals from the body [26]. Although the effectiveness of these drugs is high, quite often their use is accompanied by the appearance of undesirable effects – the elimination of useful macro- and microelements from the body with corresponding consequences, kidney damage, etc.

The considerable attention of researchers is also focused on magnetic biosorbents that are synthesised from various metal nanoparticles. In particular, positive results are shown by magnetic nanoparticles based on iron oxide, which have a high adsorption capacity due to their large surface area and pronounced reaction properties [27]. Therewith, there are still no opportunities for widespread implementation of nanotechnology achievements in practice, and certain aspects of the potential toxic effects of nanoparticles on living organisms are still being actively investigated.

Natural and synthetic antioxidants (quercetin, catechin, taurine, captopril, gallic acid, melatonin, N-acetylcysteine, alpha-lipoic acid, etc.) deserve special attention since heavy metals have pro-oxidant properties. Antioxidants affect biological systems not only by directly neutralising free radicals but also by chelating toxic metals. They can also enhance the mechanism of antioxidant protection of cells through the regeneration of endogenous antioxidants [28].

Materials and Methods

Experimental studies were performed based on the vivarium of the State Research Control Institute of Veterinary Drugs and Feed Additives in Lviv. 12 mongrel white male rats weighing 200-220 g were used in the experiments. Experimental rats were divided into a control and experimental group of 6 animals each. 16.6% aqueous solution of lead acetate at a dose of 100 mg/kg (0.60 ml/kg) of body weight (corresponding to 1/40 DL50) and 0.029% aqueous solution of cadmium chloride at a dose of 2.0 mg/kg (6.9 ml/kg) of body weight (corresponding to 1/40 DL50) were administered intragastrically for 28 days to simulate experimental chronic lead and cadmium intoxication. Additionally, the rats of the experimental group were fed food containing the feed additive Butaselmevit-Plus at a dose of 1000 mg/kg of body weight throughout the experiment. The composition of the feed additive includes such active substances as milk thistle fruits, vitamins (A, D3, E), sodium selenite, methionine [29]. In total, these components are a powerful antioxidant complex that corrects the intensity of lipid peroxide oxidation and free radical formation processes, thereby preventing the development of oxidative stress.

Experiments on rats were performed in compliance with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes [30]. During the experiment, the rats had a balanced diet, and drinking water was obtained ad libitum from glass drinkers. On days 1, 7, 14, 21, and 28 of the experiment, blood samples were taken from rats for biochemical studies from the jugular vein. The following indicators were determined in the blood serum: superoxide dismutase activity (EC 1.15.1.1) – according to the method of Dubynina et al. [31]; catalase activity (EC 1.11.1.6) – according to the Koroliuk method [31]; reduced glutathione content – according to the Butler method [31].

The resulting digital data was processed using the Statistica 6.0 software package. The reliability of differences between indicators was determined using the Student's t-test.

Results and Discussion

Endogenous antioxidants include reduced glutathione, which, as a reduced thiol with the highest concentration, has a direct effect on the redox status of cells. It neutralises free radicals, is a cofactor and substrate of the enzyme antioxidant system.

Under conditions of cadmium and lead intoxication, on the 7th day of the experiment, the content of reduced glutathione in the blood serum of rats of the control group decreased by 29.1%, and on the 14th day of the experiment – by 38.4% compared to the initial values (Table 1). On days 21 and 28 of the experiment, the content of reduced glutathione in the blood serum of rats in the control group remained lower, by 24.9% and 21.3%, respectively.

Table 1. Content of reduced glutathione in the blood serum of intoxicated rats when using Butaselmevit-Plus, mmol/l, M ± m, n = 6

Study period	Animal group	
	Control	Experimental
Initial data	2.229 ± 0.044	2.225 ± 0.042
Day 7	1.581 ± 0.041	1.864 ± 0.030*
Day 14	1.372 ± 0.039	1.825 ± 0.036*
Day 21	1.675 ± 0.050	2.067 ± 0.040*
Day 28	1.754 ± 0.043	2.207 ± 0.034*

Note: ** $P < 0.05$, compared with animals in the control group*

For the use of the feed additive Butaselmevit-Plus in rats intoxicated with lead and cadmium, it was identified that in rat blood serum in the experimental group, the content of reduced glutathione substantially increased by 17.9% on the 7th day of the experiment compared with its value in animals of the control group. The level of restored glutathione increased by 33.0% on day 14 of the experiment, while on day 21 – by 23.4% compared with the control group. The highest content of reduced glutathione in the blood serum of rats of this group was noted on the 28th day of the experiment, which is 25.8% higher than the same indicator in animals of the control group.

Superoxide dismutase is a powerful antioxidant due to its high enzyme ability to neutralise free radicals. Under the conditions of lead-cadmium intoxication in rats of the control group, a decrease in the activity of this enzyme in the blood serum on the 7th day of the experiment was established by 13.8% compared with the initial data (Table 2).

Table 2. Superoxide dismutase activity in the blood serum of intoxicated rats when using Butaselmevit-Plus, conditional units, M ± m, n = 6

Study period	Animal group	
	Control	Experimental
Initial data	1.522 ± 0.005	1.540 ± 0.005
Day 7	1.313 ± 0.004	1.471 ± 0.003*
Day 14	1.101 ± 0.004	1.354 ± 0.004*
Day 21	1.153 ± 0.002	1.421 ± 0.005*
Day 28	1.250 ± 0.003	1.492 ± 0.004*

Note: ** P < 0.05, compared with animals in the control group*

According to the results obtained, on the 14th day of studies, its activity in the blood serum of these animals was the lowest and corresponded to values 27.6% less than the initial level. Therewith, on days 21 and 28 of the experiment, there was a tendency to increase the activity of superoxide dismutase in the blood serum of rats intoxicated with lead and cadmium, although the indicators differed from the initial ones.

Throughout the experiment, the activity of superoxide dismutase in the blood serum of rats increased due to the introduction of the feed additive Butaselmevit-Plus to the diet. In particular, enzyme activity increased by 12.2% on the 7th day, and by 22.7% on the 14th day of the experiment compared with the values of the control group. The highest activity of superoxide dismutase was established in the blood serum of rats of the experimental group, when it increased by 19.2% compared with the control group on the 28th day of the experiment.

According to Table 3, in control rats, serum catalase activity decreased starting from 7th day after administration of lead and cadmium salt solutions. The lowest catalase activity in the blood serum of animals of this group was established on days 14 and 21 of the experiment, which corresponded to values of 22.7% and 20.0% lower than the initial level, respectively.

Table 3. Catalase activity in the blood serum of intoxicated rats when using Butaselmevit-Plus, μmol/min, M ± M, n = 6

Study period	Animal group	
	Control	Experimental
Initial data	6.751 ± 0.038	6.780 ± 0.040
Day 7	5.824 ± 0.052	6.192 ± 0.062*
Day 14	5.223 ± 0.084	6.303 ± 0.058*
Day 21	5.402 ± 0.054	6.423 ± 0.066*
Day 28	5.981 ± 0.062	6.542 ± 0.070*

Note: ** P < 0.05, compared with animals in the control group*

The results of the study indicate that feeding rats the feed additive Butaselmevit-Plus caused a likely increase in the activity of catalase in the blood serum. In particular, the activity of the enzyme was higher by 6.4% and 20.7% in the blood serum of animals of the experimental group, respectively, on days 7 and 14 compared with the corresponding control parameters. On the 21st day of the experiment, an increase in catalase activity by 18.9% was established in the blood serum of rats of the experimental group. The highest activity of the enzyme was established in rats of the experimental group on the 28th day of the experiment. In addition, it was 9.4% higher than the value of this indicator in the animals of the control group. Notably, that catalase is an enzyme of the antioxidant system that effectively cleaves excess hydrogen peroxide to water and molecular oxygen (catalase activity), and is also able to oxidise a number of toxic compounds in the presence of peroxides (peroxidase activity) [32].

Thus, analysing the results of the study in the conditions of chronic experimental poisoning of the rat body with lead and cadmium, it was established that the feed additive Butaselmevit-Plus has a pronounced antioxidant effect. There are two potentially possible mechanisms of action of the feed additive Butaselmevit-Plus. First, this feed additive, due to its active ingredients, suppresses the peroxide oxidation of lipids, and secondly, it activates the processes of antioxidant protection of the body.

We believe that the effectiveness of the feed additive Butaselmevit-Plus is associated with the effect of its active substances on the main pathogenetic links of the process of chronic intoxication of the rat body with lead and cadmium. Since it is the liver that neutralises xenobiotics in the body, hepatocytes are primarily damaged by the negative effects of heavy metals [11]. Previous studies in rats have shown that the elimination of endogenous intoxication syndrome helps to restore the functional state of liver cell membranes and increase the antioxidant status of the rat body [33].

The use of selenium in the feed additive Butaselmevit-Plus prevents the absorption of heavy metals in the digestive canal. Other researchers have also noted that adding selenium to animal diets provides substantial protection against cadmium toxicity by inhibiting its bioaccumulation [34]. In addition, selenium is a part of selenoproteins, which have a wide range of functions, from antioxidant and anti-inflammatory to the production of thyroid hormones. The main function of selenium in the antioxidant protection system is to take part in the construction and functioning of glutathione peroxidase, an enzyme that neutralises the products of lipid peroxide oxidation [35; 36].

The medicinal plant milk thistle (*Silybum marianum L.*) has a wide application in veterinary medicine. It contains valuable medicinal substances, namely silymarin, which includes silibinin, silidianin, silicristine, and other flavolignans. Thus, the feed additive Butaselmevit-Plus exhibits antioxidant properties due to the interaction of these flavolignans with free radicals in the liver and their conversion into less toxic compounds, which contributes to further interruption of the lipid peroxide oxidation chain and inhibition of these processes, and prevention of destruction of cellular structures [37].

In a number of studies [19; 29; 33], it was identified that silymarin acts as an antioxidant, hepatoprotective, and choleretic agent. Due to this action, the biological membranes of hepatocytes are stabilised. This leads to the restoration of the activity of hepatospecific enzymes in the blood, which ensures high therapeutic effectiveness when feeding animals the feed additive Butaselmevit-Plus.

Methionine, which is one of the components of the drug, combines enzyme and non-enzyme links of anti-radical protection of cell membranes. This amino acid in the body of rats under heavy metal intoxication contributes to the conversion of neutral lipids into phospholipids. This stabilises subcellular membranes, improves the body's antioxidant defences, and increases the resistance of liver cells to the toxic effects of lead and cadmium.

The feed supplement also contains vitamins A, E, and D_3, which during chronic lead-cadmium intoxication in combination with its other components contributed to a decrease in the intensity of free radical formation in the body of rats and had a protective effect, since, as is known [37; 38], these vitamins show the ability to prevent damage to the ultrastructure of cells.

The conducted studies and established patterns confirm the expediency of using the feed additive Butaselmevit-Plus for the prevention of lead-cadmium toxicosis in animals.

Conclusions

Studies have shown that intragastric administration of 16.6% aqueous solution of lead acetate at a dose of 100 mg/kg of body weight and 0.029% aqueous solution of cadmium chloride at a dose of 2.0 mg/kg of body weight to rats for 28 days causes changes in individual links of the antioxidant protection system. During the entire study period, there was a decrease in the content of reduced glutathione in rat blood plasma by 21.3-38.4%. Therewith, the lowest values of this indicator are recorded on the 14^{th} day of the experiment. The activity of catalase and superoxide dismutase in the blood serum of experimental rats also decreases. Therewith, chronic lead and cadmium intoxication in rats is accompanied by a decrease in the activity of the body's antioxidant defence system.

The use of the feed additive Butaselmevit-Plus at a dose of 1000 mg/kg of body weight during chronic lead and cadmium intoxication contributes to an increase in the content of reduced glutathione in rat blood serum by 17.9-33.0%, the activity of superoxide dismutase by 12.2-22.7%, and catalase by 6.4-20.7% compared to similar indicators in animals of the control group. Thus, Butaselmevit-Plus provides stabilisation of the antioxidant defence of the rat body in conditions of chronic heavy metal intoxication. This is due to the selenium, vitamins A, E, and D_3, and milk thistle, present in the supplement.

The feed supplement Butaselmevit-Plus, which contains antioxidants and natural biologically active substances, such as silymarin and a complex of fat-soluble vitamins, can be used to prevent poisoning of animals with heavy metals. It stimulates the potential ability of superoxide dismutase, catalase, and reduced glutathione to neutralise excess reactive oxygen species and lipid peroxidation products that are actively generated due to the action of heavy metals on the animal's body.

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Вплив кормової добавки «Бутаселмевіт-плюс» на антиоксидантний статус організму щурів за інтоксикації кадмієм і свинцем

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Анотація. Актуальність теми досліджень зумовлена необхідністю створення ефективних методів профілактики отруєння тварин важкими металами, адже свинець і кадмій належать до забруднювачів довкілля, що негативно впливають на сільське господарство і є потенційно небезпечними для здоров'я тварин і людей. Мета роботи полягала у встановленні впливу кормової добавки «Бутаселмевіт-плюс» на антиоксидантний захист організму щурів за хронічної дії кадмію та свинцю. Експериментальні дослідження виконували на 2 групах самців щурів, по 6 тварин у кожній. У контрольній і дослідній групах щурам задавали 16,6 % водний розчин свинцю ацетату в дозі 100 мг/кг (0,6 мл/кг) маси тіла і 0,029 % водний розчин кадмію хлориду в дозі 2,0 мг/кг (6,9 мл/кг) маси тіла. У дослідній групі щурам додатково згодовували корм, який містив кормову добавку «Бутаселмевіт-плюс» у кількості 0,1 г на 100 г маси тіла. За експериментального свинцево-кадмієвого токсикозу в сироватці крові щурів спостерігали вірогідне зниження показників системи антиоксидантного захисту (відновленого глутатіону – на 38,4 %, супероксиддисмутази – на 27,6 %, каталази – на 22,7 %). На чотирнадцяту добу досліду за сукупного введення важких металів спостерігали найнижчу активність показників системи антиоксидантного захисту в крові щурів контрольної групи. За експериментального навантаження свинцем та кадмієм, кормова добавка «Бутаселмевіт-плюс» проявляла антиоксидантні властивості, що зумовлено її хімічним складом (розторопша плямиста, селен, метіонін і вітаміни). Додавання до складу раціону кормової добавки «Бутаселмевіт-плюс» щурам дослідної групи сприяло зростанню активності супероксиддисмутази та каталази в сироватці крові, відповідно на 22,7 і 20,7 %. При згодовуванні щурам дослідної групи цієї кормової добавки встановлено також і підвищення рівня відновленого глутатіону, який досягав максимального значення на 28 добу досліду. Отже, результати дослідження підтверджують ефективність застосування добавки «Бутаселмевіт-плюс» для покращення антиоксидантного статусу тварин в умовах хронічної інтоксикації організму щурів свинцем та кадмієм. Практична цінність одержаних результатів полягає у обґрунтуванні доцільності використання у тваринництві кормової добавки «Бутаселмевіт-плюс» для профілактики негативного впливу важких металів на організм тварин

Ключові слова: важкі метали, каталаза, супероксиддисмутаза, відновлений глутатіон, розторопша плямиста, вітаміни, селен