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Determination of acute toxicity parameters of the extract of the basidial tree fungus *Inonotus obliquus* as a promising agent for veterinary medicine

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Abstract. The basidial tree fungus *Inonotus obliquus* (chaga) of the order *Hymenochaetales* is widely used in world medicine, as it is characterised by anti-inflammatory and antioxidant effects, and is effective in oncological, infectious and invasive diseases, as well as in diabetes, obesity, fatigue, liver and kidney pathologies, etc. However, the toxicological properties of chaga, which grows in Ukraine, require scientific justification. The aim of this study was to establish the parameters of acute toxicity of the aqueous extract of the basidial tree fungus *Inonotus obliquus*, which was obtained in natural conditions in Ukraine. The study was conducted on white Wistar rats according to generally accepted methods for conducting preclinical studies of new drugs. It was established that the median lethal dose of the test substance for rats after intragastric administration is 8,959 mg/kg according to the method of G. Kerber, 9,175.0 mg/kg according to the method of G. Pershin, and 9,175.0 mg/kg according to the method of B. Shtabsky – 8,890 (6,510.1 ÷ 11,269.9) mg/kg. According to the results obtained, it can be stated that the extract of the basidial wood fungus *Inonotus obliquus*, according to the classification of chemical substances by degree of danger (interstate standard 12.1.007-76), corresponds to class IV, and according to the classification of substances by toxicity – class V and the degree of toxicity "practically non-toxic substances". The established pathoanatomical changes, such as acute catarrhal gastritis, catarrhal-hemorrhagic or hemorrhagic enteritis, acute venous hyperemia of internal organs, dilatation of the wall of the right ventricle of the heart, edema of the subcutaneous tissue and skeletal muscles in the area of the right part of the scapula, manifested themselves identically in the body of the dead rats of the experimental groups and correlated with the dose of the studied extract. Determination of acute toxicity parameters is a prerequisite for studying the pharmaco-toxicological properties of medicinal substances, therefore the obtained results are promising for further preclinical and clinical studies with the aim of scientifically substantiating the use of medicinal raw materials from *Inonotus obliquus* obtained in Ukraine in veterinary medicine

Keywords: chaga; preclinical studies; laboratory animals; pathological changes; pharmacological effect

Introduction

The growing interest in the use of natural biologically active substances in veterinary medicine, in particular those obtained from medicinal mushrooms, has made this research relevant. The extract of the basidiomycete tree fungus Inonotus obliquus, which also grows in Ukraine, is considered a promising agent due to its wide range of pharmacological activity and potential for use in the prevention and treatment of animal diseases. However, the safety and acceptable doses of this extract for animals remain insufficiently studied, which necessitates the determination of its acute toxicity as a mandatory stage of preclinical studies.

The sterile (infertile) form of the basidiomycete tree fungus *Inonotus obliquus* of the order Hymenochaetales is called chaga or birch black fungus. Y. Lu *et al.* (2021) noted that the most favourable conditions for its growth are regions characterised by low temperatures. In Ukraine, chaga also occurs in the form of round (up to 30-40 cm in diameter) or elongated, dark-coloured growths formed by hardened hyphal networks of the fungus. J. Miina *et al.* (2021) indicated that the main raw material for the production of commercial goods from *I. obliquus* is its sterile conks, collected in natural conditions, mainly from birch trees.

Chaga was also obtained under experimental conditions. For example, according to data from P.T.Y. Ern *et al.* (2023), it was grown using artificial cultivation on potato dextrose agar or by inoculating birch trees.

It is known that chaga is characterised by a wide range of pharmacological effects. It has anti-inflammatory, antioxidant, antibacterial, antihelminthic and antiviral properties, and has a therapeutic effect in the complex treatment of people suffering from diabetes, obesity, cancer, liver and kidney pathologies, and fatigue. However, the above properties of chaga mushroom are not always scientifically proven and are based on observations of traditional folk medicine. It should be noted that the mechanism of pharmacological action has not been sufficiently studied. P.T.Y. Ern *et al.* (2023) pointed out the need to study the influence of various factors on the manifestation of the pharmacological effects of *I. obliquus*, as well as antagonism and synergism in the interaction between the constituent substances of chaga and other compounds or medicinal products.

S. Ghosh (2020) demonstrated that triterpenoids found in chaga are characterised by a wide range of biological activity. A study by R.W. Kou *et al.* (2021) established the anti-inflammatory effect of lanostane triterpenes and triterpenoids by inhibiting the activation of nitric oxide. Particular attention was paid to the study of biologically active substances of the fungus that have oncoprotective properties, such as betulinic acid. K.D. Kim *et al.* (2020) found that in PC3 prostate carcinoma and MDA-MB-231 breast carcinoma cell lines, when comparing the antitumour activity of ethanol, petroleum ether, ethyl acetate, butanol and water fractions extracted from *I. obliquus*, the petroleum ether extract had the highest cytotoxicity, which is explained by its high triterpenoid content. S.D. Chen *et al*. (2021) demonstrated a link between the antidiabetic properties of triterpenoids isolated from *I. obliquus* and their inhibitory activity against the brush border enzyme α-glucosidase. It was found that the use of an aqueous extract from chaga reduces the risk of liver damage under the influence of microcystin, as indicated by the absence of signs of oxidative stress, while glutathione and catalase levels remained unchanged. P.M. Ishfaq *et al.* (2022), investigating molecular docking, discovered a molecular mechanism involving the interaction of NF-κB-NIK with ergosterol peroxide. According to L.J. Dai *et al.* (2022), enzymatic analysis and inhibition kinetics analysis showed that polysaccharides isolated from *I. obliquus* exhibit significant inhibitory activity against the brush border enzyme α-glucosidase.

Despite the need for more extensive research into the pharmacokinetics and pharmacodynamics of the already known therapeutic properties of the basidiomycete tree fungus *I. obliquus,* it is important to consider the origin of this medicinal raw material. In Ukraine, the toxicological and pharmacological properties of *I. obliquus* have not been determined, and the use of its raw materials is not scientifically justified. In this regard, the aim of the scientific study was to determine the acute toxicity of the basidiomycete tree fungus *I. obliquus* collected in Ukraine as a prerequisite for further preclinical studies of samples of this medicinal raw material. The study is relevant for veterinary medicine, since establishing the toxicological profile of chaga opens up prospects for its use as an effective medicinal product for various diseases of infectious and non-infectious aetiology in animals and for their prevention. Therefore, along with studying the acute toxicity of chaga, an important task was to determine, based on an analysis of literary sources, the possible pharmacological effects it exhibits, with a view to developing new veterinary drugs.

Theoretical Overview

Analysis of scientific literature indicates considerable interest in the properties of the basidiomycete fungus *I. obliquus*, which determine its pharmacological action (Fig. 1). Accordingly, these properties correlate with the substances contained in it. Therefore, studies of the chemical composition of *I. obliquus* and the biological role of secondary metabolites (polysaccharides, polyphenols, etc.) in the body have become relevant.

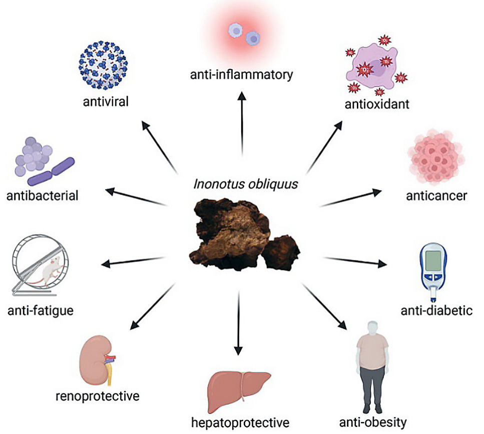

Figure 1. Pharmacological effects of exposure of *I. obliquus*

Source: *based on materials from P.T.Y. Ern et al. (2023)*

Scientists have actively researched complex high-molecular compounds of polysaccharides from chaga. For example, S.D. Chen *et al.* (2021) studied the anti-inflammatory effect of polysaccharides from *I. obliquus*. The authors found a significant decrease in the expression of interleukin IL-17 and IFN-γ mRNA and a stimulating effect on the expression of IL-4 and IL-10. K. Yan *et al.* (2021) found a decrease in the expression of tumour necrosis factor-α (TNF-α), IFN-γ, IL-1β, IL-4 and IL-6 in macrophages infected with *Toxoplasma gondii*. Immunocytochemical analysis revealed that the inhibition of the inflammatory response is mediated by the prevention of NF-κB p65 translocation from the cytoplasmic space to the nucleus. Similar results were described by R. Sang *et al.* (2022), who found overexpression of inflammatory mediators through inhibition of excessive phosphorylation of the pro-inflammatory transcription factor NF-κB p65 and inhibitor IκBα in cells infected with *Toxoplasma gondii*.

Many scientists have studied the anti-cancer properties of chaga. Studies by B. Su *et al.* (2020) have shown a significant reduction in proliferation, migration and invasion, and increased apoptosis of MG-63 and U2OS osteosarcoma cells. The anti-diabetic effect of chaga is also explained by the presence of components such as polysaccharides. T. Xu *et al.* (2021) found that the use of preparations based on this mushroom increases insulin resistance, restores glycogen levels in the liver, and has an antihyperglycaemic effect. J. Yu *et al.* (2020) proved in experiments on mice that chaga polysaccharides reduce the degree of obesity in animals kept on a diet high in fat. The results of studies by Y.J. Chou *et al.* (2016) on the effect of *I. obliquus* polysaccharides on the body demonstrated their renoprotective effect and ability to reduce fatigue in animals.

Numerous studies have been devoted to investigating the components of *I. obliquus*, such as triterpenoids. Thus, L.S. Luo *et al.* (2021) found that in hyperuricaemia in mice, triterpenoids can bind more strongly to free enzymes than to enzyme-substrate complexes, in which this inhibitory interaction reduces inflammation. According to the work of K.D. Kim *et al.* (2019), betulinic acid, isolated from chaga, as a pentacyclic triterpenoid, has biological activity against obesity in a model of mice with HFD-induced obesity. Studies by A. Peng *et al.* (2022) have found that inotodiol, lanosterol and trametenolic acid, extracted from *I. obliquus*, have a protective effect against non-alcoholic fatty liver disease, in particular, effects against lipid deposition, reduction of liver weight loss, reduction of triglyceride content in the liver, and restoration of unregulated alanine transaminase and aspartate aminotransferase levels were observed. J. Jin *et al.* (2022) demonstrated that the compound inonotuxoxide B, isolated from *I. obliquus,* has anti-fibrotic activity, as it inhibits the expression of α-smooth muscle actin and type I collagen. At the same time, it reduces the induced expression of α-SMA mRNA by platelet-derived growth factor-BB and activates phosphatidylinositol 3-kinase/protein kinase B and kinase signalling pathways regulated by extracellular signals, thereby inhibiting the viability and activation of PDGF-BB-stimulated hepatic stellate cells to protect against fibrosis. Q. Duan *et al.* (2022) observed the renoprotective effects of tramethenolic acid from *I. obliquus* in studies on white mice. In particular, blood urea nitrogen, creatinine, and urinary albumin levels increased, glomerular mesangial matrix expansion and collagen deposition decreased, contributing to the restoration of renal function. W.T. Basal *et al.* (2021) found that terpenoid compounds isolated from *I. obliquus* have antiviral properties.

Numerous studies have established that the antioxidant properties of the mushroom are due to the presence of flavonoid phenols in chaga (Abu-Reidah *et al.,* 2021). As shown in a review by K.A. Szychowski *et al.* (2021), phenolic compounds are capable of actively absorbing radicals and are characterised by their affinity for binding with the enzyme superoxide dismutase. R. Hao *et al.* (2023) investigated the effect of styrylpyranone polyphenols, namely feligridin E, on enhancing the activity of antioxidant enzymes. Y. Wang *et al.* (2021) demonstrated the iron-reducing activity of polyphenols isolated from *I. obliquus.* B.S. Hwang *et al.* (2016) described various methods for synthesising phenolic compounds from *I. obliquus*, while simultaneously enhancing their antioxidant activity.

Thus, the basidiomycete tree fungus *I. obliquus*, due to the presence of biologically active substances in its composition, can exhibit various types of pharmacological effects, which is a prerequisite for its use for therapeutic or prophylactic purposes in veterinary medicine. Such a medicinal product may have anti-inflammatory, antioxidant, antibacterial and antiviral properties, be used to treat cancer, diabetes, obesity, liver and kidney diseases, as well as to increase performance and combat fatigue. However, the toxicological and pharmacological characteristics are not fully scientifically substantiated, and potential antagonistic or synergistic interactions between *I. obliquus* and other compounds or medicinal products have not been established. Therefore, it is important to study the pharmacokinetics and pharmacodynamics of chaga samples obtained in Ukraine, as there is no such data available in the scientific literature.

The aim of this study was to analyse the main types of pharmacological action reported in the literature and to assess the results of acute toxicity tests of Inonotus obliquus extracts obtained from samples collected in Ukraine. The study will make it possible to investigate the toxicological and pharmacological characteristics of Ukrainian chaga samples, with a view to subsequently obtaining medicinal products with a broad spectrum of pharmacological action and creating new preparations for veterinary medicine.

Materials and Methods

The research was conducted in January 2025 at the scientific laboratory "Preclinical Studies of Medicines" of the Department of Vertebrate Physiology and Pharmacology of the National University of Life and Environmental Sciences of Ukraine (Kyiv, Ukraine) in accordance with the tasks of the initiative topic "Research of the pharmacotherapeutic properties of new veterinary chemotherapeutic, anti-inflammatory, antidote and metabolism-regulating agents" (state registration No. 0118U000544).

The object of the study was an aqueous extract of the basidiomycete tree fungus *I. obliquus* of the order *Hymenochaetales*. The raw material of the basidiomycete tree fungus *I. obliquus* of the order *Hymenochaetales* was collected in the Northern Polissya region (Sarny district, Rivne region). The aqueous extract was prepared according to the generally accepted method for preparing extracts from plant raw materials, which included the stages of grinding, dissolving in distilled water, and infusing for 10 days. The acute toxicity parameters of the aqueous extract of the basidiomycete wood fungus *I. obliquus* of the order Hymenochaetales were determined according to the methodological guidelines (Kotsyumbas *et al.,* 2006).

Acute toxicity was determined in white laboratory rats aged 3.5-4.0 months and weighing 180 g to 200 g. The animals were kept in plastic cages in accordance with the Regulations on the Maintenance and Use of Animals in Scientific Research and the Educational Process (2018) at a temperature of 18-20°C and relative humidity of 50%-55% under natural day-night light conditions. They were fed a complete feed mixture and had unlimited access to water and food. Before the experiment, the animals were kept in quarantine for 14 days, and feeding and watering were stopped three hours before the experiment. The test substance was administered intragastrically using a probe in the form of an aqueous extract at a rate of 5.0 mL per rat. The dose was calculated in mg of active substance per 1 kg of body weight.

To obtain preliminary information about the range of doses close to the median lethal dose, a preliminary study was first conducted, involving the administration of the test substance to three rats at doses differing by an order of magnitude. At the same time, distilled water was administered to animals in the control group (n=3). This was followed by a detailed study in which 100% mortality was observed when the test substance was administered at the maximum dose, while no deaths were observed when the minimum dose was used.

The study was conducted on 36 white rats of the *Wistar* breed. They were divided into 6 groups (6 animals in each) according to the principle of analogues. The aqueous extract was administered to the animals in the experimental groups at doses of 2,500; 5,000; 7,500; 10,000; 12,500 and 15,000 mg/kg of body weight; the animals in the control group were administered distilled water in a volume of no more than 5.0 mL. The laboratory animals were observed for 14 days, noting changes in their clinical condition over time. The animals were under constant supervision during the first day after administration of the test extract, noting behavioural characteristics, food and water intake, and recording symptoms of intoxication and animal deaths.

The median lethal dose (LD_{50}) was calculated using the methods of G. Kerber and B. Shtafsky. The method of K. Miller and M. Teinter was used to calculate confidence limits, and based on the results obtained, the studied substance was classified according to its degree of danger and toxicity (Kotsyumbas *et al.,* 2006). According to G. Kerber's method, the average lethal dose was calculated using the formula:

$$LD_{50} = LD_{100} - \frac{\Sigma zd}{m}, \quad (1)$$

where LD_{100} is the dose of the substance under study that causes the death of all animals in the group; d is the interval between each two adjacent doses; z is the arithmetic mean of the number of animals that died under the influence of two adjacent doses; m is the number of animals in the group.

The mean lethal dose was also calculated using Pershin's method, using the following formula:

$$LD_{50} = \Sigma\,[(a + b)\,(m + n)]\,/\,200, \quad (2)$$

where *a, b* are the values of adjacent concentrations under study, mg/mL; *m, n* are the frequencies of fatalities at corresponding concentrations, %.

The dependence of the mortality rate *(Y)* on the dose *(X)* was described by a straight line equation with a slope coefficient *(a)* according to B. Shtafsky using the formula:

$$Y = aX + b, \quad (3)$$

where *b* is a free member.

The corresponding values of *a* and *b* were determined using the following formulas:

$$\alpha = (Y2 - Y1) : (X2 - X1); \quad (4)$$

$$b = (\Sigma Y - \alpha \Sigma X) : n, \quad (5)$$

where *X*1 and *X*2 are the values of the two extreme doses out of the three studied doses; *Y*1 and *Y*2 are the corresponding mortality rates; *n* is the number of specified (studied) doses, which is equal to 3.

Having obtained the values of *a* and *b,* we determined *X*:

$$X = (Y + b) : \alpha\,. \quad (6)$$

Thus, by substituting the values of *Y*, which were 50%, 84% and 16%, respectively, into the formula, LD, LD_{84} and LD_{16} were found.

Statistical processing of the obtained research results was carried out using a personal computer. According to the method of K. Miller and M. Teinter, confidence limits were calculated with the determination of σ and *m* (Kotsyumbas *et al.,* 2006). Accordingly, $2\sigma = LD_{84} - LD_{16}$, then the average error of the median lethal dose was calculated using the formula:

$$m = \frac{2\sigma}{\sqrt{N'x^2}}, \quad (7)$$

where *m* is the mean error of the mean value; σ is the standard deviation; *N′* is the total number of individuals in groups in which at least one animal died or survived.

After calculating the value of *m,* we found:

$$LD \pm mt, \quad (8)$$

where *t* is Student's criterion.

In the formulas above, the symbol m is used in different ways depending on the method. Specifically, according to G. Kerber's method, m means the number of animals in a group; in Pershin's formula, it means the frequency of fatalities (%); and in Miller-Tainter's method, it means the average error of the average value. To preserve the authenticity of the original approaches, the symbols are given in their original form.

Scientific research involving animals complied with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes (1986) and Law of Ukraine No. 3447-IV (2006). All necessary interventions on animals were carried out in accordance with ARRIVE recommendations, without violating the guidelines of Directive of the European Parliament and of the Council No. 2010/63/EU (2010). The conclusion on the conduct of research was also approved by the Bioethics Committee of the National University of Life and Environmental Sciences of Ukraine, protocol No. 010/2024 dated March 28, 2024.

Results and Discussion

A preliminary study was conducted to compare toxicity at different mushroom infusion times, specifically examining extracts infused for 2 days and 10 days. The results showed greater toxicity when the extract was prepared for a shorter period of time. For the main study, the optimal dose range of the extract after ten days of infusion was determined in order to establish the acute toxicity of *I. obliquus*. In the first minutes after intragastric administration of the extract of the basidiomycete tree fungus *I. obliquus,* all groups of rats showed a stress response to the intervention. Slight agitation followed by calming was observed. The results of determining the acute toxicity of *I. obliquus* in white mice are shown in Table 1.

Table 1. Results of acute experiments involving the administration of basidiomycete mushroom extract of *I. obliquus* to white rats

Dose, mg/kg b.w.	Number of animals in thegroup i	Number of animals killed					
		per day				in total	%
		1	2	5	15		
2,500	6	-	-	-	-	0	0
5,000	6	-	-	-	1	1	17
7,500	6	-	-	-	2	2	33
10,000	6	-	-	-	3	3	50
12,500	6	-	-	5	-	5	83
15,000	6	-	1	5	-	6	100

Note: *the results of an acute experiment involving the intraperitoneal administration of an aqueous extract of I. obliquus to white rats are shown*
Source: *developed by the authors*

In rats of the sixth experimental group (at a dose of 15,000 mg/kg body weight), symptoms of depression appeared after 30 minutes. The laboratory animals hunched over and moved chaotically in the cage. After 2 hours, they became agitated, which gradually changed to depression, and an increase in heart rate and respiratory rate was observed. These signs persisted for some time, after which the rats assumed a lying position, performing swimming movements and slowly raising and lowering their tails. On the second day, one animal from the sixth experimental group died, and by the fifth day, 100% mortality was recorded in this group. The same results were observed in the fifth group (the test substance at a dose of 12,500 mg/kg body weight).

In other experimental groups, most animals gradually recovered to their physiological state, and by day 15, no mortality was observed in the first experimental group (test substance at a dose of 2,500 mg/kg body weight). At the same time, 17% mortality was observed in the second experimental group (test substance at a dose of 5,000 mg/kg body weight), 33% mortality in the third experimental group (test substance at a dose of 7,500 mg/kg body weight), 50% mortality in the fourth experimental group (test substance at a dose of 10,000 mg/kg body weight) and 83% mortality in the fifth experimental group (test substance at a dose of 12,500 mg/kg body weight). Thus, toxic effects after intraperitoneal administration to white rats are observed at doses of 5,000 mg/kg body weight and above. Under these conditions, the mortality rate in the experimental groups ranged from one to six rats (Table 2), based on which calculations were made to determine the LD_{50} (Table 3).

Table 2. Acute toxicity indicators of the extract of the basidiomycete tree fungus *I. obliquus* in white rats

Dose, mg/kg b.w.	Died/survived	Dose, mg/kg b.w.	Died/survived
2,500	0/6	10,000	3/3
5,000	1/5	12,500	5/1
7,500	2/4	15,000	6/0

Source: *developed by the authors*

Table 3. Toxicity indicators of the extract of the basidiomycete fungus *I. obliquus* determined using the method of G. Kerber

Dose, mg/kg b.w.	2,500	5,000	7,500	10,000	12,500	15,000
Survived	6	5	4	3	1	0
Died	0	1	2	3	5	6
z		0.5	1.5	2.5	4.5	5.5
d		2,500	2,500	2,500	2,500	2,500
zd		1,250	3,750	6,250	11,250	13,750

Note: *z – arithmetic mean of the number of animals that died under the influence of two adjacent doses; d – interval between each two adjacent doses*
Source: *developed by the authors*

Thus, LD_{50} was determined using formula (1), therefore:

$$m=6;\ LD_{100}=11{,}250\ mg\,/\,kg;$$
$$\Sigma zd=1{,}250+3{,}750+6{,}250+11{,}250+13{,}750=36{,}250;$$
$$LD_{50}=LD_{100}-\frac{\Sigma zd}{m}=15{,}000-\frac{36{,}250}{6}=$$
$$=15{,}000-6{,}041=8{,}959\ mg\,/\,kg.$$

Considering that it is recommended to use several methods to determine the acute toxicity parameters of new medicinal substances, these data were also calculated using G. Pershin's method (Table 4). Based on the data presented in Table 4, the results of the average lethal dose of the extract of the basidiomycete tree fungus *I. obliquus,* calculated using the method of G. Pershin, are as follows (formula 2):

Table 4. Toxicity indicators of the extract of the basidiomycete fungus *I. obliquus* determined using the method of G. Pershin

Dose, mg/kg b.w.	2,500	5,000	7,500	10,000	12,500	15,000
Observed results	0/6	1/5	2/4	3/3	5/1	6/0
Percentage of animals that died	0	17	33	50	83	100
$a+b$		7,500	12,500	17,500	22,500	27,500
$m-n$		17	16	17	33	17
$(a+b)(m-n)$		127,500	200,000	297,500	742,500	467,500

Note: *a, b – values of adjacent concentrations studied, mg/mL; m, n – frequencies of fatalities at corresponding concentrations, %*
Source: *developed by the authors*

$$\Sigma[(a+b)(m+n)]=127{,}500+200{,}000+$$
$$+297{,}500+112{,}5000=1{,}750{,}000;$$
$$LD_{50}=\frac{\Sigma\,[(a+b)(m+n)]}{200}=9{,}175.0\text{ mg/kg}.$$

According to the data obtained from studies on rats, using formula (3), the LD_{50} was established using the method of B.M. Shtabsky (Table 5).

Table 5. Toxicity indicators of the extract of the basidiomycete tree fungus *I. obliquus* determined using the method of B.M. Shtabsky

Y	*X*
33,3	7,500
50	10,000
100	12,500
$\Sigma Y=183{,}3$	$\Sigma X=30{,}000$

Note: *Y – percentage of mortality, X – dose*
Source: *developed by the authors*

Thus, according to calculations using formulas (3)-(8), the parameters of the median lethal dose of the test substance for intragastric administration to rats, calculated using the method of B.M. Shtabsky, were LD_{50} = = 8,890 (6,510.1 ÷ 11,269.9) mg/kg.

The studies have established that the LD_{50} of the test substance for rats after intragastric administration is 8,959 mg/kg according to the method of G. Kerber, 9,175.0 mg/kg according to the method of G. Pershin, and 8,890 (6,510.1 ÷ 11,269.9) mg/kg according to the method of B. Shtafsky. These data allow us to conclude that the extract of the basidiomycete fungus *I. obliquus,* according to the classification of chemical substances by degree of danger, corresponds to hazard class IV, and according to the classification of substances by toxicity, it corresponds to class V and degree of toxicity "practically non-toxic substances" (Kotsyumbas *et al.,* 2006).

During the pathological autopsy of rats from experimental groups that died during the study of the acute toxicity of the extract of the basidiomycete tree fungus *I. obliquus*, it was established that the carcasses of animals had no external damage, natural openings were closed, there were no secretions, visible mucous membranes were pale pink in colour, dry with a bluish tint, and the hair coat had no visible changes. The pathological and anatomical changes in the experimental groups of animals (Fig. 2) were identical and differed only in the intensity of the changes, which correlated with the dose of the test substance.

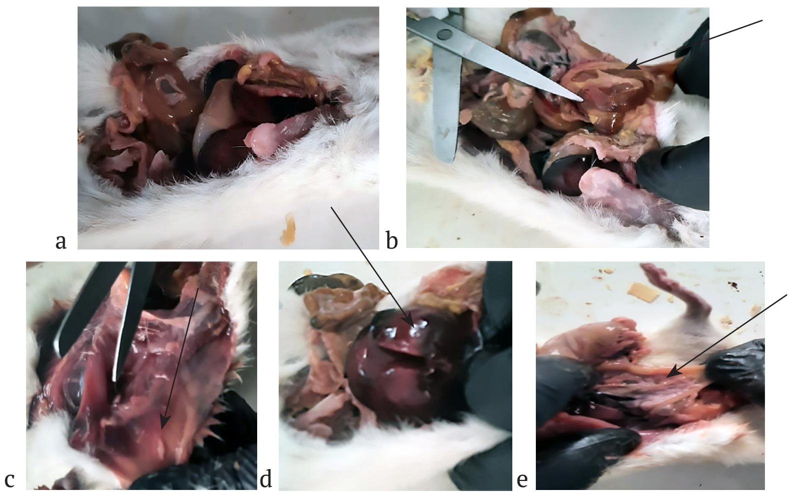

Figure 2. Pathological and anatomical changes in rats of experimental groups according to the determination of acute toxicity of the extract of the basidiomycete tree fungus *I. obliquus*
Source: *authors' photos*

Acute catarrhal gastritis, catarrhal-haemorrhagic or haemorrhagic enteritis (Figs. 2a, 2b and 2e), acute venous hyperaemia of the liver (Fig. 2d), kidneys and spleen, protein dystrophy of the liver, dilatation of the right ventricular wall of the heart, oedema of the subcutaneous tissue and skeletal muscles in the right shoulder blade area (Fig. 2c), hyperaemia and oedema of the lungs. The changes detected in animals of all experimental groups indicate the presence of poisoning by a substance that entered the body through the alimentary tract.

Thus, the results obtained confirm the acute toxicity parameters of the extract of the basidiomycete tree fungus *I. obliquus* and the pathological changes in the body of laboratory animals under such exposure. The studies conducted are a prerequisite for the next stage of preclinical research and the creation of new highly effective herbal remedies for veterinary medicine. After all, a number of modern sources of medical literature confirm the wide range of pharmacological effects.

No results of studies on the acute toxicity of chaga have been found in the literature, either in Ukraine or abroad. A more relevant area of research worldwide is the study of the properties of the constituent substances of *I. obliquus* with a view to their use for therapeutic or prophylactic purposes, and the improvement of methods for obtaining extracts from natural and artificial chaga. S. Javed *et al.* (2019) demonstrated the anti-inflammatory activity of chaga using methanol as a solvent for its extraction and found a reduction in histamine-induced TNF-α in RAW 264.7 macrophages by more than 90%. In the next stage of research, evaluation of the methanol extract in a mouse microcirculation model revealed its ability to influence vasodilation, which is observed during inflammation. W. Alhallaf & L.B. Perkins (2022) found that *I. obliquus* extracts, especially those obtained by accelerated ethanol/water extraction and hot water soaking of powdered chaga, are capable of significantly inhibiting NO, TNF-α, IL-6, and IL-1β generation in RAW 264.7 macrophages, indicating the anti-inflammatory ability of the extract under study.

S.S. Tsai *et al.* (2017) found that extracts of *I. obliquus* have anti-cancer properties and extracts from chaga obtained as a result of fermentation in a liquid state exhibit antiproliferative effects on the HCT-116 cell line through activation of the mitochondrial apoptotic pathway by enhancing the expression of proapoptotic gene mRNAs and increasing the Bax/bcl-2 ratio. K. Ryu *et al.* (2017) found that after 14 days of oral administration of methanol extracts, there was a suppression of lung tumour formation and metastasis in C57BL/6 mice that had been injected with B16F10 melanoma cells. S. Arata *et al.* (2016) demonstrated significant inhibition of tumour development in a mouse lung carcinoma model under the influence of chaga extract by reducing tumour vascularisation. At the same time, the importance of body temperature in inhibiting tumour growth was indicated, as continuous measurement of the body temperature of mice showed that consumption of *I. obliquus* extract prevented a decrease in the body temperature of mice with LLC implants.

The antidiabetic properties of chaga extracts have been established. Thus, Z. Zhang *et al.* (2021) proved that administering extracts in doses of 250 mg/kg and 500 mg/kg to C57BL/6 mice with type 2 diabetes led to improved blood glucose levels and insulin resistance, increased glycogen levels in the liver and cholesterol, and decreased total cholesterol, triacylglycerols and cholesterol. S. Chen *et al.* (2022) describe that treatment of HFD+STZ-induced diabetic mice with *I. obliquus* at a dose of 150 mg/kg significantly improved the pathological condition of fatty liver infiltration and fatty degeneration of its cells, reducing the accumulation of lipid droplets in the liver. X. Ye *et al*. (2022) found that treatment with *I. obliquus* improved the functional status of other affected organs in diabetic mice, including the kidneys, pancreas, and colon.

The renoprotective effect of chaga has been established. K.H. Chiang *et al.* (2023) reported the renoprotective effect of ethanol-ethyl acetate extracts of *I. obliquus* on nephropathic mice, where the extracts were able to effectively reduce blood creatinine and urea nitrogen levels, improve glomerular atrophy and interstitial accumulation. J. Glamočlija *et al.* (2015) demonstrated the bacteriostatic and bactericidal activity of alcohol and water extracts of *I. obliquus* against all studied Gram-positive and Gram-negative bacterial strains, with Staphylococcus aureus and Bacillus cereus being the most sensitive to the extracts. A. Milyuhina *et al*. (2021) found that although aqueous extracts of *I. obliquus* have antibacterial properties, the activity of the extracts is enhanced after microwave irradiation.

The results obtained are a prerequisite for preclinical and clinical studies of chaga samples obtained in Ukraine, with the aim of its scientifically based use in veterinary medicine for various pathologies in animals or for preventive measures. Such studies are extremely promising given the potential for creating veterinary herbal remedies based on chaga, the possibility of their use in the prevention of animal diseases; their introduction into feed as a nutraceutical; minimising the need for antibiotic therapy in veterinary medicine; creating new combinations of dietary supplements based on *I. obliquus* for animals of various species.

Conclusions

This article is devoted to the analysis of the results obtained from the study of the acute toxicity of the extract of samples of the basidiomycete tree fungus *I. obliquus* obtained in Ukraine (Rivne region). Preclinical studies, namely the establishment of the parameters of acute toxicity of the aqueous extract of chaga on laboratory animals, are a prerequisite for the experimental study of the toxicological and pharmacological properties of Ukrainian chaga samples with the subsequent production of medicinal products with a wide range of pharmacological effects. The creation of new highly effective veterinary herbal preparations for the treatment and prevention of diseases in various animal species will be of great importance in practical veterinary medicine and in ensuring the well-being of livestock.

The acute toxicity of the aqueous extract of *I. obliquus* was calculated using various generally accepted methods for preclinical studies of new substances. It was established that the LD_{50} of the studied substance for rats after intragastric administration is 8,959 mg/kg according to the method of G. Kerber, 9,175.0 mg/kg according to the method of G. Pershin, and 8,890 (6,510.1 ÷ 11,269.9) mg/kg according to the method of B. Shabsky. Therefore, the extract of the basidiomycete tree fungus *Inonotus obliquus*, according to the classification of chemicals by degree of danger, corresponds to hazard class IV, and according to the classification of substances by toxicity, class V and degree of toxicity “practically non-toxic substances”. The pathological changes observed were identical in the bodies of dead rats from different experimental groups and depended on the amount of the test substance administered. Acute catarrhal gastritis, catarrhal-haemorrhagic or haemorrhagic enteritis, acute venous hyperaemia of the liver, kidneys, spleen, protein dystrophy of the liver, dilatation of the right ventricular wall of the heart, oedema of the subcutaneous tissue and skeletal muscles in the right shoulder blade area, hyperaemia and oedema of the lungs were observed.

The determination of acute toxicity of *Inonotus obliquus* extract allowed classifying the studied substance as low-hazard (hazard class IV) and practically non-toxic (toxicity class V). The obtained LD_{50} values indicate a high safety profile of the extract under conditions of intragastric administration. The toxicological testing conducted is a necessary prerequisite for further stages of preclinical development of a medicinal product for veterinary use and can be used for scientific justification of the safety of raw materials for pharmaceutical use in the livestock industry. Further research will be aimed at conducting the next stages of preclinical and clinical studies to study the pharmacokinetics and pharmacodynamics of the active substances of *I. obliquus* in order to scientifically substantiate the use of medicinal raw materials from chaga obtained in Ukraine in veterinary medicine for the treatment or prevention of animal diseases of various aetiologies.

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Conflict of Interest

None.

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Визначення параметрів гострої токсичності екстракту базидіального деревного гриба *Inonotus obliquus* як перспективного засобу для ветеринарної медицини

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Анотація. Базидіальний деревний гриб *Inonotus obliquus* (чага) порядку *Hymenochaetales* широко використовується у світовій медицині, оскільки характеризується протизапальною і антиоксидантною діями, виявляє ефективність за онкологічних, інфекційних та інвазійних хвороб, а також за цукрового діабету, ожиріння, втоми, патології печінки і нирок тощо. Проте, токсикологічні властивості чаги, яка росте на території України, потребують наукового обґрунтування. Метою цього дослідження було встановлення параметрів гострої токсичності водного екстракту базидіального деревного гриба *Inonotus obliquus*, який одержано в природних умовах України. Дослідження проведено на білих щурах лінії Wistar згідно загальноприйнятих методик проведення доклінічних досліджень нових лікарських засобів. Встановлено, що середня смертельна доза досліджуваної речовини для щурів за внутрішньошлункового введення становить за методом Г. Кербера – 8959 мг/кг, за методом Г. Першина – 9175,0 мг/кг, а за методом Б. Штабського – 8890 (6510,1 ÷ 11269,9) мг/кг. Згідно з отриманими результатами можна стверджувати, що екстракт базидіального деревного гриба *Inonotus obliquus* згідно з класифікацією хімічних речовин за ступенем небезпечності відповідає IV класу, за токсичністю – V класу і ступеню токсичності – «практично нетоксичні речовини». Встановлені патологоанатомічні зміни, такі як гострий катаральний гастрит, катарально-геморагічний або геморагічний ентерит, гостра венозна гіперемія внутрішніх органів, дилатація стінки правого шлуночка серця, набряк підшкірної клітковини та скелетних м’язів в ділянці правої частини лопатки, проявлялися ідентично в організмі загиблих щурів дослідних груп та корелювали з дозою досліджуваного екстракту. Визначення парамерів гострої токсичності є передумовою для вивчення фармако-токсикологічних властивостей лікарських речовин, тому отримані результати є перспективою для наступних доклінічних та клінічних досліджень із метою наукового обгрунтування застосування у ветеринарній медицині лікарської сировини з *Inonotus obliquus*, одержаної на території України

Ключові слова: чага; доклінічні дослідження; лабораторні тварини; патологоанатомічні зміни; фармакологічна дія