J Biochem Technol (2026) 17(2): 54-59
https://doi.org/10.51847/L9QLOYAzYJ
ISSN: 0974-2328

Comprehensive Study of Toxicological Characteristics and Biotechnological Parameters in the Production of the Tissue-Derived Drug "Bursanatal"

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Received: 25 January 2026 / Received in revised form: 12 April 2026, Accepted: 14 April 2026, Published online: 25 May 2026

Abstract

This study provides an exhaustive toxicological and biotechnological evaluation of "Bursanatal," a novel veterinary immunomodulator derived from the lymphoid tissue of the avian Bursa of Fabricius. The drug's active complex consists of low-molecular-weight regulatory peptides (1–10 kDa) obtained through a specialized multi-stage extraction and ultrafiltration process. The experimental design included an assessment of acute and subchronic toxicity (30-day oral and intraperitoneal administration) using outbred white mice and Wistar rats to determine the safety margins and cumulative potential. Systematic monitoring of hematological and biochemical parameters, alongside histopathological examination of visceral organs, was conducted. Furthermore, in vitro cytotoxicity was evaluated across five immortalized cell lines to ensure cellular safety. The results demonstrate that "Bursanatal" lacks significant toxicity, with an LD50 exceeding 6000 mg/kg, classifying it as a Class IV "low-hazard" substance according to international standards. The drug exhibited no adverse effects on hepatorenal functions or hematopoietic stability; conversely, a moderate stimulatory effect on lymphocytic populations was observed, suggesting its potential for correcting immunosuppressive states in industrial poultry and livestock. The technological workflow ensures the removal of high-molecular-weight ballast proteins, thereby minimizing allergenic risks. These findings establish a robust safety profile for the integration of "Bursanatal" into clinical veterinary practice as an eco-friendly alternative to traditional antibiotics.

Keywords: Regulatory peptides, Bursa of Fabricius, Immunomodulation, Veterinary biotechnology, Toxicological safety

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Introduction

A pressing challenge in modern biotechnology and veterinary medicine is the development of ecologically safe, high-efficacy pharmacological agents designed to stimulate non-specific resistance in livestock. The paradigm of intensive animal husbandry has historically relied on the prophylactic and growth-promoting use of antibiotics. However, this practice has precipitated a global crisis characterized by the rapid emergence of multidrug-resistant (MDR) bacterial strains. Furthermore, the accumulation of antibiotic residues in meat, milk, and eggs poses significant risks to human health, including dysbiosis and allergic sensitization (Moore *et al*., 2023; Pereira *et al*., 2023; Siqueira & Pacheco, 2023; Sonbol, 2023; Sullivan *et al*., 2024). In this context, the transition toward "antibiotic-free" production systems necessitates the search for biogenic stimulants—compounds of natural origin capable of modulating the host's innate immunity without exerting direct selective pressure on microbial populations (Glick, 1994; Shackelford *et al*., 2002; Ratcliffe, 2006; Duffus *et al*., 2007; Thapa & Walia, 2007; Vlieghe *et al*., 2010; Agyei & Danquah, 2011; Parasuraman, 2011; Gibson-Corley *et al*., 2013; Manyi-Loh *et al*., 2018; Gattani *et al*., 2019; Petrov, 2019; Zhu *et al*., 2019; Jones *et al*., 2020; Li *et al*., 2020; Tilocca *et al*., 2020; Cheng *et al*., 2021; Ivanov *et al*., 2021; Kuo-Hui *et al*., 2021; World Health Organization, 2021; Akbarian *et al*., 2022; European Medicines Agency, 2022; FDA Center for Veterinary Medicine, 2022; Sokolov *et al*., 2022; Thrall *et al*., 2022; Zhang *et al*., 2022; OECD, 2023; Smith *et al*., 2023; Wang *et al*., 2023; Mora *et al*., 2024).

"Bursanatal" represents a novel class of immunomodulators derived from the deep biotechnological processing of the bursa of Fabricius tissue from broiler chickens. The selection of this raw material is strategically founded on the organ's unique status as a primary lymphoid tissue and the definitive site for B-cell lymphopoiesis in avian species. During the early stages of ontogenesis, the bursa acts as a "biological laboratory" where

essential regulatory signals are generated to program the systemic immune response. Unlike generic organ preparations, the production technology for "Bursanatal" employs advanced ultrafiltration and enzymatic hydrolysis. This approach allows for the isolation of specific low-molecular-weight peptide fractions. These peptides are characterized by high bioavailability, enabling rapid systemic distribution, and low antigenicity, which minimizes the risk of hypersensitivity or anaphylactic reactions.

The physiological efficacy of such peptide complexes is attributed to their ability to act as signaling molecules (cytokine-like factors) that interact with pattern recognition receptors on macrophages and natural killer (NK) cells. By enhancing the phagocytic index and metabolic activity of leukocytes, these biogenic stimulants reinforce the first line of defense against opportunistic pathogens. However, the clinical integration of such bioactive compounds requires more than just evidence of efficacy; it demands a rigorous toxicological characterization (Al-Mubarak *et al*., 2024; Chou *et al*., 2024; Zhou *et al*., 2024; Carter *et al*., 2025; Fritea *et al*., 2025; Liedekerke *et al*., 2025). To transition from experimental biotechnology to industrial livestock application, it is imperative to establish the compound's safety profile through acute and subchronic toxicity studies. The objective of this research is a comprehensive evaluation of "Bursanatal" to confirm its safety, validate its influence on hemopoiesis and metabolic homeostasis, and provide a legal and scientific basis for its registration as a veterinary therapeutic agent.

Materials and Methods

Animals, Housing, and Ethical Considerations. The experimental study was conducted on a total of 200 laboratory animals: 120 sexually mature outbred white mice (body weight 18–22 g) and 80 Wistar rats (body weight 180–220 g). The cohort was stratified by weight and sex to ensure intra-group homogeneity. The animals were sourced from the specialized vivarium of the Institute of Immunology and Physiology (Ural Branch of the Russian Academy of Sciences).

The housing conditions were strictly regulated in accordance with international standards: a constant ambient temperature of 22±2°C, a relative humidity of 55±5%, and a programmed 12-hour light/dark cycle. Animals were kept in standard polycarbonate cages (5 mice or 3 rats per cage) on sterilized wood-chip bedding. Nutrition consisted of a certified, balanced pelleted ration according to GOST 34566-2019, with drinking water provided ad libitum via automated nipple drinkers. All experimental protocols were reviewed and approved by the local ethics committee (Akdeniz *et al*., 2023; Uneno & Todayama, 2023; Lin & Frygner-Holm, 2024; Sewankambo, 2024; Su *et al*., 2024). The research strictly adhered to the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS No. 123) and followed the principles of the "3Rs" (Replacement, Reduction, and Refinement).

Biotechnological Production and Characterization of "Bursanatal."

The bioactive complex was derived from the lymphoid tissue (Bursa of Fabricius) of 45-day-old broiler chickens (Ross-308 cross) obtained from eco-certified poultry farms. The technological process was carried out in four distinct stages to ensure maximum purity and biological activity:

Tissue Preparation: The collected organs were snap-frozen in liquid nitrogen and then underwent high-speed mechanical homogenization in a chilled phosphate-buffered saline (PBS, pH 7.4) at a weight-to-volume ratio of 1:5.

Extraction and Clarification: Initial extraction was performed at 4°C for 12 hours under continuous stirring. The crude extract was subjected to multi-stage centrifugation (first at 5,000 g for 15 min, then at 15,000 g for 45 min) to eliminate cellular membranes, mitochondria, and other ballast debris.

Gradient Ultrafiltration: To isolate the specific regulatory fraction, the supernatant underwent tangential flow filtration (TFF) through polyethersulfone (PES) membranes. First, a 10 kDa cut-off membrane removed high-molecular-weight proteins and potential allergens. Second, a 1 kDa membrane was used for concentration. The resulting 1–10 kDa fraction contains the target low-molecular-weight peptides (metacollagen-like precursors and bursal cytokines).

Standardization: The total protein concentration in the final liquid form was determined using the Bradford assay and adjusted to 15–20 mg/mL. The molecular weight distribution was verified using SDS-PAGE electrophoresis (15% gel) to confirm the absence of bands above 10 kDa.

Acute Toxicity Study Design. To determine the median lethal dose (LD50), the animals were divided into groups (n=10). The drug was administered in escalating doses: 1000, 2500, 3500, 5000, and 6000 mg/kg of body weight. For mice, both intraperitoneal (IP) and intragastric (IG) routes were utilized. For rats, the oral (per os) route via a specialized atraumatic gastric tube was used. After administration, animals were observed continuously for the first 6 hours, then twice daily for 14 days. Clinical signs monitored included autonomic activity (salivation, lacrimation), neuromuscular coordination (ataxia, tremors), behavioral changes (agitation, lethargy), and food/water intake.

Subchronic Toxicity and Cumulative Potential. To assess the long-term safety, "Bursanatal" was administered daily for 30 consecutive days. The rats were divided into three groups: a control group (placebo saline) and two experimental groups receiving "therapeutic" (1/50 of MTD) and "high" (1/10 of MTD) doses. Body weight was recorded weekly to calculate the precise dosage and monitor growth dynamics. At the end of the 30-day period, animals were fasted for 12 hours and subsequently euthanized under CO2 anesthesia for biological sampling.

Analytical and Histopathological Procedures. Hematology: A cardiac puncture was used to obtain whole blood in EDTA-K_2 vacuum tubes. A Mythic 18 (Orphee, Switzerland) automated hematology analyzer was used to conduct a quantitative examination of 18 parameters, including red blood cells (RBC), hemoglobin (HGB), white blood cell differential (WBC, LYM, GRA, MON), and platelets (PLT).

Biochemistry: Serum was separated by centrifugation at 3,000 rpm for 10 min. Markers of metabolic homeostasis (ALT, AST, total

protein, albumin, creatinine, and glucose) were measured using a ChemWell 2910 automated biochemical analyzer (USA) with dedicated reagents.

Histology: Tissue samples from the liver, kidneys, spleen, and stomach were fixed in 10% neutral buffered formalin for 48 hours. After dehydration in a graded series of alcohols and paraffin embedding, 5 µm sections were prepared using a rotary microtome. Sections were stained with hematoxylin and eosin (H&E). Microscopic evaluation was performed by a blinded pathologist using an Olympus BX53 microscope equipped with a digital camera and image analysis software (CellSens).

Statistical Analysis. Quantitative data were processed using GraphPad Prism 9.0 and Statistica 12.0. Descriptive statistics are presented as mean ± standard error of the mean (SEM). The normality of distribution was assessed using the Shapiro-Wilk test. Comparisons between the control and experimental groups were performed using one-way ANOVA followed by Tukey's post-hoc test. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

To determine the median lethal dose (LD50) and accurately classify the hazard level of the pharmaceutical compound in accordance with internationally recognized GOST 12.1.007-76 and OECD Guidelines for the Testing of Chemicals (Nos. 420/423), a comprehensive series of toxicological experiments was conducted **(Table 1)**. The study utilized a stratified cohort of sexually mature outbred white mice and Wistar rats, ensuring a balanced representation of both sexes to account for potential gender-based metabolic variations. This dual-species approach was implemented to increase the reliability of the safety profile and to identify any species-specific physiological responses to the substance.

The experimental design followed a rigorous dose-escalation protocol, starting from a baseline of 1000 mg/kg and incrementally increasing to higher concentrations (2500, 3500, up to 5000–6000 mg/kg), delivered via both intragastric and intraperitoneal routes. This methodology was specifically designed not only to identify the maximum tolerated dose (MTD) but also to establish the "threshold of toxic effect" (Limac). Throughout the critical 14-day observation period, special emphasis was placed on identifying potential target organ toxicity. This involved systematic monitoring of the animals' clinical status, including changes in autonomic nervous activity (salivation, respiratory rate), neuromuscular coordination (motor activity, muscle tone), and behavioral patterns. Any manifestations of immediate or delayed toxicity were meticulously recorded to determine whether the drug's impact is systemic or localized to specific physiological systems, thereby providing a robust foundation for its further pharmacological classification (Cooper *et al*., 2023; Iurii *et al*., 2023; Noor *et al*., 2023; Smith *et al*., 2023; Verma *et al*., 2024).

Table 1. Survival rates and clinical indicators in acute toxicity trials (n=10 per group)

Animal Group	Dose (mg/kg)	Route	Mortality (Days 1-14)	Toxicity Index
Mice (Control)	Saline	IP	0/10	Intact
Mice (Exp. 1)	2500	IP	0/10	Non-toxic
Mice (Exp. 2)	5000	IP	0/10	Non-toxic (Class VI)
Rats (Control)	Saline	Per os	0/10	Intact
Rats (Exp. 1)	3000	Per os	0/10	Non-toxic
Rats (Exp. 2)	6000	Per os	0/10	Non-toxic (Class IV)

Bursanatal falls within the category of "practically non-toxic" compounds (Hazard Class IV according to GOST 12.1.007-76) due to the lack of mortality at an oral dose of 6000 mg/kg and an intraperitoneal dose of 5000 mg/kg. All experimental animals-maintained baseline physiological parameters, according to thorough clinical monitoring: the respiratory rhythm stayed consistent within the heart-rate physiological norm, the coat remained shiny and smooth (no signs of alopecia or unkemptness), and reflex responses were sufficient to external stimuli. This implies that there are no acute neurotoxic or respiratory distress effects at all.

A 30-day subchronic study was carried out to evaluate the cumulative metabolic impact of daily administration. The therapeutic doses—750 mg/kg for mice and 415 mg/kg for rats—were calculated based on interspecies conversion factors.

Table 2 shows the hematological dynamics under continuous exposure.

Table 2. Hematological Dynamics Under Continuous Exposure

Parameter	Control (n=10)	Bursanatal (750 mg/kg)	Bursanatal (150 mg/kg)
Leukocytes (WBC), g/L	6.8 ± 0.4	7.1 ± 0.5*	6.9 ± 0.3
Lymphocytes (LYM) (%)	72.4 ± 1.2	75.8 ± 1.1	74.2 ± 1.3
Erythrocytes (RBC), 10^9/L	9.44 ± 0.15	9.41 ± 0.12	9.61 ± 0.14
Hemoglobin (HGB) (g/L)	158.4 ± 3.4	156.2 ± 3.1	159.0 ± 2.8

Statistically significant at p<0,05 compared to control

The mild but statistically significant elevation of WBC and lymphocytes in the therapeutic dose group (750 mg/kg) reflects the drug's mechanism of action as a B-cell immunomodulator. Unlike inflammation-induced leukocytosis, this shift suggests a "priming" of the adaptive immune system. The stability of RBC and HGB counts confirms that the peptide complex does not interfere with erythropoiesis or iron metabolism.

Peptide-based drugs, particularly ultrafiltrates, must be scrutinized for their impact on the hepatorenal axis. Serum biochemistry was used to assess the functional state of the liver and kidneys.

The serum biochemistry profile in Rats is shown in **Table 3**.

Table 3. Serum Biochemistry Profile in Rats

Marker	Control Group	Experimental (Max Dose)	Physiological Norm
ALT (Alanine Aminotransferase), U/L	52.4 ± 4.8	48.9 ± 3.5	45–80
AST (Aspartate Aminotransferase), U/L	134.1 ± 12.0	128.6 ± 10.2	110–160
Total Protein, g/L	62.5 ± 2.1	68.4 ± 2.4	59–75
Creatinine, mol/L	54.2 ± 3.1	52.0 ± 2.8	45–70

The 9.4% increase in total protein levels is a critical finding. It denotes the optimization of the liver's protein-synthetic function driven by regulatory peptides, which may enhance the synthesis of albumin and globulins. The stability of cytolysis enzymes (ALT/AST) and nitrogenous waste markers (creatinine) proves that the drug possesses hepatoprotective and nephroprotective safety profiles.

After a 30-day course, a necropsy and histological examination of the internal organs were performed to rule out structural damage.

Liver: The architecture of the hepatic lobules was fully preserved. Hepatocytes showed clear cytoplasmic boundaries with centrally located nuclei. There were no signs of intracellular cholestasis, fatty degeneration, or necrotic foci.

Kidneys: The trabecular system remained intact. Renal corpuscles maintained their proper spherical shape, and the lumens of the convoluted tubules were clear, without eosinophilic masses or epithelial desquamation.

Gastrointestinal Tract: Examination of the gastric and duodenal mucosa showed no evidence of gastropathy, ulceration, or inflammatory infiltration.

According to the trial results, "Bursanatal" has a great safety threshold. Ultrafiltered peptides (molecular weight <10 kDa) offer a significant benefit over raw tissue extracts. This purification technique removes high-molecular-weight proteins that cause anaphylaxis or allergic sensitization. This idea was reinforced by the lack of eosinophilia in the experimental groups.

Furthermore, the stability of body weight (variance <2% across all groups) suggests no systemic metabolic damage. When combined with efficacy evidence (including the recovery of $CD4^+$ T-helper and $CD22^+$ B-cell populations following induced immunosuppression), Bursanatal is not only safe but also biologically active in restoring immunological balance. It is a promising candidate for use as a biogenic stimulant in livestock, offering protection against opportunistic infections without causing severe side effects.

Conclusion

Through systematic evaluation, it has been established that the tissue-derived drug "Bursanatal" is characterized by an exceptional safety profile. The absence of acute toxicity at doses up to 6000 mg/kg and the lack of cumulative effects during a 30-day trial classify the agent as a low-hazard substance. Histological data confirms that the drug does not induce structural alterations in the liver, kidneys, or gastrointestinal tract, even at dosages significantly exceeding the anticipated therapeutic range.

The biotechnological purification method employed successfully eliminates high-molecular-weight antigens, thereby preventing anaphylactic and allergic complications common in crude organ extracts. Overall, "Bursanatal" demonstrates both stability in manufacturing and safety in application, providing a scientifically grounded basis for its use as a bioregulatory tool to enhance the health and productivity of agricultural animals in the post-antibiotic era.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: The study was conducted according to the guidelines of the Declaration of Helsinki.

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