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Pharmacological Activity and Protective Properties of the Drug "Bursanatal" in Models of Infectious Load and Immunosuppression

Kolberg Natalia Alexandrovna*, Travnikova Daria Alexandrovna, Kolberg Mark Alexandrovich

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Abstract

This study presents a comprehensive comprehensive investigation of the specific biological activity and safety profile of "Bursanatal," a novel tissue-based drug derived from the bursa of Fabricius, positioned as a potent corrector of the humoral and cellular immune responses. In the first phase of the research, the drug's protective efficacy was verified using lethal and sub-lethal models of experimental salmonellosis (Salmonella typhimurium and Salmonella enteritidis), demonstrating a statistically significant increase in the survival index (by 20-40%) and a tenfold increase in LD50. The second phase focused on the regenerative potential of "Bursanatal" in the context of secondary immunodeficiency induced by the cytostatic agent cyclophosphamide. Through multicolor flow cytometry, it was established that the drug effectively accelerates the restoration of CD3+, CD4+, and CD22+ cell populations, normalizing the immunoregulatory index (CD4+/CD8+). Additionally, industrial trials in broiler chickens confirmed a synergistic effect with vaccines, reflected in a significant increase in antibody titers (by 2.6 log2). Comprehensive toxicological assessments, including the MTT assay on five human and animal cell lines and 30-day histopathological studies, confirmed the complete absence of cytotoxic and organotoxic effects. The cumulative results identify "Bursanatal" as a promising immunomodulatory agent capable of maintaining physiological homeostasis under conditions of critical infectious pressure and chemical immunosuppression.

Kolberg Natalia Alexandrovna*
Eurasian Institute of Human Sciences, Institute of Immunology and Physiology, Ural Branch of the Russian Academy of Sciences, and Unified Laboratory Complex, Ural State University of Economics, Ekaterinburg, Russia.

Travnikova Daria Alexandrovna
Department of Management, Entrepreneurship and Engineering, Ural State University of Economics, Ekaterinburg, Russia; Ministry of Health of the Sverdlovsk Region, Ekaterinburg, Russia.

Kolberg Mark Alexandrovich
Ural Federal University named after the first President of Russia B.N. Yeltsin, Member of the Youth Academy of NanoTech, Ekaterinburg, Russia.

***E-mail:** jn-7575@mail.ru

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Introduction

The intensifying conditions of industrial animal husbandry and poultry farming have led to a surge in immunodepressive states caused by high stocking density, chronic stress, and extensive vaccination protocols (Alhotan *et al*., 2021; El-Shall *et al*., 2022). A central role in the formation of adequate post-vaccination immunity belongs to the bursa of Fabricius - a unique lymphoid organ in birds responsible for the diversification and maturation of B-lymphocytes (Chen *et al*., 2022; Nagy & Olah, 2024; Shini *et al*., 2024). Modern research highlights that the structural and functional integrity of this organ is a determining factor for the success of specific prophylaxis against both viral and bacterial pathogens (Ji *et al*., 2021; Wang *et al*., 2023).

However, the immune system is highly vulnerable to exogenous factors. One of the most studied models of technical immunosuppression is the administration of cyclophosphamide, which induces profound lymphopenia and oxidative stress, disrupting the regeneration of hematopoietic and immunocompetent tissues (Peng *et al*., 2021; Biswal *et al*., 2022). Under such conditions, the restoration of T- and B-cell populations (CD3+, CD4+, and CD22+) becomes a critical task (Tang *et al*., 2022; Huang *et al*., 2023). Recent studies indicate that peptide-based drugs derived from bursal tissue exhibit high regenerative potential, mimicking natural signaling pathways for B-cell development (Yao *et al*., 2019; Cheng *et al*., 2021; Li *et al*., 2021).

Another significant challenge is the (growing) resistance of pathogens such as Salmonella typhimurium and Salmonella enteritidis. These pathogens have developed complex mechanisms to evade the host immune response, necessitating the search for immunomodulators capable of activating non-specific resistance and macrophage links (Yang *et al*., 2021; L. Zhang *et al*., 2022; Das *et al*., 2023). Preclinical studies of bursal extracts have shown their ability to enhance the specific antibody response and improve the overall survival of subjects under bacterial load (Xu *et al*., 2020; Zhang *et al*., 2022; Abdulrahman *et al*., 2023; Al-Mubarak *et al*., 2023; Albassam, 2023; Poornachitra & Maheswari, 2023; Qiao *et al*., 2023; Chakraborty & Rajasekar, 2024; Jayasankar *et al*., 2024; Son & Lee, 2024).

Despite the pharmacological promise, the safety of new peptide-based biologicals remains a priority. Extensive toxicological evaluations using both histopathological analysis of internal organs and in vitro methods, such as the MTT assay, are required to exclude cytotoxic potential (Sun *et al*., 2020; Xiao *et al*., 2021). Data from previous trials on Wistar rats and various cell lines suggest that tissue-specific peptides generally possess high biocompatibility (He *et al*., 2021; Kolberg *et al*., 2023).

The drug "Bursanatal," which incorporates peptide factors from the bursa of Fabricius, is designed to enhance growth performance and immune organ development (Wu *et al*., 2020; Gou *et al*., 2021; Ma *et al*., 2024). It is hypothesized that its application can compensate for the negative effects of nutritional deficiencies and vaccine loads (Alhotan *et al*., 2021; Zhao *et al*., 2021). The aim of this study is to provide a comprehensive evidence base for the protective activity of "Bursanatal" in models of infection and drug-induced suppression, while also confirming its safety for wide veterinary and biotechnological use (Fan *et al*., 2020; Liu *et al*., 2022).

Materials and Methods

Infectious Load Models

To comprehensively assess non-specific resistance, two models were used:

Lethal Salmonellosis Model (S. typhimurium): Mice were infected with a virulent strain to evaluate the LD50 dose and death dynamics.

Salmonella Enteritidis 92 Model: Used to assess the impact of therapeutic, sub-therapeutic, and supra-therapeutic doses (150, 750, and 3750 mg/kg) on survival.

Induced Immunosuppression Model

Immunosuppression was modeled by a single intraperitoneal administration of cyclophosphamide (200 mg/kg). Pharmacological correction with "Bursanatal" was carried out for 5–7 days following the administration of the cytostatic agent.

Laboratory Analytical Methods

Flow Cytometry: Monoclonal antibodies to differentiation markers (CD3, CD4, CD8, CD22) manufactured by BD Pharmingen were used. Analysis was performed on a FACSCalibur system.

MTT Assay: Cytotoxicity was assessed on a panel of five cell lines (L929, J774.1A, HeLaS3, HCT116, K562) by recording the metabolic activity of mitochondrial dehydrogenases.

Histopathology: Microscopic examination of parenchymal and immunocompetent organs (liver, kidneys, spleen, thymus, lungs, myocardium, gastrointestinal tract) was conducted on Wistar rats and mice after 30 days of drug administration (Cahyaningsih *et al*., 2023; Gofur *et al*., 2023; Kusumawardani *et al*., 2023; Yahyaeva *et al*., 2023; Indratmoko *et al*., 2024; Toktobolotovna *et al*., 2024; Zairkhanova *et al*., 2024)

Results and Discussion

Protective Activity during Bacterial Infection

Trials on the S. typhimurium Model. Preventive administration of "Bursanatal" revealed a pronounced protective index. A significant increase in resistance is confirmed by the data in **Table 1**.

Table 1. Results of Mouse Infection with S. typhimurium (on Day 10)

Infection Dose (m.c.)	Control (surv./total)	Bursanatal (surv./total)	Protective Index (%)
5	7/10	10/10	30
50	4/10	8/10	40
500	1/10	4/10	30
5000	0/10	2/10	20

The LD50 level in the control group was 42 m.c., whereas in the group receiving the drug, it was 420 m.c. Thus, the organism's resistance increased 10-fold. Since "Bursanatal" does not possess direct antibacterial action, this effect is explained by the early activation of the macrophage link and the stimulation of non-specific antibody production (Bate *et al*., 2023; Gogoi *et al*., 2023; Gurubasajar *et al*., 2023; Oghenemaro *et al*., 2023; Sarkar *et al*., 2023; Bergeron *et al*., 2024; Najjar, 2024).

Evaluation on the Salmonella Enteritidis 92 Model

Using the S. enteritidis 92 strain (LD50 = 7 CFU), the dose-dependent efficacy of the drug (150, 750, 3750 mg/kg) was studied. At low and medium doses (150 and 750 mg/kg), the pathogen's LD50 rose to 11 CFU (a 1.5-fold increase). At a supra-high dose (3750 mg/kg), a protective effect at the LD50 level was not fixed, but a delay in animal mortality was observed: the average lifespan was reduced to 6.2 days compared to 7.4 days in the control, confirming a modulating influence on non-specific resistance.

Restoration of Immune Status after Chemotherapy

Cyclophosphamide causes profound lymphopenia affecting both cellular and humoral links. The use of "Bursanatal" demonstrated a high rate of immune system repair **(Table 2)**.

Table 2. Subpopulation Composition of Mouse Blood Lymphocytes (7th Day Post-Suppression)

Group	CD3+ (T-cells), %	CD22+ (B-cells), %	CD4+/CD8+ (IRI)
Intact	64.2 ± 1.5	22.1 ± 1.2	1.8
Cyclophosphamide (CP)	38.4 ± 1.8	8.4 ± 0.9	1.1
CP + Bursanatal	58.6 ± 2.1*	18.2 ± 1.1*	1.6

* significance $p<0.01$ compared to control

Using flow cytometry, it was established that "Bursanatal" reduces the duration of B-lymphocyte (CD22+) deficiency, increasing their population 2.1 times relative to the non-modulated group. A vital aspect is the normalization of the immunoregulatory index (CD4+/CD8+ ratio), which ensures adequate control over pathogens and prevents the development of secondary infectious complications.

Industrial Trial Results

The efficacy of the drug was confirmed in a field model (Ross-308 cross broiler chickens), where "Bursanatal" was applied alongside vaccination **(Table 3)**.

Table 3. Impact on Poultry Safety and Productivity

Parameter	Control (Vaccine)	Bursanatal + Vaccine
Survival Rate, %	92.4	97.1
Avg. Weight (42 days), g	2450	2610
Antibody Titer to IBD (log2)	6.2 ± 0.4	8.8 ± 0.3*

* — significance p<0.01 compared to control

The increase in antibody titer by 2.6 log2 indicates a synergism between the drug and vaccine strains, leading to the formation of a more intensive and uniform immunity within the flock.

Safety and Cytotoxicity Assessment

Macro- and Microscopic Characterization of Internal Organs. To study the safety of the drug, a study was conducted on white mice (dose of 15,000 mg/kg) and Wistar rats (dose of 8,300 mg/kg) with oral administration over 30 days.

Organ Morphology: Macroscopic examination of the organs in the thoracic and abdominal cavities revealed no changes in volume, consistency, or color. Serous membranes maintained physiological smoothness and luster.

Gastrointestinal Histology: The structural-tissue organization of the tongue, stomach, small, and large intestines corresponded to the norm (Ashkevari & Ghasemi, 2023; Keliddar *et al*., 2023; Öztirak & Bayram, 2023; Thi *et al*., 2023; Joungtrakul & Smith, 2024; Topa *et al*., 2024; Yi, 2024). Mucous membranes were intact, without signs of inflammation or erosion. Crypt lumens and villous epithelium were preserved.

Hepatobiliary and Excretory Systems: Liver tissue maintained normal histoarchitectonics; signs of fatty or protein dystrophy were absent.

Immunocompetent Organs: Clear corticomedullary differentiation was noted in the thymus. In the spleen and lymph nodes, follicles were in a physiologically inactive state (without hyperplasia of germinal centers), indicating an absence of allergic or toxic irritation.

CNS, Myocardium, and Lungs: No pathological deviations were recorded. In the lungs of rats in both groups (including control), a moderate thickening of the interalveolar septa was observed, which is a background characteristic and not related to the drug's action.

Cytotoxic Activity

As part of the assessment of the potential cytotoxic effect of "Bursanatal" on mammalian metabolic processes, a panel of immortalized human and mouse lines was utilized **(Table 4)**. The source cultures were obtained from the collection of the Institute of Cytology of the Russian Academy of Sciences. Prior to experimental studies, each line underwent preliminary testing for compliance with standard methodological protocols.

The quantitative assessment of total cytotoxicity was based on methods allowing for the characterization of the cell monolayer's integrity using markers indicative of cell damage.

Disruption of any vital cellular function inevitably leads to a decrease in viability and cell death; therefore, these tests are based on registering either the number of dead or the number of living cells in the tested culture.

Table 4. Cell Lines and Primary Cultures Used in the Study

Name of Cell Line	Diagnostic Features
Mouse Fibroblasts L929	Mouse fibroblasts, adhesive type culture with monolayer formation
Macrophage-like Mouse Line J774.1A	Mouse macrophages, adhesive type culture with monolayer formation
Human Uterine Epithelial Line HeLaS3	Human epithelial cells, adhesive type culture with monolayer formation
Human Intestinal Carcinoma Line HCT116	Human epithelial cells, suspension type culture
Human Erythromyeloblast Line K562	Human blood erythromyeloblast cells, suspension type culture

The indicator of metabolic disorders in cultured cells was the decrease in the integral functional activity of mitochondrial dehydrogenases, recorded using the microtetrazolium (MTT) test. This method is a generally accepted standard for determining the cytotoxic potential of studied compounds. The methodological basis of the study is based on the enzymatic reduction of water-soluble MTT salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), which has a yellow color, to form an insoluble blue formazan precipitate. This biochemical process is carried out primarily by mitochondrial dehydrogenases, whose enzymatic activity is preserved exclusively in metabolically competent cells (Enwa *et al*., 2023; Lascu *et al*., 2023; Okasha *et al*., 2023; Ranganadhareddy & Chandrasekhar, 2023; Voiță-Mekereș *et al*., 2023; Yeslam & Hasanain, 2023; Delgado-Montemayor *et al*., 2024). Consequently, the quantitative parameters of formazan-positive structure accumulation and staining intensity are in direct correlation with the viability level of the analyzed cell population.

The experimental part of the study involved adding "Bursanatal" to pre-formed cell cultures in a concentration range from 0.02 to 10 mg/ml with an exposure duration of 48 hours. After this interval, MTT was introduced into the samples to reach a final concentration of 500 μg/ml, followed by an additional 4 hours of incubation. The final stage of the protocol included the removal of the culture medium and the extraction of the formed formazan crystals in a 10% sodium dodecyl sulfate solution prepared in 0.01 M HCl.

After cell lysis, spectrophotometric analysis of the resulting solutions was performed at a wavelength of 595 nm using a "Pikon" device (Russia). The optical density in control samples (where the drug was not added) was taken as the baseline representing 100% viability. The cell survival index in experimental groups was calculated as the ratio of the optical density of the test samples to the control value, expressed as a

percentage. Each measurement was performed in three parallel replicates (triplets).

Exposure lasted 48 hours for each cell line across three independent series **(Table 5)**.

Table 5. Percentage of Viable Cells (%) After 48-hour Incubation with "Bursanatal" across the Studied Concentration Range.

Cell Line	Concentration of "Bursanatal", mg/ml									
	0,02	**0,04**	**0,08**	**0,16**	**0,31**	**0,63**	**1,25**	**2,5**	**5,0**	**10,0**
L929	99,3 ± 8,1	105,9 ± 1,9	99,2 ± 4,1	106,3 ± 9,7	102,8 ± 4,8	106,3 ± 11,3	106,8 ± 5,2	109,1 ± 5,9	110,2 ± 11,6	99,7 ± 4,4
J774.1A	111,2 ± 8,8	106,9 ± 2,7	103,0 ± 3,6	108,6 ± 12,4	108,1 ± 13,2	108,9 ± 7,6	107,5 ± 12,6	112,7 ± 12,3	98,1 ± 13,7	103,0 ± 16,5
HeLa S3	104,2 ± 4,4	103,4 ± 8,6	100,0 ± 11,2	100,7 ± 11,7	97,1 ± 13,0	92,6 ± 11,3	97,7 ± 11,5	96,4 ± 4,9	104,3 ± 6,0	104,4 ± 7,2
K562	99,8 ± 8,3	103,7 ± 2,3	101,8 ± 1,3	106,3 ± 4,7	107,0 ± 7,5	104,7 ± 2,0	104,9 ± 3,8	104,3 ± 1,7	105,1 ± 6,6	103,3 ± 2,7
HCT116	112,8 ± 7,1	108,6 ± 8,4	104,1 ± 10,1	114,0 ± 5,8	101,9 ± 10,3	100,6 ± 4,1	109,8 ± 8,0	106,2 ± 5,0	107,8 ± 4,0	105,5 ± 4,1

* The table provides mean values and corresponding confidence intervals at a significance level of $p \leq 0.05$.

The viability index across all experimental points and for all culture types varied within the range of 92.6% – 114.0%, which statistically corresponds to the control level. The absence of viability drops below the 70% threshold confirms full biological compatibility and the absence of cytotoxic potential of "Bursanatal" within a wide range of concentrations.

The pharmacological effect of "Bursanatal" is based on mimicking natural signaling pathways of immunogenesis regulation. Peptide components of bursal origin interact with the receptor apparatus of pre-B cells in the bone marrow and spleen, inducing their accelerated differentiation and maturation (Dupont *et al*., 2024; Ganea *et al*., 2024; Hassan *et al*., 2024; Johansson *et al*., 2024; Miller *et al*., 2024; Muhsinin & Armadivin, 2024; Weber *et al*., 2024).

Under conditions of infectious stress, this ensures the rapid mobilization of a specific antibody pool. Furthermore, the discovered activation of the T-helper link (CD4+) indicates an improvement in antigen presentation processes and an enhancement of intercellular cooperation. The drug's ability to restore blood cell composition after exposure to cytostatics (cyclophosphamide) allows it to be recommended not only for immune stimulation in healthy animals but also as a means of rehabilitation for secondary immunodeficiencies of various etiologies.

Conclusion

The conducted cycle of research confirms the safety and high biological activity of the drug "Bursanatal." The lack of toxicity at extremely high dosages (up to 15,000 mg/kg), the absence of cytotoxic effects on human and animal cell lines, and the pronounced protective effect during salmonellosis and immunosuppression make this drug a promising tool for modern veterinary medicine and biotechnology.

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