



## Fabricius Extract Effect on Haematological Parameters of Mice Blood with Experimental Immunodeficiency

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### ABSTRACT

This article examines the effect of cyclophosphamide (CPA) on hematological parameters in C57BL/6 mice and the possibility of correcting these changes with bursa of Fabricius extract. Administration of CPA leads to the development of an immunodeficiency state characterized by severe lymphopenia, anaemia, and changes in the leukocyte population. A decrease in the number of red blood cells, haemoglobin, and haematocrit is observed, as well as changes in the parameters of red blood cells that indicate a disorder of haemoglobin synthesis. At the same time, there is an increase in the proportion of monocytes, eosinophils, and basophils. The administration of bursa of Fabricius extract has an effect on the parameters of white blood cell and increases the total number of white blood cells, as well as the proportion of middle blood cells, and granulocytes. The red blood also shows positive dynamic, but the parameters do not reach the control values. The MPV and PDV indices of platelets do not change. The results obtained show that the extract from the bursa of Fabricius promotes the restoration of haematological parameters affected by the administration of CFA and indicate the prospects for further investigation of its immunomodulatory properties.

**Keywords:** Bursa of fabricius, Immunostimulatory, Hematological parameters, Cyclophosphamide, Peptides

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### INTRODUCTION

The bursa of Fabricius extract, known for its immunostimulatory properties, has captured the interest of researchers as a potential therapeutic agent for correcting hematological parameters in mice with experimental immunodeficiency (Kolberg *et al.*, 2023). Throughout the experiments, changes in the quantity and activity of various blood cells, such as lymphocytes, monocytes, and neutrophils, were observed (Fiodorova *et al.*, 2022; Osipchuk *et al.*, 2022). Several studies have shown that administering the extract results in a statistically significant increase in T-lymphocyte numbers, indicating an improved cellular immunological response (Kolberg *et al.*, 2023). Additionally, an increase in total white blood cell count was seen, indicating immune system activation. Another notable discovery is the change in

hemoglobin and hematocrit levels, which suggests that the extract has a favorable effect on the erythropoiesis process (Kolberg *et al.*, 2023).

The ability to develop drugs that can enhance or modulate the body's immune response is well-established (Sepiashvili, 2015; Semochkin, 2023; Lan *et al.*, 2024). This is particularly important in veterinary medicine for the prevention and treatment of infectious diseases (Kolberg, 2017; Pogodaev & Botasheva, 2023; Shcherbakov *et al.*, 2023). Research in this field often focuses on various immunomodulatory agents, including those derived from natural sources (Al-Subaihawi & Abbas, 2021; Guryanova & Khaitov, 2021; Wieczorek *et al.*, 2022; Bernitsa *et al.*, 2023), synthetic peptides (Lee *et al.*, 2016; Boldyreva *et al.*, 2021; Grigorean *et al.*, 2024; Balakrishnan *et al.*, 2025; Tan *et al.*, 2025), and other biological macromolecules (Khobrakova *et al.*, 2022; Guo *et al.*, 2025; Liu *et al.*, 2025). The challenges of immunodeficiency are a broad area of study (Tuano *et al.*, 2021; Koval, 2024), and understanding immune and metabolic processes is crucial (Kolberg, 2015).

## MATERIALS AND METHODS

C57BL/6 mice were utilized for the experimental study due to their small size, ease of care, and ability to adapt well to vivarium conditions. The specific parameters involved in the study were limiting, which complicates the interpretation of results and their relevance to humans. The experimental portion of the study involved three-month-old male C57BL/6 mice that were raised and maintained in a vivarium under strict sanitary, hygienic, and veterinary standards for laboratory animals.

All manipulations and interventions within the experimental protocol adhered to the provisions of Directive 2010/63/EU of the European Parliament and the Council on the protection of animals used for scientific purposes. The study was formally approved by the Ethics Committee of the Institute of Immunology and Physiology, Ural Branch of the Russian Academy of Sciences, after receiving preliminary approval through the established procedure.

Peripheral blood parameters were assessed using the Celly 70 automated hematology analyzer (Biocode Hycel), a bioassay designed for studying biomaterials obtained from laboratory animals. Samples were collected in plastic tubes containing tripotassium salt of ethylenediaminetetraacetic acid (tricalium-EDTA), which was used as an anticoagulant.

Based on the recorded values, the analyzer automatically decoded and quantitatively assessed the following hematological parameters: WBC – absolute number of leukocytes (103/μl); Lym # – absolute number of lymphocytes (103/μl); Mid # – absolute number of medium-sized cells (103/μl); Grn # – absolute number of granulocytes (103/μl); Lym % – proportion of lymphocytes as a percentage (%); Mid % – proportion of medium-sized cells (%); Grn % – percentage of granulocytes (%); RBC – absolute number of erythrocytes (106/μl); Hb – hemoglobin concentration (g/dL); Hct – hematocrit expressed as a percentage (%); MCV – mean corpuscular volume (femtoliters); MCH – mean corpuscular hemoglobin content (picograms); MCHC – mean corpuscular hemoglobin concentration (g/dL); RDW – erythrocyte size variation (%); Plt # – absolute platelet count (103/μL); Pct – platelet crit (%); MPV – mean platelet volume (femtoliters); PDW – platelet size variation (%).

To model secondary immunodeficiency in laboratory animals, a single injection of the cytotoxic drug cyclophosphamide (Endoxan®, Baxter Oncology GmbH, Germany) was administered into the peritoneal cavity. The dosage was individually calculated for each mouse based on body weight and was set at 200 mg/kg. The solution was prepared right before use by dissolving the drug in sterile 0.9% sodium chloride solution to achieve a concentration of 20 mg/ml of the active component. Animals in the control group were given an equivalent volume of isotonic 0.9% sodium chloride solution (Rudayni et al., 2022; Wilhelmy et al., 2022; Gbon et al., 2024; Ismikhonov et al., 2024). The body weight of all animals was documented before each procedure to ensure precise dosing.

The cytostatic action of cyclophosphamide is carried out through DNA alkylation, causing cell cycle arrest at the G0/G1 and S stages due to the formation of cross-links and DNA damage.

Cyclophosphamide exerts a cytotoxic effect, by inducing cell apoptosis. As an antitumor agent, it suppresses bone marrow

cell processes and proliferation, leading to a decrease in the cellular content of hematopoietic tissue and a reduction in its functional activity.

In order to establish the immunodeficiency model, laboratory mice were administered a single intraperitoneal injection of the cytostatic agent cyclophosphamide at a dosage of 200 mg/kg of body weight. The drug was prepared by dissolving the active substance in a sterile 0.9% sodium chloride solution, resulting in a final solution concentration of 20 mg/ml. Animals in the control group received an injection of an equivalent volume of isotonic saline without the active substance.

Statistical data analysis was conducted using the STATISTICA 6.0 software package (StatSoft, Inc., 2001). Results are presented as the arithmetic mean (M) with the standard error (m). The nonparametric Mann-Whitney U-test was utilized to compare differences between two independent groups. For dependent samples, Wilcoxon tests (Wilcoxon signed-rank test) were employed, considering paired values. A significance level of  $p < 0.05$  was used during the statistical analysis, indicating a 5% threshold for result reliability.

## RESULTS AND DISCUSSION

In recent years, a variety of new biologically active substances, peptide and polypeptide complexes, and bioorganic compounds have emerged that demonstrate immunomodulatory, immunocorrective, or immunosuppressive effects. These substances, extracts, and decoctions are typically derived from immobilized proteases, allogeneic tendons, bovine lymph nodes, earthworm tissue, fish organs, eggs, milt, bird embryonic tissue, etc.

Unlike mammals and humans, in birds the central organs of the immune system include bone tissue, the thymus, and the bursa of Fabricius.

The bursa of Fabricius is a central organ of the avian immune system, playing a crucial role in immune cell development alongside the bone marrow and thymus. Its primary function is to create conditions for the formation, maturation, development, and differentiation of B lymphocytes, which, along with T lymphocytes, mediate the adaptive immune response. The bursa of Fabricius is where B lymphocytes are trained to recognize foreign antigens from their own, which is essential for the prevention and control of autoimmune reactions. Anatomically, the bursa of Fabricius is located on the dorsal surface of the cloaca, serving as its diverticulum.

The uniqueness of the bursa of Fabricius lies in the fact that it carries out two processes simultaneously: the antigen-independent process of B-lymphocyte formation and the antigen-dependent process associated with the development of antibody-secreting plasma cells in the bursa.

The bursa of Fabricius plays a key role in the formation and differentiation of immune system cells, particularly B lymphocytes. Plasma cells, which synthesize antibodies, are derived from lymphocytes in the bursa of Fabricius. Their initial maturation takes place in the gland's cortex, where they acquire the ability to recognize antigens through specific receptors. Unlike the bone marrow, the bursa of Fabricius specializes in producing B lymphocytes. These lymphocytes not only give rise to plasma cells but also play a key role in the maturation, formation, and training of B cells. The process involves several stages of selecting cells capable of recognizing their own

histocompatibility antigens, highlighting the gland's importance in developing effective adaptive immunity.

In birds, the bursa of Fabricius functions to generate a variety of B-lymphocyte clones capable of synthesizing and secreting immunoglobulins (Fiodorova *et al.*, 2022).

The first class of immunoglobulins discovered in the lymphocytes of the bursa of Fabricius during ontogenesis, both in the cytoplasm and on the cell surface, was immunoglobulin M (IgM).

The bursa of Fabricius itself is capable of synthesizing peptides that play a key role in the immune response. The bursa is involved in regulating peripheral immune responses mediated by the nervous and endocrine systems. This regulation occurs through peptides from the bursa of Fabricius, as well as through direct modulation of the functional capacity of lymphoid cells by hormones from the thymus and pituitary gland.

The functional significance of peptides from the Bursa of Fabricius extends beyond immunological functions. Peptides also play a significant role in neuroendocrine interactions with the immune system. The polypeptide complex of the Bursa of Fabricius, along with other biologically active compounds of the Bursa (known as bursamedins), regulates the hypothalamic - thymus - Fabrician - gonadal axis. They stimulate and regulate the secretion of hormones from the hypothalamus, pituitary gland, and thyroid gland, while also influencing and activating the adrenal cortex and gonads.

Peptide proteins from the bursa of Fabricius play an active role in the immune defense against reovirus infection (DRV), a deadly avian virus from the Reoviridae family (Deana *et al.*, 2022; Ikhile & Enabulele, 2023; Samaranayake *et al.*, 2024).

Four distinct peptide fractions, known as BP-I, BP-II, BP-III, and BP-IV, were isolated and identified from the bursa of Fabricius. In further research, the authors investigated the immunoadjuvant properties of the BP series peptides (Deana *et al.*, 2022; Spirito *et al.*, 2022; Ikhile & Enabulele, 2023; Samaranayake *et al.*, 2024).

During the experiments, it was discovered that the BP-I peptide has a significant stimulating effect on the cellular mechanisms of the immune response, increased the secretion of Th1 (interferon gamma) and Th2 (interleukin-4) cytokines and also enhanced cytotoxic T-lymphocyte (CTL) response to the H9N2 virus. BP-II primarily boosted the production of specific antibodies, particularly neutralizing antibodies, and also increased the secretion of Th1 and Th2 cytokines. In contrast, BP-III did not show a significant impact on antibody production or cell-mediated immune responses compared to the control group. BP-IV, on the other hand, triggered a robust immune response at both the humoral and cellular levels (Spirito *et al.*, 2022; Wu *et al.*, 2022).

Recently, a new peptide, BP-IV, was isolated from the bursa of Fabricius (Shaheen *et al.*, 2023; Galea-Holhoş *et al.*, 2024). This compound was found to stimulate the formation of colony-forming units of pre-B cells and to be involved in the regulation of B-lymphocyte differentiation processes. Furthermore, BP-IV exhibits pronounced immunomodulatory activity, influencing antigen-specific responses through both humoral and cellular immunity. This effect was observed in chickens and laboratory mice previously immunized with an inactivated form of the avian influenza virus (AIV), belonging to the H9N2 subtype. The peptide resulted in increased production of specific antibodies directed against AIV, as well as increased synthesis of key

cytokines.

The results of the study allowed the authors to reconsider the use of a potential reagent candidate for B-cell development and future immunopharmacological applications (Abuzinadah, 2024).

Host defense peptides are a diverse group of small cationic peptides that serve as important first-line defenses against pathogens in birds, animals, and humans. In a study examining the expression patterns of all known cathelicidins,  $\beta$ - defensins, and NK lysin in several tissue samples from the bursa of Fabricius, CATHB1 was found to be expressed. The resulting bursa peptide demonstrated antibacterial activity against *E. coli* in animal experiments showing dose-dependent efficacy.

Isolated cells from the Bursa of Fabricius have shown that, unlike typical mammals, chicken MHC (the BF-BL region of the B locus) has strong genetic associations with resistance and susceptibility to infectious pathogens, as well as vaccine response. The authors demonstrated that chicken MHC encodes a single, dominantly expressed class I molecule whose peptide-binding motifs can determine resistance to viral pathogens such as Rous sarcoma virus and Marek's disease virus.

Synthesized active peptides from the bursa of Fabricius: Tyr - Glu - Gly, Trp - Thr - Ala - Glu - Glu - Lys - Gln - Leu and Lys - Glu - Glu - Leu - Asn - Glu, Glu - Arg - Asp - Pro, increase the phagocytic index and contribute to an increase in phagocytic numbers. On this background, an observed increase in oxygen-dependent metabolism in peritoneal macrophages has been noted.

The bursa of Fabricius plays a crucial role in the development of adaptive immunity in birds. This gland facilitates the maturation of B-lymphocytes, which collaborate with T-lymphocytes to recognize and destroy pathogens. This synergy between B-lymphocytes and T-lymphocytes promotes the development of central tolerance, preserving the body and preventing the development of various autoimmune diseases. These functions make the bursa of Fabricius a relevant target in the search for and development of new treatments for immune disorders. According to research by Goretsky, Doroshenko, Chirkina, Sheybak (2011), and other scientists, lymphocytes in the bursa of Fabricius contain significant amounts of free proteinogenic amino acids. Their concentration is 1.8 times higher than that in spleen lymphocytes and 20% higher than in thymus cells. The data obtained highlight the important role of the Bursa of Fabricius in the functioning of both the central and peripheral components of the avian immune system, demonstrating its exceptional ability to maintain the body's immune homeostasis.

Bioorganic preparations from the bursa of Fabricius and extracts from this gland contain biologically active substances that can modulate the immune response (Abuzinadah 2024; Galea-Holhoş *et al.*, 2024). However, further research is needed to study their composition, chemical and biological properties, mechanisms of action, and potential clinical applications in more detail (Spirito *et al.*, 2022; Wu *et al.*, 2022; Samaranayake *et al.*, 2024). The use of extracts, biogenic complexes, ointments, creams, and emulsions based on bursa of Fabricius tissue is considered a promising approach to restoring the body's immune system. These medications can be used effectively not only for general immunocorrection but also in the treatment of inflammatory processes, both acute and chronic, as well as illnesses defined by compromised immune response, such as

immunodeficiency and autoimmune diseases.

It should be noted that further research in this area opens up broad opportunities for the development of new therapeutic and preventative approaches. Specifically, this refers to the potential effectiveness of Bursa Fabricius extracts as part of a comprehensive treatment for oncological and autoimmune pathologies and immune disorders of various origins and as a preventative measure for immune dysregulation that can lead to the development of chronic and difficult-to-treat diseases (Deana et al., 2022; Ikhile & Enabulele, 2023).

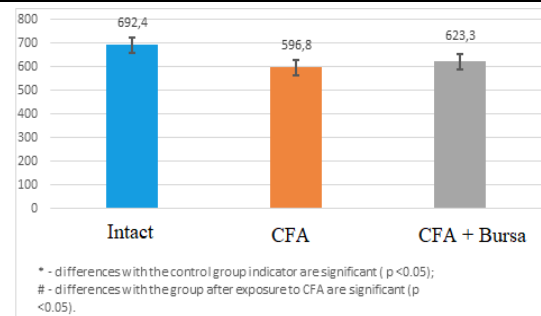
The hematological study results, which are displayed in **Table 1** and **Figures 1-4**, consistently validate that cyclophosphamide administration causes laboratory animals to develop an immunodeficiency status. It was discovered that the administration of CFA to C57BL/6 mice caused severe lymphopenia, which was a reduction in both absolute and relative lymphocyte levels by about half as compared to intact animals, when choosing parameters for the white blood cell composition. There was no discernible difference between the peripheral blood's total leukocyte count and the control values. This phenomena can be explained by the fact that mice receiving injections of cyclophosphamide had higher levels of the middle cell fraction, namely monocytes, eosinophils, and basophils. During the drug's action, nonspecific immune response factors are probably activated, which results in a rise in the number of cellular elements. This kind of reaction is common during the acute or subacute stages of exposure to different xenobiotics, and other authors' research has verified it.

**Table 1.** Hematological parameters of peripheral blood in C 57 BL /6 mice after administration of cyclophosphamide and extract from bursa of Fabricius

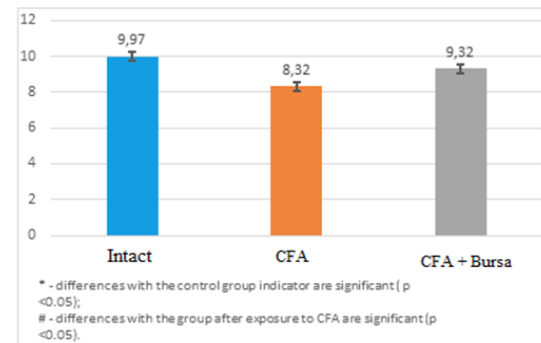
| Indicator                   | Intact           | CFA               | CFA + Bursa         |
|-----------------------------|------------------|-------------------|---------------------|
| Leukocytes, 103/ $\mu$ l    | 4.07 $\pm$ 0.45  | 4.32 $\pm$ 1.63   | 6.21 $\pm$ 0.65*    |
| Lymphocytes, 103/ $\mu$ l   | 3.18 $\pm$ 0.38  | 1.38 $\pm$ 0.44*  | 1.47 $\pm$ 0.25*    |
| Average cells, 103/ $\mu$ l | 0.74 $\pm$ 0.12  | 2.73 $\pm$ 1.07*  | 4.27 $\pm$ 0.59*    |
| Granulocytes, 103/ $\mu$ l  | 0.13 $\pm$ 0.03  | 0.23 $\pm$ 0.12   | 0.43 $\pm$ 0.12*    |
| Lymphocytes, %              | 78.53 $\pm$ 1.13 | 34.79 $\pm$ 2.32* | 24.28 $\pm$ 2.17*   |
| Average cells, %            | 18.37 $\pm$ 1.09 | 61.68 $\pm$ 1.94* | 68.35 $\pm$ 1.33* # |
| Granulocytes, %             | 3.63 $\pm$ 0.21  | 4.53 $\pm$ 0.47*  | 7.49 $\pm$ 1.32*    |
| Erythrocytes, 106/ $\mu$ l  | 9.97 $\pm$ 0.25  | 8.32 $\pm$ 0.25*  | 9.32 $\pm$ 0.25*    |
| Hemoglobin, g/ dL           | 14.17 $\pm$ 0.47 | 11.38 $\pm$ 0.23* | 13.35 $\pm$ 0.38*   |
| Hematocrit, %               | 42.27 $\pm$ 1.33 | 35.15 $\pm$ 1.21* | 38.97 $\pm$ 1.15*   |
| MCV, fl                     | 42.31 $\pm$ 0.37 | 42.37 $\pm$ 0.21  | 42.22 $\pm$ 0.23    |
| MCH, pg                     | 14.12 $\pm$ 0.32 | 13.79 $\pm$ 0.17  | 14.07 $\pm$ 0.33    |
| MCHC, g/dl                  | 33.37 $\pm$ 0.57 | 32.57 $\pm$ 0.41  | 32.72 $\pm$ 0.38    |
| RDW, %                      | 15.77 $\pm$ 0.19 | 15.79 $\pm$ 0.13  | 15.75 $\pm$ 0.23    |
| Platelets, 103/ $\mu$ l     | 692.4 $\pm$ 31.8 | 596.8 $\pm$ 33.1  | 623.3 $\pm$ 32.2    |
| Thrombocrit, %              | 0.38 $\pm$ 0.03  | 0.36 $\pm$ 0.15   | 0.38 $\pm$ 0.02     |
| MPV, fl                     | 5.37 $\pm$ 0.05  | 5.99 $\pm$ 0.18*  | 5.93 $\pm$ 0.07*    |
| PDW, %                      | 10.39 $\pm$ 0.12 | 12.35 $\pm$ 0.17* | 11.37 $\pm$ 0.05*   |

\* - statistically significant differences compared to the control group (p < 0.05);

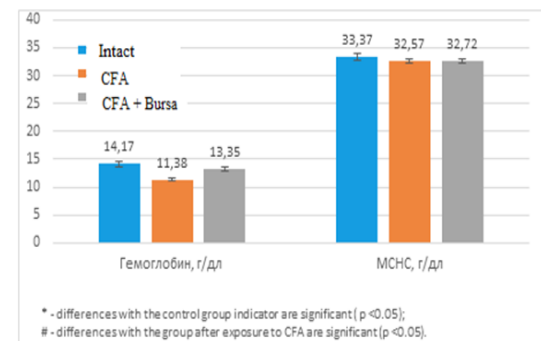
# - statistically significant differences compared to the group exposed to cyclophosphamide (CFA) (p < 0.05).



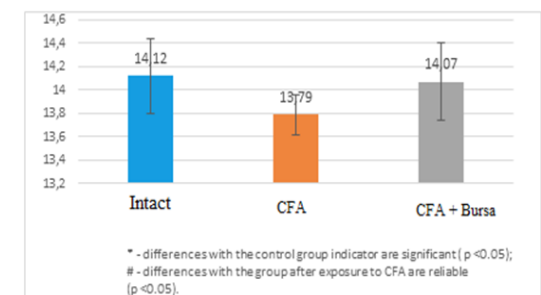
**Figure 1.** Platelets in the peripheral blood of mice C57BL/6 lines after administration of cyclophosphamide and extract from the Bursa of Fabricius



**Figure 2.** Erythrocytes in the peripheral blood of C57BL/6 mice after administration of cyclophosphamide and bursa of Fabricius extract



**Figure 3.** Hemoglobin and mean corpuscular hemoglobin concentration in the peripheral blood of C57BL/6 mice following administration of cyclophosphamide and Bursa of Fabricius extract



**Figure 4.** Average hemoglobin content in peripheral blood erythrocytes of C57BL/6 mice after administration of cyclophosphamide and Bursa of Fabricius extract

The cytotoxic effect of cyclophosphamide (CFA) is evident in alterations in red blood cell parameters. Anemia development in mice with experimental immunodeficiency is characterized by a decrease in red blood cell count, resulting in lower hemoglobin levels and hematocrit. Additionally, a decrease in other red blood cell parameters, such as MCH (mean hemoglobin content in one red blood cell, reflecting oxygen carried by each cell), and MCHC (indicator of hemoglobin saturation in red blood cell) is observed. These changes indirectly suggest disruption in hemoglobin synthesis in the bone marrow. Despite a stable platelet count, an increase in mean platelet volume (MPV) and platelet size variability (PDW) is noted. These changes typically indicate activation of the hemostatic system, often occurring with anemia, inflammatory reactions, and intoxication due to cyclophosphamide (CFA) administration.

Mice treated with Bursa of Fabricius extract for seven days (CFA+Bursa group) showed an increase in white blood cell counts. There was a noticeable rise in the total leukocyte count, as well as in the absolute and relative counts of mid-sized cells and granulocytes, when compared to intact animals. It can be inferred that the increase in leukocyte counts is linked to the alterations in the counts of mid-sized cells, such as monocytes, basophils, and eosinophils, which play a crucial role in both specific and nonspecific immune responses. The dynamics of lymphocytes remained stable, with no significant changes detected in their absolute or relative counts.

## CONCLUSION

The study revealed a significant increase in red blood cell count, as well as an increase in hemoglobin and hematocrit concentrations in animals receiving the extract. However, these parameters were 1.1–1.2 times lower than the control results. This may be due to the insufficient duration of therapy, as animals were only given the drug for seven days. Thus, a tendency toward restoration of erythropoietic activity is observed, but a longer course of treatment with the extract is required for full restoration of red blood cell counts.

Administration of the bursa extract did not affect platelet MPV and PDV indices, as their values did not change in relation to animals that did not receive the extract.

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**FINANCIAL SUPPORT:** None

**ETHICS STATEMENT:** The study was conducted according to the guidelines of the Declaration of Helsinki.

## REFERENCES

Abuzinadah, S. H. (2024). An *in vitro* investigation of home bleaching and its impact on the surface texture of dental cosmetic biomaterials. *International Journal of Dental Research and Allied Sciences*, 4(1), 16–22. doi:10.51847/uzY8DPehMS

- Al-Subaihawi, R. A., & Abbas, R. J. (2021). Evaluation of the efficacy of asparagus (*Asparagus officinalis* L.) root powder and aqueous extract on the physiological and immunological performance of broilers. *Indian Journal of Ecology*, 48(5), 1551–1556.
- Balakrishnan, A., Winiarek, G., Hołowka, O., Godlewski, J., & Bronisz, A. (2025). Unlocking the secrets of the immunopeptidome: MHC molecules, ncRNA peptides, and vesicles in immune response. *Frontiers in Immunology*, 16, 1540431.
- Bernitsa, S., Dayan, R., Stephanou, A., Tzvetanova, I. D., & Patrikios, I. S. (2023). Natural biomolecules and derivatives as anticancer immunomodulatory agents. *Frontiers in Immunology*, 13, 1070367.
- Boldyreva, Y. V., Lebedev, I. A., & Zakharchuk, E. V. (2021). Oligopeptides as biochemically significant molecules. *Bulletin of the Ural Medical Academic Science*, 18(2), 138–146.
- Deana, N. F., Seiffert, A., Aravena-Rivas, Y., Alonso-Coello, P., Muñoz-Millán, P., Espinoza-Espinoza, G., Pineda, P., & Zaror, C. (2022). Review of available studies and guidelines in the field of prevention of COVID-19 infection in dental centers. *Annals of Dentistry and Medical Assistance Journal*, 2(1), 1–7. doi:10.51847/4VxEtFTTh77
- Fiodorova, O. A., Sivkova, E. I., & Nikonov, A. A. (2022). Safeguarding beef cattle from gnats and gadflies in the southern Tyumen region. *International Journal of Veterinary Research and Allied Sciences*, 2(2), 8–13. doi:10.51847/iVXOeXmSNZ
- Galea-Holhoş, L. B., Delcea, C., Siserman, C. V., & Ciocan, V. (2024). A review of advances in age estimation of human remains using dental characteristics. *International Journal of Dental Research and Allied Sciences*, 4(1), 23–28. doi:10.51847/Eupv55HsYd
- Gbon, G. A., Boga, J. P., & Johnson, F. (2024). Managing *Anomala denuda* (Coleoptera: Scarabaeidae), a pest of maize, through the use of an aqueous extract derived from *Ricinus communis*. *Entomology Letters*, 4(2), 1–10. doi:10.51847/wYk22SDv3m
- Grigorean, G., Du, X., Kuhfeld, R., Haberl, E. M., & Lönnnerdal, B. (2024). Effect of *in vitro* digestion on bioactive peptides related to immune and gut health in intact cow's milk and hydrolyzed protein-based infant formulas. *Nutrients*, 16(19), 3268.
- Guo, J., Wei, T., Chen, J., Hong, A., He, Q., Lin, Y., Ren, Z., & Qin, T. (2025). Structural characterization and immune activity evaluation of polysaccharide purified from *Viola philippica*. *International Journal of Pharmaceutics*, 125689.
- Guryanova, S. V., & Khaitov, R. M. (2021). Strategies for using muramyl peptides—modulators of innate immunity of bacterial origin—in medicine. *Frontiers in Immunology*, 12, 607178.
- Ikhile, F. O., & Enabulele, J. E. (2023). Assessing Riyadh dentists' awareness of orthodontic emergencies and treatment approaches. *Annals of Dentistry and Medical Assistance Journal*, 3(2), 20–26. doi:10.51847/5i5zja3v5w
- Ismikhonov, A. G., Dadaeva, G. T., Dzhabrailov, S. M., Maysigova, J. B., Semenov, M. R., & Dzagurova, L. A. (2024). The role of selenium-containing compounds in periodontal and dental disease management. *Annals of Orthodontics and*

- Periodontics Speciality, 4, 32–38. doi:10.51847/pB7YqtH50J
- Khobrakova, V. B., Khalzanova, A. V., Olennikov, D. N., & Abidueva, L. R. (2022). Influence of individual substances isolated from *Silene jeniseensis* Willd on the state of the main parts of immunity at experimental immunodeficiency. *Acta Biomedica Scientifica*, 7(5-2), 222–229.
- Kolberg, N. A. (2015). Immunity and metabolic processes of animals under the application of the immunomodulator "Bursanatal." *Agro-Food Policy of Russia*, (8), 68–70.
- Kolberg, N. A. (2017). Tissue preparation "Bursanatal." Its effect on resistance and immunity in infectious diseases. *Innovative Technologies in Agriculture*, 21–34.
- Kolberg, N. A., Mukhlynina, E. A., Brilliant, S. A., Danilova, I. G., Gette, I. F., & Ulitko, M. V. (2023). Immunotropic effect of bursa of Fabricius extract from broiler chickens on C57BL/6 and C57BL/10 mice with experimental immunodeficiency syndrome. *APK Rossii*, 30(2), 275–283.
- Koval, A. N. (2024). Changes in the energy metabolism of the myocardium of rats under the influence of ionizing radiation. *Problems of Health and Ecology*, 21(1), 89–92.
- Lan, Y., Lin, X., Yu, J., Wang, L., Sun, L., & Huang, Z. (2024). Assessment of the implementation of accelerated drug marketing registration procedures for antineoplastic and immunomodulating agents in China: based on 2016–2022 review data. *Frontiers in Pharmacology*, 15, 1345672.
- Lee, M. O., Jang, H. J., Rengaraj, D., Yang, S. Y., Han, J. Y., Lamont, S. J., & Womack, J. E. (2016). Tissue expression and antibacterial activity of host defense peptides in chicken. *BMC Veterinary Research*, 12(1), 231.
- Liu, P., Zhu, R., Gu, Y., Xu, Z., Zou, H., Gu, J., Yuan, Y., Liu, Z., & Bian, J. (2025). Effects of *Ganoderma* spent substrate containing polysaccharides and triterpenoids on the growth performance, antioxidant capacity and immunity level of chickens. *International Journal of Biological Macromolecules*, 145318.
- Osipchuk, G., Povetkin, S., Shpak, T., Verevkin, M., Bondarenko, N., & Kravchenko, N. (2022). Utilization of biologically active compounds from plant materials in specific physiological states of cows. *International Journal of Veterinary Research and Allied Sciences*, 2(2), 21–26. doi:10.51847/wNzvM95prz
- Pogodaev, V. A., & Botasheva, V. A. (2023). Fattening and meat qualities of piglets when stimulated with the drug "Immunostimulating Serum." *Izvestia Orenburg State Agrarian University*, 1(99), 328–333.
- Rudayni, H. A., Basher, N. S., Al-Keridis, L. A., Ibrahim, N. A., & Abdelmageed, E. (2022). Exploring the effectiveness of *Ocimum basilicum* extracts in mosquito larvae management. *Entomology Letters*, 2(1), 12–18. doi:10.51847/uplmR4jWMM
- Samaranayake, L., Tuygunov, N., Schwendicke, F., Osathanon, T., Khurshid, Z., Boymuradov, S. A., & Cahyanto, A. (2024). Artificial intelligence in prosthodontics: transforming diagnosis and treatment planning. *Asian Journal of Periodontics and Orthodontics*, 4, 9–18. doi:10.51847/nNyZ6VD1da
- Semochkin, S. V. (2023). Prospects for the use of immunomodulatory drugs and cereblon E3 ligase modulators in the treatment of multiple myeloma. *Clinical Oncohematology. Basic Research and Clinical Practice*, 16(3), 229–241.
- Sepiashvili, R. I. (2015). Immunomodulatory drugs in clinical practice: classification, basic principles and methods of application, indications and contraindications. *Allergy and Immunology*, 16(2), 189–195.
- Shaheen, R. S., Alsaffan, A. D., Al-Dusari, R. S., Helmi, R. N., & Baseer, M. A. (2023). Self-reported oral hygiene and gum health among dental and medical students, dentists, and physicians in Saudi Arabia. *Turkish Journal of Public Health Dentistry*, 3(1), 9–16. doi:10.51847/SZCGti8IFn
- Shcherbakov, P. N., Stepanova, K. V., & Zhuravel, N. A. (2023). Application of immunostimulating therapy at respiratory pathology of calves of different sex and age groups. *Izvestia Orenburg State Agrarian University*, 2(100), 173–178.
- Spirito, F. D., Iacono, V. J., Alfredo, I., Alessandra, A., Sbordon, L., & Lanza, A. (2022). Impact of COVID-19 awareness on periodontal disease prevention and management. *Asian Journal of Periodontics and Orthodontics*, 2, 16–26. doi:10.51847/t8D9TJGOCU
- Tan, S., Yang, W., Ren, Z., Peng, Q., Xu, X., Jiang, X., Wu, Z., Oyang, L., Luo, X., Lin, J., et al. (2025). Noncoding RNA-encoded peptides in cancer: biological functions, posttranslational modifications and therapeutic potential. *Journal of Hematology & Oncology*, 18(1), 20.
- Tuano, K. S., Seth, N., & Chinen, J. (2021). Secondary immunodeficiencies: an overview. *Annals of Allergy, Asthma & Immunology*, 127(6), 617–626.
- Wieczorek, P. P., Hudz, N., Yezerska, O., Horčinová-Sedláčková, V., Shanaida, M., Korytniuk, O., & Jasicka-Misiak, I. (2022). Chemical variability and pharmacological potential of propolis as a source for the development of new pharmaceutical products. *Molecules*, 27(5), 1600.
- Wilhelmy, L., Willmann, J. H., Tarraf, N. E., Wilmes, B., & Drescher, D. (2022). Managing first molar agenesis: a long-term assessment of space closure and implant options. *Annals of Orthodontics and Periodontics Speciality*, 2, 1–7. doi:10.51847/ryKxA1287r
- Wu, K., Yin, W., Liang, X., & Yang, Z. (2022). The impact of obesity and demographic factors on periapical lesions, dental caries, and oral health in adults. *Turkish Journal of Public Health Dentistry*, 2(2), 13–22. doi:10.51847/MzsbLBIXDE