MERAL Publications and Solutions Pvt. Ltd.

Original Article

Effect of the extract from the bursa of Fabricius on bone marrow of experimentally immunodeficient mice

Kolberg Natalia Alexandrovna[1*], Travnikova Daria Alexandrovna[2], Kurilenko Marina Anatolyevna[3], Poryadin Vyacheslav Borisovich[4]

[1]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. [2]Department of Management, Entrepreneurship and Engineering, Ural State University of Economics, Ekaterinburg, Russia; Ministry of Health of the Sverdlovsk Region, Ekaterinburg, Russia. [3]LDF "Medik" LLC, Ekaterinburg, Russia. [4]Unified Laboratory Complex, Ural State University of Economics, Ekaterinburg, Russia; Department of Management, Entrepreneurship and Engineering, Ural State University of Economics, Ekaterinburg, Russia.

Correspondence: 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. jn-7575@ mail.ru

Received: 24 May 2025; **Revised:** 26 September 2025; **Accepted:** 04 October 2025

ABSTRACT

This study explores the impact of the extract from the bursa of Fabricius on the bone marrow of mice with CPA-induced immunodeficiency. Myelogram analysis revealed that CPA administration resulted in lymphopenia and suppression of lymphopoiesis, while granulocyte sprouts are activated, indicating a non-specific immune response. The treatment of mice with CPA-induced immunodeficiency with the extract from the bursa of Fabricius stimulated the lymphoid lineage in the bone marrow, as evidenced by an increase in lymphoblasts and mature lymphocytes. However, there was no significant restoration of lymphocyte numbers in peripheral blood, possibly due to the lack of antigen stimulation. The extract also led to an increase in neutrophilic and erythroid cell content. Additionally, administration of the extract from the bursa of Fabricius stimulated cell mitotic activity and increased the total number of myelokaryocytes. These findings suggest a significant immunotropic effect of the extract on bone marrow under conditions of immunodeficiency, resulting in the activation of lymphoid and erythroid sprouts, as well as an increased leukocyte and granulocyte content. The demonstrated ability of the extract to counteract the cytostatic effect of CPA highlights the potential for further research into isolating and identifying active peptides with immunostimulatory properties.

Keywords: Bone marrow, Cell cycle, Immune modulation, Secondary immunodeficiencies, Myelogram

Introduction

Secondary immunodeficiencies are acquired pathological conditions where there is a disruption in the immune response mechanisms, leading to a reduced overall immune system activity and its ability to fight against infectious agents effectively.

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Alexandrovna KN, Alexandrovna TD, Anatolyevna KM, Borisovich PV. Effect of the extract from the bursa of Fabricius on bone marrow of experimentally immunodeficient mice. J Adv Pharm Educ Res. 2025;15(4):15-21. https://doi.org/10.51847/8VVSOY7vW9

Immunodeficiency can occur independently or develop secondarily due to various external and internal factors. Factors contributing to weakened immune defenses include excessive physical activity, cancer, inadequate protein intake, dysfunction of regulatory systems, exposure to toxins, and prolonged use of drugs. Immunodeficiency states are relatively common and are characterized by an increased susceptibility to viral and bacterial pathogens [1-20].

Secondary immunodeficiencies, which involve impaired immune responses and increased susceptibility to pathogens, can develop under the influence of factors such as cyclophosphamide (CPA), a commonly used agent to induce immunodeficiencies in laboratory animals. With the increasing need for innovative immunotropic drugs, bioorganic materials derived from animals, such as bursa extract, show promise. Bursa extract has low

toxicity and specific effects, making it appealing for developing immunomodulatory treatments. Despite its known immunostimulatory properties, the impact of bursa extract on central immune organs like the bone marrow remains understudied, highlighting the importance of researching its effects on the bone marrow of mice with experimental immunodeficiency [5-8, 21-36].

Materials and Methods

C57BL/6 mice were utilized for the experiments due to their small size, low maintenance requirements, and ability to adapt well to vivarium conditions [37-39]. However, limitations arise from the specific parameters associated with these animals, complicating result interpretation and their applicability to humans. The experimental portion of the study involved three-month-old male C57BL/6 mice raised and housed in the vivarium in strict adherence to the sanitary, hygienic, and veterinary standards for laboratory animals [6, 40-48]

All manipulations and interventions in the experimental protocol adhered to Directive 2010/63/EU of the European Parliament and the Council regarding the protection of animals used for scientific purposes. The study received official approval from the Ethics Committee of the Institute of Immunology and Physiology of the Ural Branch of the Russian Academy of Sciences, following the established procedure.

The standard conditions in the vivarium included a constant air temperature of +20–22° C, free access to food (Delta Feeds, a mixed food for laboratory mice and mice - LbK 120 C-19, RF) and water. The experimental animals were randomly divided into three groups with the same number of six mice in each group.

Three experimental groups were formed:

1. Control group of mice (n = 6),
2. Animals (n = 6) in which immunodeficiency was modelled (CPA)
3. The animals (n = 6) were injected intraperitoneally with a bursa extract at a dose of 0.1 ml/20 g against the background of immunodeficiency modelling.

The experimental procedures were terminated, and the animals were excluded from the study on the seventh day after the creation of the experimental state of immunodeficiency. Animals in all experimental groups were premedicated 15-20 minutes prior to planned euthanasia: a 2% solution of xylazine was administered intramuscularly at a rate of 1 ml per 1 kg body weight, as was the drug Zoletil-100 at a dose of 0.3 ml/kg. All procedures were carried out in accordance with the approved protocols and ethical standards for the treatment of laboratory animals.

To model the secondary immunodeficiency state 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 calculated individually for each mouse based on body weight and was 200 mg/kg. The solution was prepared immediately before administration by dissolving the drug in a sterile 0.9% sodium chloride solution so that the concentration of the active component was 20 mg/ml. The animals in the control group received an equivalent volume of isotonic 0.9% sodium chloride solution. Before the manipulations were carried out, the body weight of all animals was recorded to ensure accurate dosing.

The mechanism of the cytostatic effect of CPA is based on DNA alkylation. CPA arrests the cell cycle in stages G0/G1 and S through the formation of cross-links and DNA damage.

Cyclophosphamide has a cytotoxic effect that induces cell apoptosis. As an antitumor agent, it inhibits the processes and proliferation of bone marrow cells, resulting in a decrease in the cellular elements in the hematopoietic tissue and a reduction in its functional activity.

To establish the immunodeficiency model, laboratory mice were administered a single intraperitoneal injection of the cytostatic drug, cyclophosphamide, at a dose of 200 mg/kg body weight. The drug was dissolved in a sterile 0.9% sodium chloride solution to achieve a final concentration of 20 mg/ml. The control group of animals received an injection of an isotonic solution without the active substance added.

To quantify the total number of myelokaryocytes extracted from the femoral marrow, a method involving mechanical disruption of the tissue with a rubber bulb into a test tube containing a 3% acetic acid solution with methylene blue as a coloring agent was used. The cell suspension was homogenised by pumping it through a needle attached to a syringe and then collected in a leucocyte pipette. The sample was diluted 20-fold with the same acetic acid solution.

The Goryaev chamber was cleaned with acetic acid solution before use, and the contents of the pipette were added carefully to the chamber. The cells were counted in 20 large squares of the chamber.

The total number of myelokaryocytes was calculated using the following formula:

$$K = n \times 20 \times 250 \times 4000 / 20 \quad (1)$$

Where:

- TMC – total myelokaryocyte count;
- n — the number of cells counted;
- 20 — the dilution coefficient;
- 250 is — the conversion factor for the volume of one large square (1/250);
- 4000 — the multiplier for recalculating the concentration from 1 µl to a total volume of 4000 µl;
- 20 – the number of large squares taken into account.

In order to evaluate not only the total number but also the distribution of myelokaryocytes in the bone marrow smear, they were morphologically differentiated. The starting material was obtained by flushing bone marrow tissue into a petri dish with a drop of isotonic solution. The tissue fragments were carefully

dispersed with sterile forceps until a homogeneous cell suspension was achieved. The resulting suspension was applied to a clean glass slide to create a smear. Once the preparation had naturally dried, it was fixed in ethyl alcohol. Staining was performed using the Romanovsky-Giemsa method with a 15-minute exposure time. After staining was completed, the slides were washed under running water. The morphological analysis of the cell elements was conducted at a magnification of ×100 using an immersion system on a Leica DM 2500 microscope (Germany).

The analysis revealed data on the absolute number of myelokaryocytes (in millions of cells per femur), categorized by their morphological subtypes, and the percentage distribution of different cell forms was calculated.

Results and Discussion

When examining the qualitative and quantitative composition of bone marrow cells, known as myelogram, in laboratory mice of the C57BL/6 line after a single injection of cyclophosphamide (CPA), a decrease in the total number of lymphoid cells was observed compared to intact animals. This decrease affected both mature lymphocytes and their precursors, lymphoblasts **(Table 1)**.

Table 1. Content of lymphocytes of different subpopulations in C57BL6 mice with CPA-induced immunodeficiency after 7-day administration of the extract from the bursa of Fabricius

Indicator	Reference	CPA	CPA+ bursa
T, %	32,250 [27,300;37,900]	62,800 [59,300; 75,000] *	75,950 [70,900; 78,100] * *
T, 10 ^{9} /l	1,384 [1,142;1,592]	0.654 [0.511; 0.740] *	0.75 2 [0.681; 0.910] *
B, %	60,400 [53,700;63,900]	5,600 [4,500; 6,200] *	10,000 [6,900; 10,800] * *
B, 10^{9}/ l	2,268 [2,077;2,945]	0.043 [0.031; 0.071] *	0.108 [0.057; 0.118] * **
NK, %	7,900 [7,500;8,900]	28,250 [16,500; 33,100] *	11,900 [10,200; 22,000] * *
NK, 10^{9}/ l	0.318 [0.261;0.410]	0.221 [0.147;0.382]	0.13 1 [0.094; 0.157] *
CD8+, %	10,750 [10,200;11,800]	24,250 [23,800; 24,900] *	28,500 [27,600; 30,800] * *
CD8+, 10^{9}/ l	0.449 [0.416;0.505]	0.253 [0.160; 0.335] *	0.29 2 [0.264; 0.331] *
CD4+, %	20,350 [16,700;23,400]	37,850 [33,300; 43,500] *	45,200 [42,600; 45,800] *
CD4+, 10^{9}/ l	0.812 [0.691;0.956]	0.35 9 [0.338; 0.384] *	0.44 3 [0.404; 0.533] *
B1, %	0.350 [0.200;0.400]	0.100 [0.000;0.200]	0.150 [0.100;0.300]
B1, 10^{9}/ l	0.014 [0.012;0.018]	0.001 [0.000; 0.002] *	0.00 2 [0.001; 0.003] *
In memory, %	0.300 [0.100;0.400]	0.000 [0.000; 0.000] *	0.050 [0.000; 0.100] *
In memory, 10^{9}/ l	0.013 [0.005;0.013]	0.000 [0.000; 0.000] *	0.00 1 [0.000; 0.001] *
B2, %	60,005 [53,000;63,450]	5,400 [4,420; 5,860] *	9,850 [6,400; 10,670] * *
B2, 10^{9}/ l	2,244 [2,058;2,924]	0.04 3 [0.030; 0.069] *	0.105 [0.052; 0.116] *

* significant difference from the reference indicator ($p < 0.05$)

** - significant difference from CPA group ($p < 0.05$)

However, within the same group of mice, an increase in the content of basophilic and neutrophilic cells was noted, including band, segmented, and juvenile forms of neutrophils, as presented in **Table 2**.

The changes in the myelogram are consistent with previously obtained data regarding the dynamics of peripheral blood indices after the introduction of CPA. These results confirm the development of lymphopenia caused by the suppression of lymphocyte growth in the bone marrow.

Additionally, activation of granulocyte sprouts in the bone marrow is observed, leading to a non-specific immune response to the drug. This phenomenon reflects an increase in the proportion of granulocytes and medium cells in the leukocyte formula of the blood, indicating a systemic reaction of the body to the cytotoxic effect of CPA.

Another consequence of the change is a decrease in the number of reticular cells in C57BL/6 mice after exposure to cyclophosphamide, resulting in the accumulation of mature forms of the erythroid series and their precursors. These changes indicate a shift in the hematopoietic balance toward erythropoiesis, with suppressed lymphopoietic activity in the bone marrow **(Table 2)**.

Table 2. Bone marrow myelogram parameters in C57BL/6 mice after exposure to CPA and administration of the extract from the bursa of Fabricius (x106 cells/femur)

Cell Type	Reference	CPA	CPA+bursa
Erythroblasts	0.49±0.01	0.52±0.01	0.75±0.09* #
Pronormoblast	0.49±0.02	0.54±0.02	0.83±0.03* #

Basophilic normoblasts	0.95±0.03	0.95±0.06	1.45±0.07* #
Polychromatophilic normoblasts	1.07±0.06	1.23±0.12	1.79±0.05* #
Oxyphilic normoblasts	0.72±0.09	0.81±0.09	1.25±0.05* #
Reticular cells	0.29±0.01	0.17±0.04 *	0.46±0.05* #
Normocytes	1.72±0.05	1.95±0.07 *	2.52±0.08* #
Erythroid series	5.35±0.13	6.09±0.25 *	8.68±0.12* #
Myeloblasts	0.53±0.05	0.55±0.03	0.73±0.05* #
Promyelocytes	0.52±0.02	0.59±0.01	0.82±0.02* #
Myelocytes	0.71±0.04	0.67±0.03	0.85±0.07* #
Metamyelocytes	0.82±0.02	0.63±0.05	1.32±0.07* #
Band neutrophils	1.31±0.05	1.98±0.02 *	2.28±0.12* #
Segmented neutrophils	4.09±0.22	5.03±0.12 *	6.58±0.12* #
Neutrophils young	4.98±0.13	6.17±0.07 *	7.34±0.23* #
Neutrophilic series	12.91±0.15	15.58±0.12 *	20.00±0.42* #
Basophilic series	0.45±0.03	0.83±0.01 *	0.65±0.04* #
Eosinophilic series	0.07±0.04	0.08±0.02	0.11±0.04
Monocytes	0.88±0.01	0.87±0.02	1.55±0.05* #
Macrophages	1.16±0.07	0.99±0.06	1.59±0.04* #
Monocytic series	2.03±0.09	1.87±0.05	3.12±0.09* #
Lymphoblasts	1.03±0.03	0.63±0.02 *	1.54±0.05* #
Lymphocytes	1.23±0.05	0.79±0.07 *	1.71±0.04* #
Plasma cells	0.22±0.01	0.27±0.05	0.33±0.02
Lymphoid series	2.38±0.04	1.68±0.05 *	3.57±0.07* #
Megakaryocytic series	0.04±0.03	0.05±0.03	0.05±0.02
Mitoses	0.02±0.03	0.01±0.01	0.12±0.03 * #
Total cells	23.52±0.24	27.23±0.23 *	36.85±0.79* #

* - statistically significant differences compared to the control group ($p < 0.05$);
# - significant differences relative to the indicators of the group receiving CPA ($p < 0.05$).

The likely cause of induction is the direct stimulating effect of bursal peptides, as well as an indirect effect through the activation of morphogenesis factors produced by the liver for hematopoietic cells involved in erythro- and myelopoiesis processes. This observation suggests that bone marrow progenitor cells may be in G-1 phase with a transition to the S phase of the cell cycle **(Figure 1)**.

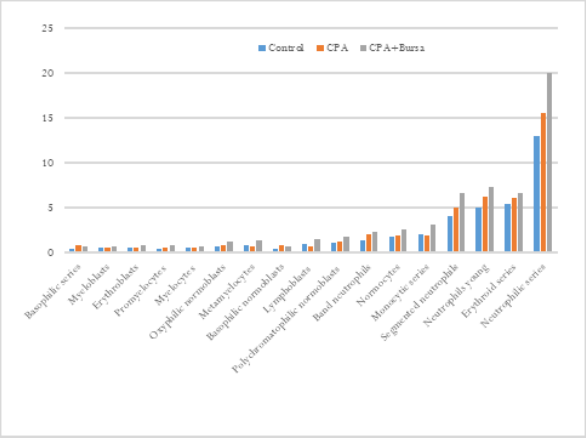

Figure 1. Bone marrow myelogram parameters in C57BL/6 mice after administration of CPA and the extract from the bursa of Fabricius (x 106 cells/femur)

The consistent number of immature erythrocyte precursors in mice after CPA administration confirmed the hematological analysis data, indicating the development of an anemic condition. This was also evidenced by a decrease in the level of young forms of erythrocytes in the bone marrow.

It is important to note that the total number of myelokaryocytes increased by 10% compared to the control group, which is associated with the rapid growth of neutrophilic cell lines. In animals with experimental immunodeficiency, the use of extract from the bursa of Fabricius led to the activation of lymphoid growth in the bone marrow. This effect was achieved by increasing the content of lymphoblasts and mature lymphocytes, as well as increasing the total number of lymphoid line cells compared to intact individuals and groups without treatment.

However, no significant lymphocyte restoration was observed in the peripheral blood. This is likely due to the absence of an antigenic stimulus necessary for the migration of lymphocytes from the bone marrow into systemic circulation. Other studies have shown that stimulation of lymphocyte production with bursal peptides becomes more pronounced only after prior sensitization of the body with viruses or other antigens. Thus, in this case, lymphoid cells increased the reserve population, which

can be activated when the antigen load increases due to viral or bacterial pathogens.

In C57BL/6 mice, treatment with the extract from the bursa of Fabricius increased the content of neutrophilic cell lines and their precursors compared to the control sequence, as well as to the model of immunodeficiency without therapy. An increase in the number of erythroid elements in all experimental groups after extract administration was also detected **(Table 2)**, indicating a multifactorial effect of the drug on hematopoietic processes.

The observed increase in the proliferation of leukocytes and erythroid precursors following the introduction of the extract from the bursa of Fabricius was evidenced by a significant increase in the total number of nuclear cells in the bone marrow, which was approximately 1.5 times higher than that in the control group. Additionally, an increase in mitotic activity was observed, indicating a higher frequency of cell divisions.

Conclusion

Thus, it has been established that the extract from the bursa of Fabricius has a pronounced immunotropic effect on the bone marrow when modeling immunodeficiencies. It stimulates the mitotic activity of cells, increases the total number of myelokaryocytes, and simultaneously activates lymphoid and erythroid sprouts. These changes were accompanied by an increase in the absolute leukocyte and granulocyte content in the peripheral blood, as well as a tendency to normalize the erythrocyte indices.

The ability of the extract to compensate for the cytostatic effect of CPA opens up prospects for further research aimed at isolating and identifying active peptides with immunostimulating activity. The obtained data allow us to consider the extract from the bursa of Fabricius as a potential basis for creating drugs intended to correct immunodeficiency processes.

Acknowledgments: The authors thank the administration of the Ural State University of Economics for the opportunity to research its basis.

Conflict of interest: None

Financial support: None

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

References

1. Kolberg NA, Mukhlynina EA, Brilliant A. Immunotropic effect of the extract of the bursa of Fabricius of broiler chickens on C57BL/6 and C57BL/10 mice with experimental immunodeficiency syndrome. AIC of Russia. 2023;30(2):275-83.
2. Dotsenko EA, Rozhdestvensky DA, Yupatov GI. Immunodeficiencies and some immunomodulatory agents. Bull Vitebsk State Med Univ. 2014;13(3):103-20.
3. Zurochka AV, Zurochka VA, Dobrynina MA, Gritsenko VA. Immunobiological properties of granulocyte-macrophage colony-stimulating factor and synthetic peptides of its active center. Med Immunol. 2021;23(5):1031-54.
4. Ismailov IZ, Zurdinov AZ, Sabirova TR. Development and use of immunomodulators at the present stage: problems and prospects. Sci J. 2017;1:11-4.
5. Kruchinin AG, Agarkova EYu. Biologically active milk peptides: a review. Food ind. 2020;12:92-6.
6. Kryachko OV. Pathogenetic aspects of bioregulation of functions in animals when using peptide bioregulators. Issues Regul Framework Vet Med. 2021;3:74-7.
7. Korzhenevsky AA, Korzhenevskaya NP. Immunotherapy at the present stage: types and tactics of application. Bull Peoples' Friendship Univ Russia. Ser: Med. 2022;26(4):404-21.
8. Zinchenko RV. Immunomodulators in the complex therapy of cancer patients (literature review). Povolzhsky Oncol Bull. 2014;1:57-64.
9. Deigin V, Linkova N, Volpina O. Advancement from small peptide pharmaceuticals to orally active piperazine-2,5-dion-based cyclopeptides. Int J Mol Sci. 2023;24(17):13534.
10. Fetse J, Kandel S, Mamani UF, Cheng K. Recent advances in the development of therapeutic peptides. Trends Pharmacol Sci. 2023;44(7):425-41.
11. Guryanova SV, Khaitov RM. Strategies for using muramyl peptides – modulators of innate immunity of bacterial origin – in medicine. Front Immunol. 2021;12:607178.
12. Lee MO, Jang HJ, Rengaraj D, Yang SY, Han JY, Lamont SJ, et al. Tissue expression and antibacterial activity of host defense peptides in chicken. BMC Vet Res. 2016;12(1):231.
13. Purohit K, Reddy N, Sunna A. Exploring the potential of bioactive peptides: from natural sources to therapeutics. Int J Mol Sci. 2024;25(3):1391.
14. Iglesias V, Bárcenas O, Pintado-Grima C, Burdukiewicz M, Ventura S. Structural information in therapeutic peptides: emerging applications in biomedicine. FEBS Open Bio. 2025;15(2):254-68.
15. Durcan L, Petri M. Immunomodulators in SLE: clinical evidence and immunologic actions. J Autoimmun. 2016;74:73-84.
16. Ahmad S, Khan TM, Ayub F, Mubarak N, Khaliel AM, Elhanish AAS, et al. Meta-analysis of urinary tract infections among patients with chronic kidney disease. Bull Pioneer Res Med Clin Sci. 2022;1(2):7-27. doi:10.51847/KZV1W3ahoN
17. Saravanakumar V, Masi C, Neme I, Arjun K, Dinakarkumar Y. Geographical comparison of phytoconstituents in Euphorbia hirta: a pilot study in Ethiopia and India. Bull

Pioneer Res Med Clin Sci. 2022;1(2):34-41. doi:10.51847/ErNYBrhrFF

18. Reshetnikov AD, Barashkova AI. The role of veterinary innovations in reindeer husbandry for climate change adaptation. Int J Vet Res Allied Sci. 2022;2(1):1-8. doi:10.51847/UlrjooXH9s
19. Fiodorova OA, Sivkova EI, Nikonov AA. Safeguarding beef cattle from gnats and gadflies in the Southern Tyumen Region. Int J Vet Res Allied Sci. 2022;2(2):8-13. doi:10.51847/iVXOeXmSNZ
20. Després L, David J, Gallet C. Advancements in identifying insect resistance to chemical control. Int J Vet Res Allied Sci. 2023;3(2):1-6. doi:10.51847/Zs6BfQoNxB
21. Kashina SV. Characteristics of the immunological properties of the drug vermin. [dissertation abstract]. Perm; 1999. 21 p.
22. Liu XD, Qian Y, Jung YS, Chen PY. Isolation and immunomodulatory activity of bursal peptide, a novel bursal peptide from the chicken bursa of Fabricius. J Vet Sci. 2015;16(4):501-7.
23. Butter C, Staines K, van Hateren A, Davison TF, Kaufman J. The peptide motif of the single dominantly expressed class I molecule of the chicken MHC can explain the response to a molecularly defined vaccine of infectious bursal disease virus (IBDV). Immunogenetics. 2013;65(8):609-18.
24. Hussain A, Shadma W, Maksood A, Ansari SH. Protective effects of Picrorhiza kurroa on cyclophosphamide-induced immunosuppression in mice. Pharmacogn Res. 2013;5(1):30-5.
25. Tuano KS, Seth N, Chinen J. Secondary immunodeficiencies: an overview. Ann Allergy Asthma Immunol. 2021;127(6):617-26.
26. Eldeniz FC, Gul Y, Yorulmaz A, Guner SN, Keles S, Reisli I. Evaluation of the 10 warning signs in primary and secondary immunodeficient patients. Front Immunol. 2022;13:900055.
27. Krasnova OA, Minaychev VV, Akatov VS, Fadeev RS, Senotov AS, Kobyakova MI, et al. Improving the stability and effectiveness of immunotropic squalene nanoemulsion by adding turpentine oil. Biomolecules. 2023;13(7):1053.
28. Park JE, Kim DH. Advanced immunomodulatory biomaterials for therapeutic applications. Adv Healthc Mater. 2025;14(5):2304496.
29. Rao Muvva J, Ahmed S, Rekha RS, Kalsum S, Groenheit R, Schön T, et al. Immunomodulatory agents combat multidrug-resistant tuberculosis by improving antimicrobial immunity. J Infect Dis. 2021;224(2):332-44.
30. Fraser A, Poole P. Immunostimulants versus placebo for preventing exacerbations in adults with chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2022;11(11):013343.
31. Ghadiri N, Javidan M, Sheikhi S, Taştan Ö, Parodi A, Liao Z, et al. Bioactive peptides: an alternative therapeutic approach for cancer management. Front Immunol. 2024;15:1310443.
32. Mubayrik AFB, Al-Turck K, Aldaijy RE, Alshehri RM, Bedaiwi AA, Alofisan AO, et al. Understanding the dangers of sun exposure and the importance of photoprotection practices in public awareness. Turk J Public Health Dent. 2022;2(1):1-8. doi:10.51847/32g0nPWudc
33. Kwatra D, Venugopal A, Anant S. Studying the efficacy of tolmetin radiosensitizing effect in radiotherapy treatment on human clonal cancer cells. Bull Pioneer Res Med Clin Sci. 2024;3(2):22-8. doi:10.51847/Uuhjk0fMC8
34. Lobach EY, Ageenko DD, Poznyakovsky VM, Pastushkova EV, Tokhiriyon B, Saulich NA. Exploring the role of Pantohematogen-S in deer antler products: characterization and authenticity verification. Int J Vet Res Allied Sci. 2023;3(1):26-31. doi:10.51847/FHHvX2ADoM
35. Perrine KTA, Moïse AAA, Claver KA, Tenon C, Brice BJ, Herve KK, et al. Assessment of the impact of Ocimum gratissimum L. (Lamiaceae) extracts on Nasutitermes termites, cocoa pests in Côte d'Ivoire. Entomol Lett. 2023;3(1):7-17. doi:10.51847/gYbXNUKPX6
36. Canassa VF, Baldin ELL. Impact of sorghum genotypes on nymphal development and reproduction of Melanaphis sacchari. Entomol Lett. 2022;2(2):10-8. doi:10.51847/QgKDLAX7eV
37. Shen F, Bao L. Studying the effects of music on the time to gain independent oral feeding in premature infants. J Integr Nurs Palliat Care. 2025;6:1-6. doi:10.51847/xBTC4CiH10
38. İlhan N, Telli S, Temel B, Aştı T. Investigating the sexual satisfaction mediating role in the relationship between health literacy and self-care of men with diabetes and women's marital satisfaction. J Integr Nurs Palliat Care. 2022;3:19-25. doi:10.51847/sFjL3OLpqg
39. Ağaçkıran M, Avşaroğullar OL, Şenol V. Examining the frequency of violence versus nurses and the factors affecting it in hospitals. J Integr Nurs Palliat Care. 2023;4:11-6.
40. Karaulov AV. Immunomodulators: from the past to the future. Eff Pharmacother. 2013;27:4-5.
41. Mandro NN, Litvinova ZA, Pashchenko YuO. The effect of a preparation from small cattle bone marrow cells on blood parameters of laboratory animals. Bull Altai State Agrarian Univ. 2023;2(220):77-81.
42. Otani IM, Lehman HK, Jongco AM, Tsao LR, Azar AE, Tarrant TK, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: a work group report of the AAAAI primary immunodeficiency and altered immune response committees. J Allergy Clin Immunol. 2022;149(5):1525-60.
43. Davydova VN, Sorokina IV, Volod'ko AV, Sokolova EV, Borisova MS, Yermak IM. The comparative immunotropic activity of carrageenan, chitosan, and their complexes. Mar Drugs. 2020;18(9):458.
44. Enwa FO, Jewo AO, Oyubu LO, Adjekuko CO, Effiong V. Incidence of vaginal infections among females of different

age categories in Delta State, Nigeria. Bull Pioneer Res Med Clin Sci. 2022;1(1):18-23. doi:10.51847/C1oahQ115n

45. Dhanasekar P, Rajayyan JS, Veerabadiran Y, Kumar KS, Kumar KS, Chinnadurai N. Evaluation of alum and purification process of water by coagulation method. Bull Pioneer Res Med Clin Sci. 2022;1(2):1-6. doi:10.51847/R8GyfOmMDh
46. Uneno Y, Morita T, Watanabe Y, Okamoto S, Kawashima N, Muto M. Supportive care requirements of elderly patients with cancer refer to Seirei Mikatahara General Hospital in 2023. J Integr Nurs Palliat Care. 2024;5:42-7. doi:10.51847/lmadKZ2u1J
47. Cirik VA, Aksoy B, Bulut E. Studying the relationship between the attitude towards gender roles of parents and the quality of parent-child relationship in nurses. J Integr Nurs Palliat Care. 2023;4:30-7. doi:10.51847/90pkztCQgl
48. Graefen B, Hasanli S, Fazal N. Behind the white coat: the prevalence of burnout among obstetrics and gynecology residents in Azerbaijan. Bull Pioneer Res Med Clin Sci. 2023;2(2):1-7. doi:10.51847/vIIhM1UG2l