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Research Article

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Cytoprotective and immunostimulatory properties of *Stachys sieboldii* and *Stevia rebaudiana* under metabolic stress in rats

This study evaluated the protective effects of *Stachys sieboldii* and *Stevia rebaudiana* extracts on bone marrow and spleen cells in rats subjected to a high-fat, high-sucrose (HFHS) diet. Prepubertal Wistar rats were randomly assigned to four groups (control, HFHS, HFHS+*Stachys*, HFHS+*Stevia*) and maintained for 30 days. Spleen and bone-marrow cellularity and cell viability were quantified. The HFHS diet increased the proportion of non-viable cells and reduced nucleated-cell counts in both organs. *Stachys* primarily enhanced splenic immune-cell proliferation (higher nucleated-cell concentration), whereas *Stevia* produced a stronger cytoprotective response, reducing the fraction of dead cells in bone marrow. Taken together, these findings suggest complementary actions: *Stachys* acts as a pro-proliferative modulator of splenic immune cells, while *Stevia* protects hematopoietic cells from HFHS-induced damage. These results highlight the potential of these plant extracts as dietary components for supporting immune and hematopoietic function and provide a basis for their further investigation in preventive and immunomodulatory applications.

Keywords: immunity, bone marrow, spleen, high-fat diet, HFHS, *Stevia rebaudiana, Stachys sieboldii.*

Introduction

In recent decades, dietary patterns worldwide have undergone significant changes due to globalization, industrialization, and urbanization [1]. Traditional diets, rich in natural foods, are gradually being replaced by high-fat, high-carbohydrate diets, which have become readily accessible due to the expansion of the food industry [2].

Modern diets in both developed and developing countries differ significantly, yet share a common feature: increased consumption of refined carbohydrates and saturated fats. In Western countries, such as the United States, Canada, and much of Europe, diets are characterized by high intake of processed foods, sugary beverages, fast food, and sweets [3; 4; 5]. In developing nations, including China, India, and countries in Africa, traditional diets rich in vegetables, legumes, and whole grains are also giving way to more modern "Western" diets. This shift is linked to urbanization and globalization, which make Western foods more available and appealing [6; 7]. Despite differences in traditional diets, the outcomes of this dietary shift are similar: sharp increases in obesity, cardiovascular disease, and metabolic disorders are observed in both developed and developing countries [8; 9].

A high-fat, high-carbohydrate diet not only disrupts metabolic processes but also significantly impacts the immune and hematopoietic systems, making this issue relevant for research and prevention [10; 11]. Biologically active supplements (BAS) can notably influence the spleen and bone marrow, especially through their antioxidant and anti-inflammatory properties, which may support normal immune and hematopoietic functions. For instance, quercetin, a natural flavonoid with powerful antioxidant and anti-inflammatory properties [12], has been shown in animal studies to increase lymphocyte and macrophage counts in the spleen [13]. In one study on rats undergoing chemotherapy, quercetin supplementation helped restore spleen function by increasing the concentration of nucleated cells, such as lymphocytes, by reducing oxidative stress and inflammation in spleen tissue [14].

Echinacea, widely used as an immune-stimulating agent, has shown beneficial effects on hematopoiesis in bone marrow [15]. Studies on mice revealed that echinacea intake increases the number of nucleated cells, such as macrophages and neutrophils, in the bone marrow [16]. This effect is associated with activation of stem cell proliferation and accelerated tissue repair processes after exposure to inflammatory agents or infections. An increase in the total cellular mass of the spleen and bone marrow was also observed, indicating a recovery of immune function [17].

Resveratrol, known for its antioxidant properties, positively affects bone marrow hematopoiesis, particularly under conditions of chronic inflammation [18]. In a study on mice with induced inflammation, resveratrol supplementation helped reduce bone marrow cell damage, maintaining normal stem cell proliferation [19]. In the spleen, an increase in lymphocyte counts and improved function were observed, attributed to resveratrol's immunomodulatory effects [20]. This highlights resveratrol's role in supporting normal hematopoietic processes under stress or inflammation.

Currently, research continues into the properties and medicinal potential of well-known BAS, such as *Stevia rebaudiana* and *Stachys sieboldii*.

Stachys (*Stachys sieboldii*) is a plant used in traditional medicine due to its rich content of bioactive compounds, such as phenolic compounds, flavonoids, and essential oils [21]. These substances have antioxidant, anti-inflammatory, and immunostimulatory properties. *Stachys* extracts are used for treating inflammation, enhancing immune function, and accelerating wound healing [22]. *Stachys* tubers, which have a nutty flavor, are rich in nutrients and are consumed as a dietary product, particularly beneficial for individuals with diabetes due to their blood sugar-regulating properties [21]. In modern medicine, *Stachys* is being investigated as an agent for enhancing immune response and reducing inflammation.

Stevia (*Stevia rebaudiana*) is well-known for its natural sweeteners, stevioside and rebaudioside, which are calorie-free and highly sweet-tasting [23]. Stevia also contains flavonoids and antioxidants that have anti-inflammatory and antioxidant effects. Stevia extracts are used to reduce blood sugar levels, making it popular among individuals with diabetes and those who monitor their weight. In cooking, stevia leaves are used as a natural sugar substitute in beverages, baked goods, and other dishes [24]. The medicinal properties of stevia include blood glucose regulation, improvement of the body's antioxidant status, and reduction of cardiovascular disease risk [25].

The aim of this study is to evaluate the effects of adding *Stachys sieboldii* and *Stevia rebaudiana* extracts to a high-fat, high-sucrose diet on the cellularity and viability of spleen and bone marrow cells in rats, as well as to determine their potential as cytoprotective and immunostimulatory agents.

The novelty of this work lies in the fact that, for the first time, a study is conducted on how adding plant-based products derived from *Stachys sieboldii* and *Stevia rebaudiana* to a high-fat, high-sugar diet affects the cellularity and integrity of spleen and bone marrow cells in rats under metabolic stress. Additionally, a direct comparative analysis of the cytoprotective and immunostimulatory properties of *Stachys sieboldii* and *Stevia rebaudiana* is carried out—an approach not previously presented in the scientific literature.

Experimental

Material preparation. In this experiment, a choice was made between two cultivated varieties of *Stachys sieboldii*: "Bochonok" and "Rakushka", both of which are successfully grown, including in Central Kazakhstan (2023–2025), due to their good adaptation to local conditions and status as garden crops. However, the "Rakushka" variety was selected for this study due to its specific biochemical composition. It contains a higher concentration of antioxidants, including phenolic compounds and flavonoids, as well as a significant amount of ascorbic acid and bioactive glycosides [26].

For the purpose of this study, the "Rakushka" variety was cultivated in experimental introduction fields at the Phytochemistry Holding research facility in Karaganda (Kazakhstan). After reaching maturity, the tubers were harvested and processed at the same facility. The roots were thoroughly washed three times with tap water to remove any adhering sand and dust. They were then lyophilized for 72 hours to preserve their bioactive compounds and ground into a fine powder. The resulting *Stachys sieboldii* root powder was stored at -70 °C until it was incorporated into the experimental diets for rodents.

The powdered organic extract of *Stevia rebaudiana* leaves was purchased online (SweetLeaf, Gilbert, Arizona, USA). The dosage was calculated based on the allowable daily dose recommended by the United States Food and Drug Administration (FDA) (5 mg/kg) [27]. These doses were determined as follows: the allowable daily dose was multiplied by the average weight of the rats and then divided by the group's average daily fluid intake. Dosages were recalculated weekly to account for weight gain and changes in fluid intake.

Animal experiments and diets. The experimental subjects consisted of 40 juvenile Wistar rats. The average body weight of the animals at the beginning of the experiment was 50–70 g. Juvenile rats were selected for the experiment at 21 days of age. The animals were housed in the vivarium of Karaganda Medical University under controlled conditions at 18±2 °C, 55 % ± 5 % humidity, and a 12-hour light-dark cycle (8:00–20:00). Throughout the experimental period, the animals had free access to food and water. The rats were randomly assigned to one of four experimental groups (n = 10 per group):

- Group 1: 10 juvenile males on a standard, balanced vivarium diet.
- Group 2: 10 juvenile males on a daily high-fat, high-sucrose diet (HFHS).
- Group 3: 10 juvenile males on a daily high-fat, high-sucrose diet supplemented with *Stachys sieboldii* (HFHS + Stachys).
- Group 4: 10 juvenile males on a daily high-fat, high-sucrose diet supplemented with *Stevia rebaudiana* (HFHS + Stevia) (Table 1).

Table 1

Composition of the experimental diet

Components (g/kg)	**1 group Intact**	**2 group HFHS**	**3 group HFHS + Stachys**	**4 group HFHS + Stevia**
Corn	200	80	80	80
Rice	200	200	200	200
Bone meal	120	120	120	120
Sucrose	—	100	100	100
Soy oil	75	—	—	—
Lard	—	200	200	200
Gluten	200	200	200	200
Salt	3.5	3.5	3.5	3.5
Mineral mix	35	35	35	35
Vitamin mix	16.5	16.5	16.5	16.5
Inert material	150	45	45	45
Total (g)	1000	1000	1000	1000
Nutrient composition (%)				
Protein	24.8	19.2	19.2	19.2
Carbohydrate	49.6	43.4	43.4	43.4
Lipids	25.6	37.4	37.4	37.4
Stachys sieboldii root powder	—	—	5	—
Stevia rebaudiana leaf powder	—	—	—	5
Energy density (kcal/g)	3.55	4.49	4.49	4.49

In this diet, the total carbohydrate content in the HFHS groups appears lower compared to the control group. This is explained by the substantial increase in dietary fat (lard) in the HFHS diet, which altered the overall macronutrient distribution while maintaining a total feed mass of 1000 g/kg. Additionally, this is due to the replacement of corn, which was reduced from 200 g/kg in the control group to 80 g/kg in the HFHS groups (corn contains both digestible carbohydrates and dietary fiber), with sucrose, which is fully digestible. When adjusted for fiber content, the actual intake of digestible carbohydrates is higher in the HFHS groups. Since sucrose is completely digestible and does not contribute to dietary fiber, the shift from complex carbohydrates to simple sugars resulted in a decrease in total carbohydrate mass despite the increased sugar content.

The experiment lasted for 30 days. The study was conducted in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg 1986), OECD GLP guidelines, EAEU Good Laboratory Practice Regulations No. 81, and the Order of the Minister of Health of the Republic of Kazakhstan No. MoH RK-151/2020, dated October 23, 2020, titled “On Approval of the Regulation on the Central Commission on Bioethics”. The study was approved by the decision of the Bioethics Committee of “Karaganda Medical University” on 17.06.2021, protocol No.165.

Determination of cellularity and viability of bone marrow and spleen. To assess the cellularity of bone marrow and spleen, the spleen and femur were extracted from each animal, washed in physiological saline, and blotted dry on filter paper. Using a homogenizer, cell suspensions from each organ of individual rats were prepared in Hank’s solution. The spleen and bone marrow suspensions were filtered through a nylon mesh to remove stromal elements, and the concentration of nucleated cells (NC) was counted using a standard method with a Goryaev chamber.

To identify non-viable cells, a 0.4 % trypan blue (TB) solution was used as a stain. The TB solution was prepared according to the manufacturer’s instructions for the cell counter: a weighed portion of dry TB ($C_{34}H_{28}N_6O_{14}S_4$; Mikroskopie, Germany) was added to a solution of 0.81 % sodium chloride (NaCl; Sigma-Aldrich, USA) and 0.06 % potassium phosphate trihydrate ($K_2HPO_4{\cdot}3H_2O$; Merck, Germany) in distilled water, mixed until dissolved at room temperature, filtered through a 0.22 μm filter, and stored in a dark glass container at 4 °C. For viable cell counts, the cell suspension was mixed with TB solution at a 10:1 ratio, and a drop of the suspension was placed in the chamber. Using a microscope, stained and unstained cells were counted. The cell concentration in 1 ml (C) was determined using the formula: $C = kn \times 10^4$, where n is the number of cells counted in the Goryaev chamber, and k is the dilution factor (for staining with 0.4 % TB at a 10:1 ratio, $k = 1.1$).

Viability (V) of the cell population was calculated using the formula and expressed as a percentage: $V = (1 - m/N) \times 100$, where m is the number of stained cells, and N is the total number of cells [28].

Statistical methods. One-way ANOVA was used for statistical data analysis to identify differences between groups. Tukey’s multiple comparison test was applied for pairwise comparisons. Results were considered statistically significant at $p < 0.05$. All analyses were performed using GraphPad Prism 8 software.

Results

*Concentration of nucleated cells in the spleen of immature rats***.** The data obtained showed that the HFHS diet led to a 13.49 % increase in the concentration of nucleated cells in the spleen ($p < 0.0074$) compared to the control group. This may indicate a response to metabolic stress and inflammation (Fig. 1).

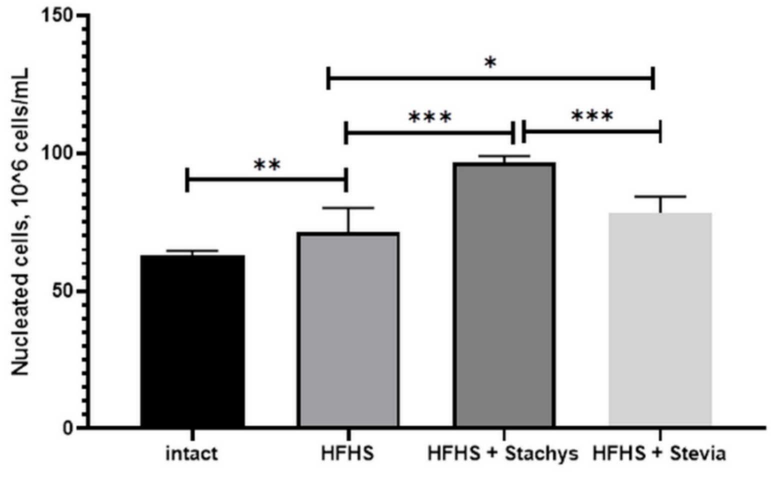

Figure 1. Concentration of nucleated cells in the spleen of immature rats in the experiment

The addition of *Stachys* to the HFHS diet resulted in a 35.55 % increase ($p < 0.0001$) in the number of nucleated cells in the spleen compared to the HFHS group, indicating a significant stimulation of immune cell proliferation. *Stevia* increased spleen nucleated cell concentration by 10.06 % ($p < 0.0289$) compared to the HFHS group, which also indicates a positive effect, though less pronounced than that of *Stachys* (Fig. 1).

*Cell viability in the spleen of immature rats***.** The HFHS diet led to an 89.23 % increase in the percentage of dead cells compared to the control ($p < 0.0001$), indicating a negative impact on spleen immune cells (Fig. 2).

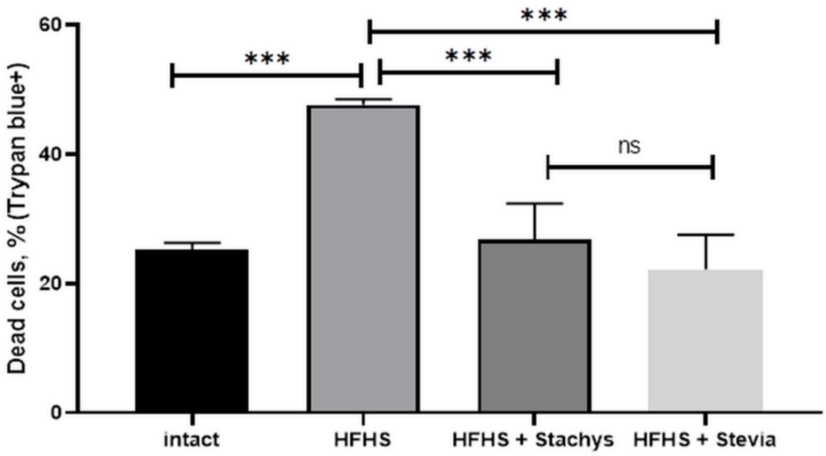

Figure 2. Cell viability indicators in the spleen of immature rats in the experiment

The addition of *Stachys* to the diet reduced the percentage of dead cells by 43.90 % ($p < 0.0001$) compared to the HFHS group, thus improving cell viability. *Stevia* showed an even more pronounced effect, reducing the percentage of dead cells by 53.45 % ($p < 0.0001$) relative to HFHS, indicating a stronger cytoprotective effect (Fig. 2).

Concentration of nucleated cells in the bone marrow of immature rats. In examining the concentration of nucleated cells in the bone marrow, it was found that the HFHS diet reduced the number of nucleated cells in the bone marrow by 34.38 % ($p < 0.0001$) compared to the control, indicating suppression of hematopoiesis (Fig. 3).

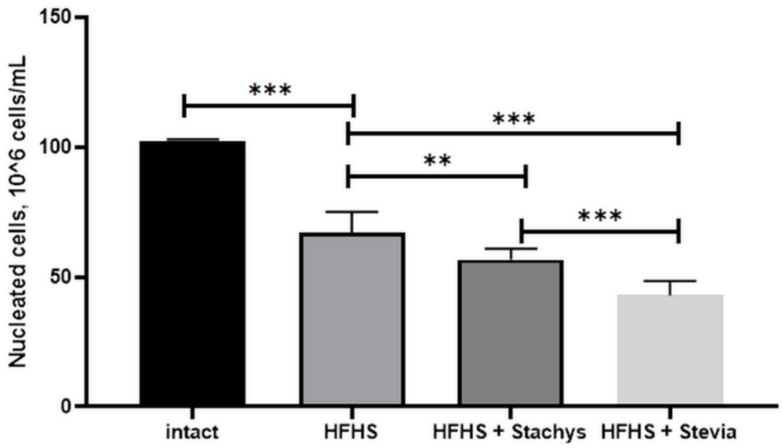

Figure 3. Concentration of nucleated cells in the bone marrow of immature rats in the experiment

Stachys, when added to the diet, further reduced the nucleated cells in the bone marrow by 15.55 % ($p < 0.0004$) compared to the HFHS group, which may indicate a negative impact on bone marrow. *Stevia* also decreased the number of nucleated cells in the bone marrow by 36.13 % ($p < 0.0001$) relative to HFHS, indicating a more significant suppression than observed with *Stachys* (Fig. 3).

Bone marrow cell viability in immature rats. The HFHS diet increased the percentage of dead cells by 4.6 times ($p < 0.0001$) compared to the control, showing a strong negative effect on bone marrow cells (Fig. 4).

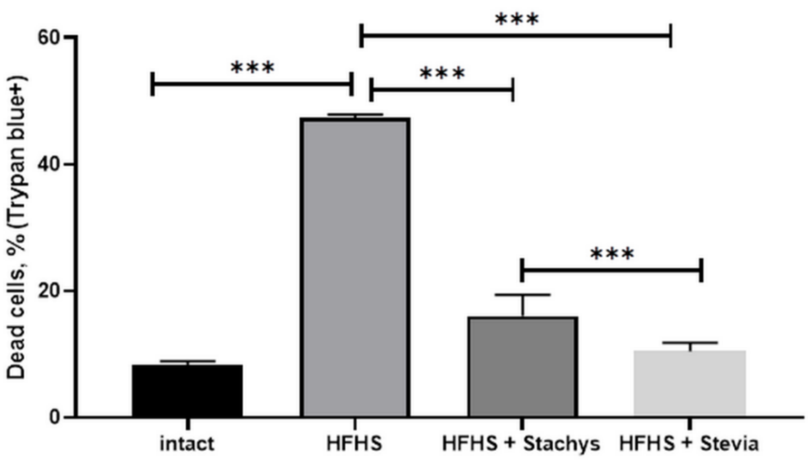

Figure 4. Viability indicators of bone marrow cells in immature rats in the experiment

Adding *Stachys* to the diet reduced the percentage of dead cells by 66.09 % ($p < 0.0001$) relative to HFHS, indicating a substantial protective effect. *Stevia* provided an even more pronounced reduction of 77.90 % ($p < 0.0001$) relative to HFHS, indicating stronger cytoprotective action in bone marrow (Fig. 4).

Discussions

Adding plant products to the HFHS diet differentially reshaped hematopoietic outcomes. Relative to HFHS alone, *Stevia* reduced the proportion of trypan-blue–positive cells by 53.45 % in the spleen and by 77.90 % in the bone marrow, indicating robust preservation of cell viability. HFHS by itself increased cell death and lowered nucleated-cell concentration in both tissues, consistent with diet-induced metabolic stress and inflammation. The pattern observed here is coherent with published evidence describing anti-inflammatory and anti-apoptotic actions of *Stevia*, including down-regulation of NF-κB/MAPK signaling [29]. Cai et al. (2023) noted *Stevia*'s ability to inhibit NF-κB and MAPK signaling pathways, associated with inflammation and apoptosis, leading to reduced extracellular matrix degradation and cell apoptosis [30].

Additionally, Gupta et al. (2021) demonstrated *Stevia*'s antioxidant and antidiabetic properties in rats with alloxan-induced diabetes. Oral administration of steviosides for 21 days normalized blood glucose levels, restored antioxidant potential, and improved lipid profiles. This indicates *Stevia*'s potential to improve metabolic status and reduce oxidative stress, supporting our observations of its cytoprotective effect [31].

Regarding the concentration of nucleated cells, *Stevia* increased their count in the spleen by 10.06 % compared to the HFHS group. Although this effect was less pronounced than that of *Stachys*, it still indicates a positive influence of *Stevia* on the immune system. Moubder et al. (2024) in their study noted that *Stevia* leaf extract increases levels of pro-inflammatory cytokine IL-1β and immunoglobulin A (IgA), indicating its immunomodulatory action [32].

On the other hand, *Stachys* showed a more pronounced effect on the proliferation of immune cells. In our study, adding *Stachys* to the HFHS diet increased the concentration of nucleated cells in the spleen by 35.55 % compared to the HFHS group. This may indicate stimulation of immune function and enhancement of immune response. However, in the bone marrow, *Stachys* further decreased the number of nucleated cells by 15.55 % compared to the HFHS group, suggesting a complex impact on hematopoiesis.

Studies by Kim et al. (2024) revealed that extracts of *Stachys affinis* possess antioxidant and anti-inflammatory properties confirmed by molecular docking. The phenolic compounds in the extract demonstrated the ability to interact with cyclooxygenase-2 (COX-2), reducing inflammation [33]. Slimani et al. (2023) found that *Stachys circinata* extract increases levels of antioxidant enzymes and exhibits cytotoxic effects on cancer cells, indicating its antiproliferative properties [34].

In terms of bone marrow cell viability, *Stachys* reduced the percentage of dead cells by 66.09 % relative to the HFHS group. Although this effect was less pronounced than that of *Stevia*, it still indicates a significant protective effect. Bayat et al. (2020) showed that *Stevia* increases the expression of antioxidant genes and improves kidney function in diabetic rats, which is consistent with our observation of its stronger cytoprotective action [35].

In summary, our data and findings from other studies emphasize the differences in the mechanisms of action of *Stevia* and *Stachys*. *Stevia rebaudiana* possesses strong cytoprotective effects, protecting cells from oxidative stress and apoptosis. This may be due to its ability to inhibit pro-inflammatory signaling pathways and increase antioxidant enzyme activity. *Stachys sieboldii*, on the other hand, stimulates immune cell proliferation, likely by influencing redox balance and modulating signaling pathways responsible for cell proliferation.

It is important to note that both plants exhibit protective properties against the negative effects of an HFHS diet, but with different emphases. This opens up the possibility for their combined use to achieve a more comprehensive therapeutic effect. For example, combining the cytoprotective effect of *Stevia* with the immunostimulatory effect of *Stachys* could provide more effective protection of the immune system and hematopoiesis from metabolic stress.

Conclusion

Metabolic disorders caused by unbalanced diets require an integrated approach to prevention and treatment. Energy-dense, unbalanced diets impair immune and hematopoietic compartments; prevention should therefore address both survival and renewal of cells. In our model, *Stevia* was superior for maintaining viability in both spleen and (particularly) bone marrow, whereas *Stachys* more effectively expanded the splenic pool of nucleated cells, consistent with immune-cell proliferation. Selection can thus be purpose-driven: *Stevia* when limiting cell death is the primary goal, and *Stachys* when the aim is to increase immune-cell numbers. A combined approach may be reasonable but warrants additional work on dosing, safety, and interactions. By delineating these complementary profiles, the study provides a basis for developing nutritional adjuncts and phytotherapeutic candidates to support hematopoiesis and immune function.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Pozdnyakova Ye.V.** — conceptualization, methodology, supervision, writing — original draft, writing — review & editing; **Murzatayeva A.M.** — investigation, data curation, formal analysis, visualization, writing — review & editing; **Sailau A.S.** — investigation, data curation, formal analysis, visualization, writing — original draft.

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Егеуқұйрықтардағы күйзеліс метаболизмі кезіндегі *Stachys sieboldii* және *Stevia rebaudiana* өсімдіктерінің цитопротекторлық және иммунитет стимулдеуші қасиеттері

Зерттеудің мақсаты майлар мен көмірсуларға бай диетамен (HFHS) тамақтандырылған егеуқұйрықтардағы *Stachys sieboldii* және *Stevia rebaudiana* сығындыларының сүйек кемігі мен көкбауыр жасушаларына қорғаныш әсерін бағалау. Зерттеудің негізгі бағыты осы өсімдіктердің цитопротекторлық және иммунитет стимулдеуші қасиеттерін зерттеу. Жұмыстың әдістемесі төрт топқа бөлінген, яғни жыныстық жетілмеген (өсімтал) Wistar егеуқұйрықтарына эксперименттер жүргізуді қамтыды. Атап айтсақ: бақылау тобы, HFHS тобы, *Stachys sieboldii* қосылған HFHS тобы және *Stevia rebaudiana* қосылған HFHS тобы. Көкбауыр мен сүйек кемігі жасушаларының жасушалық қасиеті мен тіршілік қабілеті 30 күн бойы бағаланды. Нәтижелер бойынша HFHS диета өлі жасушалардың көбеюіне және көкбауыр мен сүйек кемігіндегі ядросы бар жасушалардың концентрациясының төмендеуіне себеп болғанын көрсетті. *Stachys sieboldii* көкбауырдағы иммундық жасушалардың пролиферациясын айтарлықтай ынталандырып, ядросы бар жасушалардың концентрациясын арттырды, ал *Stevia rebaudiana* сүйек кемігіндегі өлі жасушалардың пайызын төмендете отырып, айқынырақ цитопротекторлық әсер көрсетті. Бұл зерттеудің құндылығы *Stachys sieboldii* және *Stevia rebaudiana* сығындыларының гемопоэтикалық жүйеге әртүрлі әсері және осы сығындыларды профилактикалық және иммундық қолдауға арналған қолданбаларда пайдалану мүмкіндігін ашады. Нәтижелердің практикалық маңыздылығы бұл өсімдіктерді биологиялық активті қоспалар құрамында, қантүзу және иммундық жүйелердің қалпын жақсарту үшін қолдануға болады.

Кілт сөздер: иммунитет, сүйек кемігі, көкбауыр, майға бай диета, HFHS, *Stevia rebaudiana, Stachys sieboldii*

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Цитопротекторные и иммуностимулирующие свойства *Stachys sieboldii* и *Stevia rebaudiana* в условиях метаболического стресса у крыс

Цель данного исследования — оценить протективные эффекты экстрактов *Stachys sieboldii* и *Stevia rebaudiana* на клетки костного мозга и селезёнки у крыс, получавших диету с высоким содержанием жиров и сахаров (HFHS). Мы проверили, способны ли экстракты *Stachys sieboldii* и *Stevia rebaudiana* противодействовать повреждениям, вызываемым диетой HFHS. Неполовозрелых крыс линии Wistar рандомизировали на четыре группы (контроль, HFHS, HFHS+*Stachys*, HFHS+*Stevia*) и содержали в течение 30 суток. Количественно оценивали клеточность селезёнки и костного мозга, а также жизнеспособность клеток. Диета HFHS увеличивала долю нежизнеспособных клеток и снижала концентрацию ядросодержащих клеток в обоих органах. *Stachys* главным образом усиливал пролиферацию иммунных клеток селезёнки (повышал концентрацию ядросодержащих клеток), тогда как *Stevia* вызывала более выраженный цитопротекторный ответ, уменьшая долю погибших клеток в костном мозге. В совокупности данные указывают на комплементарные действия — *Stachys* как пропролиферативный модулятор селезёнки и *Stevia* как протектор клеток кроветворной системы, что обосновывает целесообразность их рассмотрения в рамках стратегий питания для сохранения функций иммунной системы и кроветворения. Значимость данного исследования заключается в выявлении различающихся эффектов экстрактов *Stachys sieboldii* и *Stevia rebaudiana* на гемопоэтическую систему, что открывает потенциал их использования в профилактических и иммуноподдерживающих приложениях. Практическая ценность результатов состоит в возможности включения этих растений в состав диетических добавок для улучшения функции иммунной системы и кроветворения.

Ключевые слова: иммунитет, костный мозг, селезенка, высокожировая диета, HFHS, *Stevia rebaudiana, Stachys sieboldii*

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