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A.K. Shokan[1,2*], D.M. Yergozova[1,2], T.N. Kobylina[1,2], N.O. Kudrina[1,2], Yu.A.Litvinenko[1,2] G.A. Seitimova[1,2], T.E. Kulmanov[1], N.V. Terletskaya[1,2], I.M. Zharkova[1]

[1]Al-Farabi Kazakh National University, Almaty, Kazakhstan
[2]Institute of Genetic and Physiology, Almaty, Kazakhstan
*e-mail: aksholpan.shokan@gmail.com
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Effect of the complex extract from *Rumex* plants on quantitative parameters of blood cells and bone marrow in *vivo*

Abstract. Assessment of the composition of peripheral blood cells and red bone marrow in preclinical studies is a key component of program for analysis of biologically active compounds obtained from the plant materials. Current study concerns effect of the complex extract from *Rumex* plants *(R. confertus, R. tianschanicus, R. thyrsiflorus*) on parameters of blood cells and bone marrow of laboratory animals. During the study, data were obtained on the effect of the extract on hematopoiesis when administered at 100 mg/kg of animal weight. The results obtained show that application of the extract is accompanied by a statistically significant increase in the number of neutrophil precursors, such as myeloblasts and band neutrophils ($p \leq 0.05$). According to our results the extract we obtained from *Rumex* plants does not cause inhibition of early bone marrow precursors and is safe and non-toxic.
Key words: *Rumex*, extract, peripheral blood cells, red bone marrow, hematopoiesis.

Introduction

One of the crucial elements during the of assessment anticancer, anticonvulsant, antimicrobial, and anti-inflammatory medications is examination of the red bone marrow (RBM), which stands as a crucial element in evaluating a potential drug in preclinical studies. This becomes particularly pertinent when [1]. Should a drug under scrutiny possess a high likelihood of impacting RBM, it becomes imperative to establish a procedure for bone marrow extraction to compute the myelogram, alongside ensuring the availability of a specialist capable of conducting such analysis. In cases where the investigated drug is entirely novel or its effects on RBM remain untested, and significant alterations in peripheral blood counts are detected, the decision to delve into RBM studies should precede the final phase of the investigation [2].

Use of medicinal plants and their substances is not only a growing global trend [3-11]. Our studies show that biologically active compounds (BAC) of the *Rumex* genus have wound-healing properties and a chemical structure comparable to drugs for the treatment of gastric reflux [12]. In Kazakhstani Tien Shan, a wild variety of *Rumex (R.) tianschanicus* grows – one of the industrial crops offered for harvesting [10]. A study of the composition of *R. tianschanicus* showed the presence of flavonoids, which are renowned for their anti-inflammatory effect, in the leaves, roots and stems of the aforementioned plants [14]. In addition, the plant contains anthracene derivatives, which are reported to have a protective effect on the stomach. Furthermore, components like tannins, naphthols, coumarin and polysaccharides were also found in the plants [15].

To evaluate diseases, blood and bone marrow characteristics are often examined. The research [16] advises the use of the bone marrow cytology and preclinical toxicity studies as the basis for determining the effects of test materials on the hematological system. In some studies, the etiology of hematological changes is determined by analyzing indicators of total lymphocytes, granulocytes and hemoglobin. Mohamed et al. [17] illustrated the changes that occur with acetylsalicylic acid treatment, including noteworthy neutropenia, lymphocytopenia and eosinophilia, while basophils and monocytes are intermediate. Rats with inflammation tend to have more white blood cells overall [18]. According to

the studies [19], some animals may have delayed erythropoiesis and suppressed myelopoiesis, which may lead to a decrease in peripheral red blood cells and granulocytes.

Materials and methods

Experimental animals. Animals used in this experiment were thirty white mongrel laboratory rats of both sex of three months' age, weight 180-220 g. Rats were acquired from the biological clinic of Al-Farabi Kazakh National University. The lab rats were kept in cages made of wire mesh, given a vitamin-enriched and well-balanced meal diet and unlimited access to water. Lab rats were divided into three groups, each consisting of 10 rats. Order No. RK DSM-255/2020 by the Minister of Health Care, Republic of Kazakhstan from December 11, 2020 established the guiding principles for animal research. All preclinical animal experiments were conducted with the approval of the ethical commission of the Institute of Genetics and Physiology (protocol No. 07-05/68 from June 17, 2020). In addition, throughout the course of the study, the behavior and health of the experimental animals were observed and evaluated to those of the control animals. The regional ethical commission gave its approval for application of animals in this experiment as part of a Program-Target Financing "Adoption of innovative genomic technologies for defending organisms from mutagenic effects, increasing the productivity of natural resources, and improving the quality of life of the population."

Collection of raw materials. Taking into account the data obtained on the area of germination in the territories of our mountains, it can be assumed that the species under study feels good in such conditions. This is an indicator that it is not for nothing that this species is medicinal and grows in mountainous areas and we collected it. The place of growth of this species where we collected it (Figure 1).

Figure 1 – Scheme map with marks of plants collection

Plant materials were collected in the large Almaty gorge (Almaty region, Kazakhstan) at coordinates N 43° 03′ 27, E 76° 58′ 17, an altitude of 2511 m above the sea level.

Phytochemical analysis. Qualitative reactions with minor modifications were carried out for the presence of the main groups of biologically active compounds in the extract from *Rumex* plants, using standard methods. Phytochemical analysis of the underground part of sorrel for various classes of compounds was carried out using two-dimensional and one-dimensional paper chromatography methods by comparison with taps in various solvent systems: butyl alcohol-acetic acid-water (40:12.5:29); butyl alcohol-acetic acid-water (4:1:5); 2% acetic acid and 15% acetic acid using specific developers; the following were found: carbohydrates (reactions with o-toluidine and urea), anthraquinones (by reaction

with alkali), flavonoids (Gage's reaction), phenols (reaction with iron-ammonium alum).

Determination of the quantitative content of the main groups of biologically active substances. According to generally accepted methods of the State Pharmacopoeia of the Republic of Kazakhstan, 1st edition and the State Pharmacopoeia of the USSR, the quantitative contents of the main groups of biologically active substances were determined [28].

Design of studies. Two groups of the animals (each with ten rats) were formed randomly. The first group was a control group, the second group obtained 100 milligrams of extract per kilogram. The water and extracts were administered perioral for 10 days using a pipette. The lab rats were subsequently sacrificed through the cardiac fence while sedated. Saline solution was used to obtain a sample of bone marrow, which was then sent for cytological staining. Also to ensure the reliability of the results, the experiment was repeated 3 times.

Carrying out hematological analysis. The results of a general blood test were obtained on a hematological analyzer Sysmex KX-21 (Japan), which includes 18 counting parameters: red blood cells (10^{12}/L), leukocytes (10^9/L), platelets (10^9/L), hemoglobin (g/L), hematocrit (L/L), erythrocyte indices (fL), platelet indices (fL), lymphocytes, neutrophils, mixed cells (% and 10^9/L).

Evaluation of bone marrow cytology. Twenty treated rats and ten control rats were studied. Bone marrow was extracted using the left and right tibias. After the bone was dissected neatly, the bottom section of the tibia was compressed using fine forceps. The fractured top end's thick pink marrow was taken and put on a glass slide. A droplet of saline was added as a diluent and delicately mixed with the marrow. Giemsa's guidelines were followed while staining thin smears with Azur-eosin and May-Grunwald (Pappenheim modification). First, a suitable amount of undiluted May-Grunwald stain is applied to the smear. Then, the stain is drained off the glass after 3 minutes, and the smear is stained for 10-12 minutes with a Giemsa stain solution before being rinsed with clean tap water. This staining approach combines the May-Grunwald stain's ability to detect cell granularity with the evident staining of the nucleus structure with Giemsa solution. Several hundred cells were discovered and counted. I.A. Kassirsky and G.A. Alekseev's classifications assisted in cell identification. Each sample was analyzed and cell counted using microscope Micro Opix MX 700 (T) (West Medica, Brown Boveri-StaBe 6, B17-1 2351 Wiener Neudorf, Austria), with HD camera CAM V1200C (West Medica, Brown Boveri-StaBe 6, B17-1 2351 Wiener Neudorf, Austria).

Statistical analysis. To show all data, the mean and standard error of the mean are employed. The Student t-test was used to examine the statistical significance of group differences; the significant result was $p \leq 0.05$.

Results and discussion

The impact of *R. tianschanicus* extract on red bone marrow cytology. Figure 2 illustrates a wide range of blood cells, primarily progenitors and a few mature cells. According to Figure 3, the inflammatory process begins when the number of neutrophil progenitors grows. Finally, Figure 4 illustrates the blood count slowly improving, demonstrating the calming impact of extract therapy.

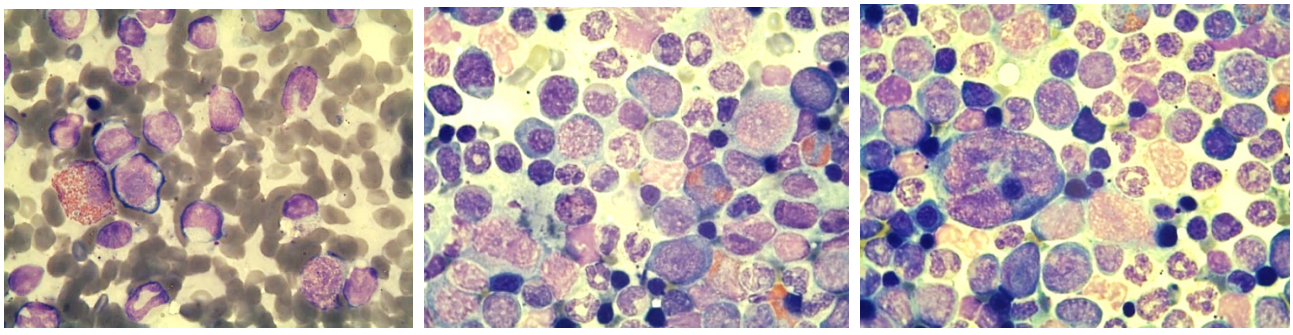


Figure 2 – Photomicrograph of control group's cytology of red bone marrow (May Grunwald-Giemsa (MGG) staining, magnification × 100, immersion oil)

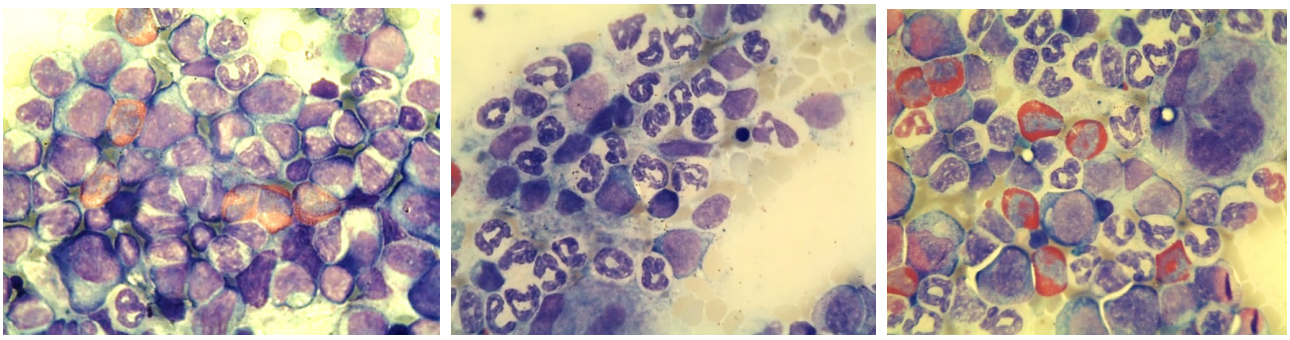


Figure 3 – Photomicrograph of acute gastritis group' cytology of red bone marrow (May Grunwald-Giemsa (MGG) staining, magnification × 100, immersion oil)

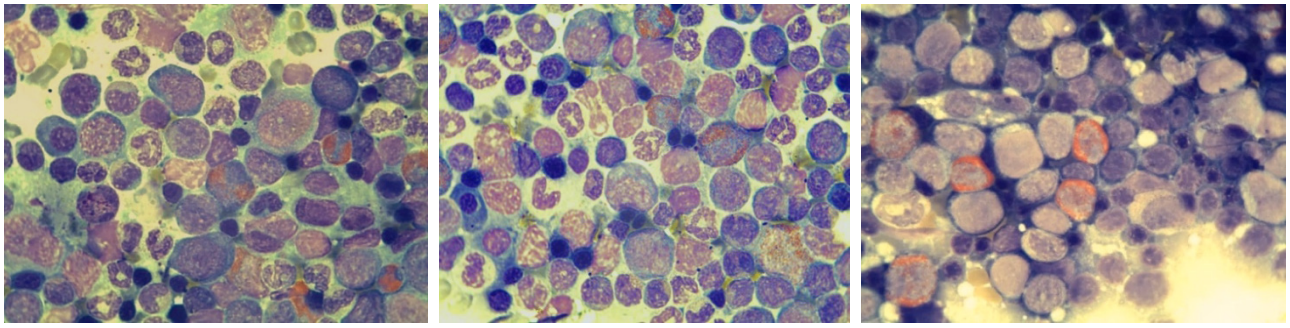


Figure 4 – Photomicrograph of extract treatment group' cytology of red bone marrow (May Grunwald-Giemsa (MGG) staining, magnification × 100, immersion oil)

According to a morphological study of the structure, there were no unusual forms or qualitative abnormalities in gastritis and treatment.

The obtained data for determining the quantitative content of biologically active compounds in the underground part of sorrel extract show that this plant material is rich in flavonoids and polyphenols. The results of the analysis are presented in Table 1.

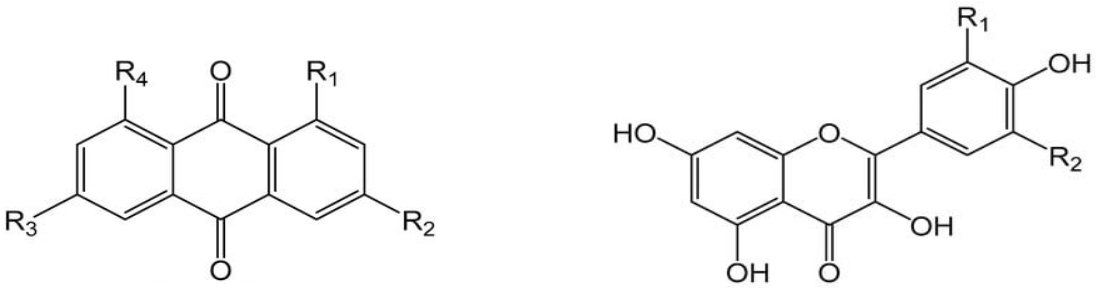
From the Table 1 we can conclude that, in terms of the quantitative content of biologically active compounds, the content of flavonoids and polyphenols dominates in the lower layers of *R. tianschanicus* and the herbal medicine obtained on its basis.

As a result of the research, two known compounds, flavonoids and anthraquinones, were isolated from the complex extract *Rumex*. As shown in other studies, these compounds have anti-inflammatory and cell proliferation-stimulating activity and can be used in the treatment of gastrointestinal diseases [11-13].

Figure 5 shows the structure of isolated compounds from an extract obtained from the roots of *R. tianschanicus*

Table 1 – Quantitative content of the main groups of biologically active compounds (BAC)

BAC	Raw material %	Phytoexract, %
Flavonoids	5.92	14.6
Carbohydrates	2.4	1.2
Polyphenols	3.54	10.1
Phenol- and -hydroxycinnamic acids	1.36	4.8
Polysaccharides	3.52	1.4
Anthraquinones	2.2	1.78



A – anthraquinones **B –** flavonoids

Figure 5 – R_1=OCH_3, R_2=H (Isoramnetin), R_1=OH, R_2=H (Quercetin), R_1=OH, R_2=OH (Myricetin) [12].

The experiment to study chronic toxicity was completed by killing the animals to obtain peripheral blood samples, which later served as material for hematological analysis. The study of the complex extract *Rumex* is confirmed by comparative hematological parameters of the blood of experimental animals of the control group, acute and chronic toxicity of the complex extract *Rumex,* the data of which are given in the table below.

Table 2 – Comparative hematological parameters of the blood of experimental animals of the control group, acute and chronic toxicity of the complex extract *Rumex*

Hematological indicator	International abbreviation	Control	Chronic toxicity
Total number of leukocytes, 10^9/L	WBC	6.13±1.03	7.70±1.05
Total number of red blood cells, 10^{12}/L	RBC	5.97±1.21	7.39±1.26
Hemoglobin level, g/L	HGB	164.20±16.32	172.80±13.85
Total platelet count, 10^9/L	PLT	919.20±154.32	719.00±152.62
Absolute neutrophil content, 10^9/L	Neut	2.76±0.54	3.14±0.51
Relative content of neutrophils, %	Neut	48.16±2.57	43.26±12.72
Absolute lymphocyte count, 10^9/L	Lymph	2.69±0.71	3.30±0.56
Relative content of lymphocytes, %	Lymph	39.40±3.65	50.96±6.57
Absolute monocyte count, 10^9/L	Mono	0.45±0.11	0.56±0.11
Relative content of monocytes, %	Mono	7.34±1.68	7.48±1.64
Absolute eosinophil count, 10^9/L	Eos	0.16±0.09	0.29±0.13
Relative content of eosinophils, %	Eos	2.62±0.98	3.22±0.69
Absolute basophil content, 10^9/L	Baso	0.04±0.06	0.24±0.43
Relative content of basophils, %	Baso	0.27±0.30	0.43±0.46

According to the results from the Table 2, when studying the chronic toxicity of a complex extract of plants of the genus *Rumex*, there were no statistically significant differences ($p<0.05$) between hematology parameters. A comparative analysis of the hematological parameters of animals in the control and experimental groups after oral administration of the extract revealed that the total number of leukocytes in the control group was $6.13±1.03×10^9$/l, in the group with acute toxicity $6.48±1.62×10^9$/l, and in the group with chronic toxicity toxicity was $7.70±1.05×10^9$/l and did not reveal a statistically significant difference ($p<0.05$).

The total number of red blood cells in the control group was $5.97±1.21×10^{12}$/l, in the experimental group with acute toxicity $6.38±0.85×10^{12}$/l, in the third group after experimental treatment – $7.39±1.26×10^{12}$/l.

The hemoglobin level in the control was 164.20±16.32 g/l, in the experiment with acute toxicity it was within 170.00±19.04 g/L, and in animals in the chronic toxicity group it was 172.80±13.85 g/L.

However, it was found that the concentration of the extract has a beneficial effect on the total number of platelets, from 919.20±154.32×10^9/l in the control group to 825.80±175.41×10^9/l in the group with acute toxicity and, accordingly, in the group with chronic toxicity, and amounted to 719.00± 152.62×10^9/l. The absolute and relative content of neutrophils is 2.76±0.54×10^9/l and 48.16±2.57% in the control group, in the group with acute toxicity 2.95±1.04×10^9/l and 45.60±9.45 % and in the group with chronic toxicity 3.14±0.51×10^9/l and 43.26±12.72%. The absolute and relative content of lymphocytes 2.69±0.71×10^9/l and 39.40±3.65% in the control group is higher than in the group with acute toxicity, which is 3.27±1.15×10^9/l and 49.80±7.16%, and the group with chronic toxicity is correspondingly higher – 3.30±0.56×10^9/l and 50.96±6.57%. The absolute and relative content of monocytes was 0.45±0.11×10^9/l and 7.34±1.68% in the control group, in the group with acute toxicity of 0.49±0.09×10^9/l and 7. 70±0.84% and groups with chronic toxicity – 0.56±0.11×10^9/l and 7.48±1.64%. The absolute content of eosinophils was 0.16±0.09×10^9/l and the relative content was 2.62±0.98% in the control group and in the group with acute toxicity, the indicators of which were 0.20±0.10×10^9/l and 3.04±0.95 %, and in the group with chronic toxicity 0.29±0.13×10^9/l and 3.22±0.69% no statistically significant changes were revealed ($p \leq 0.05$). Also, considering the absolute and relative content of basophils in all three groups, no statistically significant changes were revealed ($p \leq 0.05$), which is 0.04±0.06; 0.04±0.04; 0.24±0.43×10^9/l and 0.27±0.30; 0.49±0.47; 0.43±0.46%. Thus, all hematological blood parameters in experimental animals were within the physiological norm, which indicates the absence of toxic effects of the *Rumex* complex extract and its negative impact on hematopoiesis.

It has been established that with long-term use under the experimental conditions no hematotoxic effect was noted. With the chronic use of the complex extract *Rumex*, there are no changes in hematopoiesis indicators and no inhibition of hematopoiesis has been detected, there are no pronounced changes in the leukocyte formula, and according to the level of eosinophils and basophils, there are no allergic reactions. Thus, it can be noted that the *Rumex* complex extract is non-toxic. Consequently, no statistically significant changes $p \leq 0.05$ in many quantitative indicators of myelogram cell types except for the number of mature neutrophils, eosophilic metamyelocytes, monocytes and mast cells were noted. The detected statistically significant changes $p \leq 0.05$ in the number of mature neutrophils were 4.60±0.30 in the control group and decreased in the group with the introduction of the extract of eosophilic metamyelocytes *Rumex* to 1.11±0.12. The amount was calculated in the control – 1.80±0.07 and statistically significant changes $p \leq 0.05$ were recorded in relation to the group with the introduction of the complex extract *Rumex* – 1.12±0.21. In the control group, the number of monocytes was 0.17±0.07 and increased 2-fold in the group with the introduction of the complex extract *Rumex* – 0.37±0.03 relative to the control, which was also statistically detected at $p \leq 0.05$. And the most statistically significant change ($p \leq 0.05$) of more than 30 times was observed in the number of mast cells in the control group – 0.67±0.02 and a decrease to – 0.01±0.001 in the group with the introduction of the complex extract *Rumex.*

The findings demonstrate inflammation of the stomach lining mucous membrane by an increased number of neutrophil progenitors, including myeloblasts and band neutrophils. Along with the fact that extract therapy decreased the number of neutrophil progenitors, it is assumed that the inflammation of the stomach mucosa decreased. With therapy, the initial inflammatory reaction subsided. Despite a rise in eosinophil and basophilic myelocyte production, the morphology remained unchanged. More study of this phenomenon is necessary. We may infer that the extract has a beneficial impact on the activation of erythropoiesis from the alterations in red blood cell progenitors, particularly polychromatic and orthochromatic normoblasts, as demonstrated by a sharp decline in acute gastritis with a return to the original levels in a stable condition. In addition, the number of lymphocytes dramatically increased during extract treatment, which may indicate that lymphopoiesis was activated. An increase might be attributed to the extract's unresearched immunostimulating abilities. Overall, extract has no adverse effects on the bone marrow's ability to produce blood cells.

Our data indicate a decrease in the total number of platelets associated with the use of this phytoextract, as a previously studied manifestation of *R. acetosa* antiplatelet activity by Jeong D. et al. [20]. In other hematological parameters of the control groups and with the introduction of the extract, slight increases were observed and no statistically significant

changes were detected (P<0.05), however, the level of hemoglobin increased in the group with the introduction of the complex herbal medicine *Rumex* in relation to the control group, although in another study, Islam R. et al. observed lower hemoglobin (HGB) in those receiving ethanol extract than in the control group [21]. In a recent investigation on the protection of hematopoiesis of the proposed extract following breast cancer [22]. The ratio of myeloid cells was reduced following the administration of the recommended extract. Similar to our findings, after extract therapy, the number of common lymphoid progenitors rises. The number of monocytes, lymphocytes, and eosinophils is decreasing while the number of neutrophils, erythrocytes, and platelets is increasing [23].

Applying a massive dosage of cortisone was found to significantly raise the ratio of myeloid to erythroid cells, taking into account earlier studies [24] concerning bone marrow. The experiment excluded the idea of decreasing RBC progenitors and growing myeloid progenitor cells, revealing information about the overall bone marrow cellularity. Myeloid proliferation or/and prevention of discharge from the bone marrow into the circulation are hypothesized to cause an increase in myeloid line cells. Data on the impact of hormone administration on the bone marrow is supported by several investigations [25]. Our conclusions were reinforced by 2015 research by Ayodeji on the age-dependency of blood parameters and biochemical markers during healing chronic toxicity. They showed that in younger rats, the lymphocyte count rose and the neutrophil count fell (3 and 6 month). The rats we utilized for the experiment and the young rats from their study are of similar age [26]. And against the background of experimental therapy with a complex phytopreparation based on *Rumex*, were not detected any functional changes in the organs of the digestive system. During experimental administration of the extract, no deterioration or side effects were observed in rats [27]. Overall, the results confirm the beneficial and non-toxic effects of complex extract of *Rumex* plants.

Conclusion

This investigation aimed to determine how Rumex extract affected myelograms and whether it would be useful in treating chaotic toxicity. The rat myelogram study's findings confirmed the predictable hypothesis. This study offers new understandings of the quantitative features of the rat myelogram during chronic toxicity and the potential therapeutic value of complex phytopreparation based on *Rumex*. The work proves that extract is not cytostatic and has erythropoiesis activation properties. Due to its therapeutic benefits against chronic toxicity, we believe the phytoextract examined in this work merits greater attention and encourage additional research into it.

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Information about authors:

Shokan Aksholpan Kanatkyzy (corresponding author) – PhD student at the Department of Biodiversity and Bioresources, al – Farabi Kazakh National University, junior researcher at Institute of Genetic and Physiology (Almaty, Kazakhstan, email: aksholpan.shokan@gmail.com)

Yergozova Diana Maratkyzy (corresponding author) – PhD student at the Department Biodiversity and Bioresources, al – Farabi Kazakh National University, Senior Assistant at Institute of Genetic and Physiology (Almaty, Kazakhstan, email: diana.yergozova@gmail.com)

Kobylina Tatyana Nikolaevna – PhD student at the Department of Biodiversity and Bioresources, al – Farabi Kazakh National University, researcher at Institute of Genetic and Physiology (Almaty, Kazakhstan, email: tanya_tanichka_87@mail.ru)

Kudrina Nataliya Olegovna – Candidate of Biological Sciences, Senior Lecturer at the Department of Biodiversity and Bioresources, al-Farabi Kazakh National University, Leading researcher at Institute of Genetic and Physiology (Almaty, Kazakhstan, email: kudrina_nat@mail.ru)

Litvinenko Yuliya Alekseevna – Candidate of Chemistry Sciences, Deputy head of the department for educational, method. and educational work, senior teacher at the Department of Chemistry and Technology org. substances, natural compounds and polymers, al – Farabi Kazakh National University, Leading researcher at Institute of Genetic and Physiology (Almaty, Kazakhstan, email: Yuliya_litvinenk@mail.ru)

Seytimova Gulnaz Absattarovna – Associate Professor at the Department of Chemistry and Technology org. substances, natural compounds and polymers al – Farabi Kazakh National University, Leading researcher at Institute of Genetic and Physiology (Almaty, Kazakhstan, email: sitigulnaz@mail.ru)

Kulmanov Timur Esengalievich – candidate of Medical Sciences, Leading researcher, Head of Pharmacological research laboratory at the Institute of Genetic and Physiology (Almaty, Kazakhstan, email: kulmanovlux@mail.ru)

Terletskaya Nina Vladimirovna – Candidate of Biological Sciences, Associate professor at the Department of Biodiversity and Bioresources, al-Farabi Kazakh National University, Leading researcher, Head of laboratory at the Institute of Genetic and Physiology (Almaty, Kazakhstan, email: teni02@mail.ru)

Zharkova Irina Maratovna – Candidate of Biological Sciences, Deputy Head of Department on scientific and innovative work and international relations, Senior Lecturer at the Department of Biodiversity and Bioresources, al – Farabi Kazakh National University (Almaty, Kazakhstan, email: Irina.Zharkova@kaznu.kz)