PHARMACOLOGICAL PROPERTIES OF ENDEMIC PLANTS GROWING IN THE STEPPEs OF KAZAKHSTAN

The number of people who suffer from secondary immunodeficiency diseases is increasing. Secondary immunodeficiency diseases develop due to environmental degradation, abuse of various preservatives, stabilizers in foods and long-term storage products, abuse of the use of drugs with a cytostatic effect, the use of antibiotics in the cultivation of cattle and poultry. The compounds were obtained from plants of the Halostachys caspica (Pall) C.A.Mey.ex Schrenk, Suaeda microphylla Pall., Climacoptera obtusifolia (Schrenk) Botsch. Plant extracts were investigated on myelostimulating activity. The compounds obtained from the Halostachys caspica (Pall) C.A.Mey.ex Schrenk by means of water-alcohol extraction without heating showed high myelostimulating activity. It effectively stimulated erythro-, thrombocyto- and leukopoiesis, and in stimulating the leukocyte population, it equally effectively increased the values of granulocyte and agranulocyte leukocytes. The compounds derived from the Suaeda microphylla Pall. and Climacoptera obtusifolia (Schrenk) Botsch showed low myelostimulating activity. It should be noted that the water-alcohol extracts of plants without heating showed higher activity than the extracts that have undergone thermal heating.

Key words: myelostimulating activity, endemic plants, steppe of Kazakhstan.
су-спирттік экстракттау арқылы алынған каспийлік соляноколосник өсімдігінің сығындысы екендігі анықталды. Ол эритро-, тромбоцито- және лейкопоэзды эффективті түрде стимулады, сондықтан каараты және агроноцистардың түзілінің бірдей маңызды стимулады адам. Тегісжапырақты климакоптера өсімдік соляноколосник екітіннің сығындасында миелостимулаушы асері солайылдың орташа сығындасында ануы жетекчи. Екітіндегі сығындасының ағыс ұзының ең ең түсіндіретін және жарықтың жоғары түрдегі сығындасы алуы жетекчи. Бұл өсімдіктердің қыздырусынан су- спирттік экстрактимен алынған су-спирттік экстракттарының белсенділігі термиялық өңдеуден өткен өсімдік сығындасына қарағанда белсенді жоғары екендігін атап айтып кеткен жөн.

Түйін сөздер: миелостимулаушы белсенділік, ендемик өсімдіктер, Қазақстанның аридті аймағы.

**Introduction**

The number of people who suffer from secondary immunodeficiency diseases is increasing. Secondary immunodeficiency diseases develop due to environmental degradation, abuse of various preservatives, stabilizers in foods and long-term storage products, abuse of the use of drugs with a cytostatic effect, the use of antibiotics in the cultivation of cattle and poultry [1]. Various toxic chemical compounds: Sturdart solution, trinitrotoluene, pesticides, especially organochlorine preparations, lindane (gamma-hexachlorocyclohexane) and dichlorodiphenyltrichloroethane also cause severe pancytopenia. The choice of effective myelostimulating drugs that can restore parameters of peripheral blood in a short period of time is very limited [2]. Thus, pharmacological screening of myelostimulating drugs is relevant. In addition, myelostimulators are widely used in ophthalmology, surgery, cosmetology and biotechnology.

**Materials and Methods**

The following plant extracts were received for research: EES.SES/N – 50% water-ethyl alcoholic extract of the plant *Halostachys caspica* (Pall) *C.A.Mey. ex Schrenk* with heating, EES.SEB / N
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50% water-ethyl alcoholic extract of the plant Halostachys caspica (Pall) C.A.Mey. ex Schrenk without heating, CIE.SV – 70% water-ethyl alcohol extract plant Suaeda microphylla Pall. without heating, COBE – 70% water-ethyl alcohol extract of Climacoptera obtusifolia (Schrenk) Botsch. without heating, COFL – 70% water-ethyl alcohol extract of plant Climacoptera obtusifolia (Schrenk) Botsch. without heating, COLE – aqueous extract of the plant Climacoptera obtusifolia (Schrenk) Botsch. without heating (Table 1).

**Table 1** – Active compounds obtained by water and water-ethyl extraction of plants

| № | Drug code | Plant | Chemical composition of plants |
|---|-----------|-------|--------------------------------|
| 1 | EES.SES/N | 50% water-ethyl alcohol extract of a plant with heating Halostachys caspica (Pall) C.A.Mey. ex Schrenk | Flavanoids, free organic acids, amino acids, alkaloids, saponins, tannins |
| 2 | EES.SEB/N | 50% water-ethyl alcohol extract of a plant without heating Halostachys caspica (Pall) C.A.Mey. ex Schrenk | Flavanoids, free organic acids, amino acids, alkaloids, saponins, tannins |
| 3 | CIE.SV | 70% water-ethyl alcohol extract of a plant without heating Suaeda microphylla Pall. | Flavanoids, free organic acids, amino acids, alkaloids, saponins, coumarins |
| 4 | COBE | 70% water-ethyl alcohol extract of a plant without heating Climacoptera obtusifolia (Schrenk) Botsch. | Flavanoids, free organic acids, amino acids, alkaloids, saponins, tannins |
| 5 | COLE | Aqueous extract of the plant without heating Climacoptera obtusifolia (Schrenk) Botsch. | Flavanoids, free organic acids, amino acids, alkaloids, saponins, tannins |
| 6 | COFL | 70% water-ethyl alcohol extract of a plant without heating Climacoptera obtusifolia (Schrenk) Botsch. | Flavanoids, phenolic acids |

Healthy, mature animals of laboratory rats of both sexes, 10–15 weeks of age, weighing 210–280 g, were used in the work. The scatter in the groups according to the initial body weight did not exceed ± 10%. The animals were received simultaneously from one nursery – the biological clinic of the Faculty of Biology and Biotechnology of the Al-Farabi Kazakh National University. Before and during the experiment, the control and experimental animals were kept in the same standard conditions, 6 animals per cage. All types of experiments were carried out in compliance with the chronobiological principles of work and in accordance with the “Rules for conducting preclinical (non-clinical) research on biologically active substances” [8]. Blood sampling was performed from the orbital vein of rats anesthetized with weak ether anesthesia at 09.00 in the morning. A blood test was performed on a hematological analyzer for laboratory animals “Abacus junior VET” (manufactured by Diatron, Denmark). The blood leukogram was monitored by microscopic examination of a smear stained by Romanovsky-Giemsa on an SA3300C microscope for microscopy and digital micrograph under immersion (magnification 7x100) with 500 cells on each smear[6]. Myelosuppression was induced by administering cytostatic compound benzopyrene at a dose of 30 mg / kg body weight of the animal dissolved in saline in a volume of 0.5 ml three times with an interval of 24 hours [5, 7]. Then, on the 6, 8, 10 day of the observation, once time in day, intramuscularly was injected: to the 1st group – the EEC.SES/N compound at a dose of 5 mg / kg (for all test compounds, physiological saline was the solvent), in a volume of 0.5 ml, The 2nd group – compound EES.SEB/N at a dose of 5 mg / kg in a volume of 0.5 ml, the 3rd group – compound CIE.SV at a dose of 5 mg / kg in a volume of 0.5 ml; in group 5, compound COFL in a dose of 5 mg / kg in in volume of 0.5 ml; in group 7, the drug is compared pantohematogen the dose 0, 4 mg / kg in a volume of 0, 5 ml, 8th group – placebo (saline) in a volume of 0 5 ml and 9th group of animals was intact. Statistical data processing was performed with casting the Student’s confidence interval.
Results and Discussion

Already on the 1st day after administration, it was possible to register severe immunosuppression with lesions of leukocyte cells and erythrocyte cells. For control of the level of damage to the blood-forming pools was taken the 3rd day after the administration of the immunosuppressant. After analyzing the hemogram of blood, it was found that the leukocyte pool suffered greatly. The total leukocyte index from the level of intact animals (9.15 ± 1.36) · 10^9 / L of blood dropped to (2.37 ± 0.16) · 10^9/L by 3.86 times (p≤0.05). In the leukogram, the absolute and relative values of agranulocytic and granulocytic leukocytes decreased. Among agranulocytes, the absolute values of lymphocytes from (5.46 ± 0.18) · 10^9/L of blood dropped 3.41 times to (1.60 ± 0.2) · 10^9/L, while the relative values from index of intact animals (68.03 ± 12.3)% of blood fell only 1.44 times to (47.2 ± 1.8)% of blood. A similar trend was observed with respect to other subpopulations of cells.

Absolute values fell by more than 2 times, and relative values decreased by less than 1.5 times. For example, the absolute values of monocytes from the value (0.5 ± 0.02) · 10^9 / L of blood decreased to the value (0.12 ± 0.10) · 10^9/L of blood, i.e. 4.17 times (p≤0.05), while the relative value (6.28 ± 1.24)% fell only to (4.9 ± 1.3)% which was only 1.28 times the difference in the meanings. Granulocyte cells with (3.64 ± 1.22) · 10^9/L fell to (0.65 ± 0.3) · 10^9/L, i.e. 5.6 times (p≤0.01). The relative value of granulocytes from (40.0 ± 8.36)% decreased 1.52 times, reaching a value (26.18 ± 4.5)%.

In the blood leukogram absolute values are more important in the diagnosis than the relative values of the blood leukogram. Changes in the values of erythrocyte and platelet cells were recorded, but more than 2-fold reduction was not registered. The level of erythrocyte cells (6.5 ± 1.56) · 10^12 / L of blood reached the value of (4.93 ± 1.3) · 10^12 / L of blood, i.e. a decrease was observed 1.32 times. Hemoglobin levels fell 4.51 times. In intact animals, it was (140.7 ± 16.7) g / L of blood. After intoxication fell to (90.75 ± 12.0) g / L of blood. But the hematocrit value from the value (39.8 ± 0.91)% fell to 2.88 times (p≤0.05) times, reaching the value (21.21 ± 2.58)%.

A critical decrease was observed among platelets. The level of intact animals was (660.25 ±42.3) · 10^10/L of blood and with an artificially induced immunosuppressive syndrome was (70.5 ± 43.2) · 10^10/L of blood, which amounted to more than 9.36-fold decrease (p≤0.01). Having caused an artificial immunosuppressive syndrome, animals were treated with new compounds of plant origin. The compounds were obtained from the following plants: Halostachys caspica (Pall) C.A.Mey. ex Schrenk, Stuæda microphylla Pall., Climacoptera obtusifolia (Schrenk) Botsch. The compounds were obtained by water – ethyl and water extraction of plants, with and without heating. After the introduction of the studied compounds, the following results were obtained on the basis of which it is possible to isolate the most active compound EES.ESB/N. This compound was distinguished by a high myelostimulating activity in the series of compounds obtained from other plants and in the series of compounds obtained from the Halostachys caspica (Pall) C.A.Mey. ex Schrenk. In the group with administration of EEC.SEB/N the level of leukocytes was (6.9 ± 0.4) · 10^9 / L with a control value (2.79 ± 0.93) · 10^9/L (p ≤0.05) and with a value at intact animals (10.4 ± 0.19) · 10^9/L of blood. In the blood leukogram, both in relative and absolute values, positive changes have occurred. The relative value of lymphocytes increased 1.4 times to (70.1 ± 2.3)% against the control value (50.65 ± 14.65)% and with the value of intact animals (73.0 ± 3.8)% (Figure 1). More significant changes can be seen in the change in the absolute values of lymphocytes with the indicator (4.8 ± 0.05) · 10^9 / L opposes to control value (1.6 ± 0.9) · 10^9/L, which is a 3-fold difference (p≤0.05) and with the value of intact animals (7.6 ± 0.1) · 10^9/L (Figure 1). Positive dynamic was observed in the granulocyte leukocyte series, but within 8-10%.

Compound EEC.SEB/H reliably stimulated myelopoiesis of erythrocyte, platelet and leukocyte cell generation. Stimulation of erythropoiesis was effective and the level of erythrocytes on the 7th day of observation reached the value (7.43 ± 0.1) · 10^12 / Lof blood against the control indicator (3.67 ± 0.1) · 10^12/L of blood and with the value of intact animals (7.5 ± 0.28) · 10^12/L (Figure 2). The hemoglobin level reached the value of healthy animals (121.0 ± 1.0) g/L with the control value (96.0 ± 1.0) g/L and the value of intact animals (140.7 ± 4.3) g/L. And the hematocrit level was also very high (37.8 ± 0.91)% against the control value (28.1 ± 0.84)% and the value of intact animals (39.8 ± 0.91)%.

The recovery in the leukocyte pool was not as intense as in the platelet(Figure 2). With the value of platelets after administration of benzopyrene (70.5 ± 4.3) · 10^9 / L, the level of platelets after administration of EEC.ESB/N increased to (691.2 ± 11.0) · 10^9/L against the control value (447.0 ± 5.1) · 10^9/L with a value at intact animals (660.0 ± 25.0) · 10^9/L. Similar changes occurred in terms of thrombocrit, average platelet volume and platelet distribution.
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Figure 1 – Peripheral blood hemogram: total leukocyte indicators, $\cdot 10^9$ / L (A), absolute lymphocyte evidence, $\cdot 10^9$ / L (B), absolute monocytec cosinophilic indicators, $\cdot 10^9$ / L (C), and absolute granulocytic indicators, $\cdot 10^9$ / L (D). 1-data of the group with the introduction of the compound EES.SES/N, 2-data of the group with the introduction of the compound EES.SEB/N, 3-data of the group with the introduction of the compound CIE.SV, 4-data of intact animals, 5-data of the control group with pantohematogen, 6-placebo group data with the introduction of nat. solution. The abscissa axis – the number of groups, the axis of ordinate- blood indicates.

Figure 2 – Peripheral blood hemogram: total erythrocyte indicators, $\cdot 10^{12}$ / L (E) and hemoglobin index, g / L (F), total platelet indicators, $\cdot 10^9$ / L. 1-data of the group with the introduction of the compound EES.SES / N, 2-data of the group with the introduction of the compound EES.SEB/N, 3-data of the group with the introduction of the compound CIE.SV, 4-data of intact animals, 5-data of the control group with the introduction pantohematogen, 6-placebo group data with the introduction of nat. solution. The abscissa axis – the number of groups, the axis of ordinates – blood indices.
When benzopyrene intoxication was observe a sharp decrease in blood parameters: erythrocyte, leukocyte, platelets. So immediately after the administration of benzopyrene the level of erythrocytes was \((4.93 \pm 0.5) \cdot 10^{12}/L\) with hemoglobin \((90.75 \pm 12.0)\) g/L, hematocrit \((21.21 \pm 7.79)\)%.

After 7th days in the control group with the introduction of saline solution, the level of erythrocytes was \((3.67 \pm 0.1) \cdot 10^{12}/L\) with hemoglobin \((96.0 \pm 1.0)\) g/L, hematocrit \((28.1 \pm 0.84)\)%; i.e. not registered positive dynamics in the erythrocyte pool. A similar pattern was observed in the leukocyte cell pool. Immediately after intoxication, the level of leukocytes was \((2.37 \pm 0.16) \cdot 10^{9}/L\) of blood. After 7th days the level of leukocytes was \((2.79 \pm 0.93) \cdot 10^{9}/L\) with absolute lymphocytic index \((1.6 \pm 0.2)\) \cdot 10^7/L and absolute agranulocytes index \((1.5 \pm 0.9)\) \cdot 10^9/L.

In a series of compounds derived from various plants, only compounds derived from plant *Halostachys caspica* (Pall) C.A.Mey.ex Schrenk can effectively stimulated myelopoiesis of blood at benz(a)piren myelosuppression. Among series of compounds obtained from one plant of the *Halostachys caspica* (Pall) C.A.Mey.ex Schrenk only compound obtained from plant without heating (EEC.SEB/N) that showed high activity compared to the extract of the plant with heating (EES.SES/N). The next compound investigated on myelostimulating activity was a compound obtained from the plant *Suaeda microphylla* Pall., which received the code CIE.SV. It was inferior in activity to the compounds obtained from the plant *Halostachys caspica* (Pall) C.A.Mey.ex Schrenk, but exceeded in activity at the compounds obtained from the plant *Climacoptera obtusifolia* (Schrenk) Botsch. The compound CIE.CV very effectively stimulated platelet cell proliferation. The level of platelets after treatment was \((718.2 \pm 21.0) \cdot 10^{12}/L\) with a control value \((447.0 \pm 51.0) \cdot 10^{12}/L\), i.e. despite an increase in the erythrocyte pool, hemoglobin levels did not increase. It could also be noted in other values of the erythrocyte pool: the average volume of erythrocytes, the average hemoglobin content, the width of the distribution of erythrocytes, etc. The values in the group of administration of the compound COFL did not differ from the control values. Similar changes were observed in the platelet pool. There was an increase in the total platelet count to \((881.0 \pm 86.0) \cdot 10^{12}/L\) of blood, which was 2-fold difference from the control value \((447.0 \pm 51.0) \cdot 10^{12}/L\).

With a significant increase in lymphocytic index. With a total leukocyte index \((4.7 \pm 0.2) \cdot 10^{9}/L\), the relative lymphocyte count was \((78.2 \pm 5.5)\)% with an absolute value \((3.7 \pm 0.05) \cdot 10^{9}/L\). At the same time, in intact animals the relative value of lymphocytes was \((73.0 \pm 3.8)\)% with an extreme variation (70-75)% and the absolute value was \((7.6 \pm 0.1) \cdot 10^{9}/L\), i.e. CIE.SV compound very effectively and quickly stimulated the proliferation and release of lymphocytic cells into peripheral blood.

In a series of activity of the newly synthesized compounds, the compounds obtained from the plant *Climacoptera obtusifolia* (Schrenk) Botsch. were in third place. Among three compounds more active was the COFL compound. It stimulated erythrocyte- thrombocyte- and leukopoiesis. During the stimulation of erythropoiesis, the level of erythrocytes reached the value \((5.94 \pm 0.12) \cdot 10^{9}/L\) of blood with the control value \((3.67 \pm 0.1) \cdot 10^{9}/L\). The hemoglobin level was \((99.0 \pm 0.1)\) g/L with a control value \((96.0 \pm 1.0)\) g/L, i.e. despite an increase in the erythrocyte pool, hemoglobin levels did not increase.

Having caused an artificial immunosuppressive syndrome, animals were treated with new compounds of plant origin. The compounds were obtained from the following plants: *Halostachys caspica* (Pall) C.A.Mey.ex Schrenk, *Suaeda microphylla* Pall., *Climacoptera obtusifolia* (Schrenk) Botsch. The compounds were obtained by water – ethyl and water extraction of plants, with and without heating.
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Figure 3 – Peripheral blood hemogram: total erythrocyte indicator, \( \cdot 10^{12}/L \) (E) and hemoglobin index, g / L (F), total platelet indicator, \( \cdot 10^{9} / L \). 1-data of the group with the introduction of the compound COFL, 2-data of the group with the introduction of the compound COBE, 3-data of the group with the introduction of the compound COLE, 4-data of the intact animals, 5-data of the control group with the introduction of pantohematogen, 6-data of the placebo group with the introduction of physical solution. Abscissa axis – numbers of groups, axis of ordinates – blood indicators.

Figure 4 – Peripheral blood hemogram: total leukocyte indicator, \( \cdot 10^{9} / L \) (A), absolute lymphocyte evidence, \( \cdot 10^{9} / L \) (B), absolute monocyteceosinophilic indicator, \( \cdot 10^{9} / L \) (C), and absolute granulocytic indicator, \( \cdot 10^{9} / L \) (D). 1-data of the group with the introduction of the compound COFL, 2-data of the group with the introduction of the compound COBE, 3-data of the group with the introduction of the compound COLE, 4-data of the intact animals, 5-data of the control group with the introduction of pantogematogen, 6-data of the placebo group with the introduction of physical solution. The abscissa axis – the number of groups, the axis of ordinate – blood indices.
Thus, among the activity of compounds derived from plants of the *Halostachys caspica* (Pall) C.A.Mey.ex Schrenk, *Suaeda microphylla* Pall., *Climacoptera obtusifolia* (Schrenk) Botsch. the most active ones obtained from the plant *Halostachys caspica* (Pall) C.A.Mey.ex Schrenk should be distinguished. In a series of compounds obtained from the plant of the *Halostachys caspica* (Pall) C.A.Mey.ex Schrenk should be isolated extract EEC. SEB/N, not passed thermal heating. It effectively stimulated erythropoiesis, thrombocytopoiesis, and leukopoiesis, it equally effectively increased the values of granulocyte and agranulocyte leukocytes.

The extract obtained from the same plant of the *Halostachys caspica* (Pall) C.A.Mey.ex Schrenk, but which the last heating (EEC.SES/N) practically did not stimulate platelet and leukocyte cell proliferation. The next most active was the extract obtained from *Suaeda microphylla* Pall.- CIE. SV. It was inferior in activity to the compounds obtained from the plant *Climacoptera obtusifolia* (Schrenk) Botsch. Compounds extracted from plant *Climacoptera obtusifolia* (Schrenk) Botsch did not stimulate leuko- and erythropoiesis.

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