

ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ
Өсімдіктердің биологиясы және биотехнологиясы институтының

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ИЗВЕСТИЯ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН
Института биологии и биотехнологии растений

NEWS

OF THE NATIONAL ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN
of the Institute of Plant Biology and Biotechnology

**SERIES
OF BIOLOGICAL AND MEDICAL**

3 (333)

MAY – JUNE 2019

PUBLISHED SINCE JANUARY 1963

PUBLISHED 6 TIMES A YEAR

ALMATY, NAS RK

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«ҚР ҰҒА Хабарлары. Биология және медициналық сериясы».

ISSN 2518-1629 (Online),

ISSN 2224-5308 (Print)

Меншіктенуші: «Қазақстан Республикасының Ұлттық ғылым академиясы» РҚБ (Алматы қ.)

Қазақстан республикасының Мәдениет пен ақпарат министрлігінің Ақпарат және мұрағат комитетінде
01.06.2006 ж. берілген №5546-Ж мерзімдік басылым тіркеуіне қойылу туралы куәлік

Мерзімділігі: жылына 6 рет.

Тиражы: 300 дана.

Редакцияның мекенжайы: 050010, Алматы қ., Шевченко көш., 28, 219 бөл., 220, тел.: 272-13-19, 272-13-18,
<http://biological-medical.kz/index.php/en/>

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Типографияның мекенжайы: «Аруна» ЖК, Алматы қ., Мұратбаева көш., 75.

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«Известия НАН РК. Серия биологическая и медицинская».

ISSN 2518-1629 (Online),

ISSN 2224-5308 (Print)

Собственник: РОО «Национальная академия наук Республики Казахстан» (г. Алматы)

Свидетельство о постановке на учет периодического печатного издания в Комитете информации и архивов Министерства культуры и информации Республики Казахстан **№5546-Ж**, выданное 01.06.2006 г.

Периодичность: 6 раз в год

Тираж: 300 экземпляров

Адрес редакции: 050010, г. Алматы, ул. Шевченко, 28, ком. 219, 220, тел. 272-13-19, 272-13-18,
www.nauka-nanrk.kz / biological-medical.kz

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Адрес типографии: ИП «Аруна», г. Алматы, ул. Муратбаева, 75

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News of the National Academy of Sciences of the Republic of Kazakhstan. Series of biology and medicine.

ISSN 2518-1629 (Online),

ISSN 2224-5308 (Print)

Owner: RPA "National Academy of Sciences of the Republic of Kazakhstan" (Almaty)

The certificate of registration of a periodic printed publication in the Committee of information and archives of the Ministry of culture and information of the Republic of Kazakhstan N 5546-Ж, issued 01.06.2006

Periodicity: 6 times a year

Circulation: 300 copies

Editorial address: 28, Shevchenko str., of. 219, 220, Almaty, 050010, tel. 272-13-19, 272-13-18,
<http://nauka-nanrk.kz/biological-medical.kz>

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Address of printing house: ST "Aruna", 75, Muratbayev str, Almaty

NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 5 – 10

<https://doi.org/10.32014/2019.2519-1629.24>

UDC 614.2:613.1:551.577.7

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**THE IMPACT OF THE BACKGROUND RADIATION
ON THE HEALTH**

Background: Background ionizing radiation is present in all environments on Earth. There is no consensus on the effects of radiation at different levels on the human body. There is a huge gap in the information concerning the impact of radiation on health.

Objective: To determine the impact of natural background radiation on health.

Methods and materials: We conducted a literature review. A search for English-language literature published between 2013 and 2018 related to background radiation and its effect on human health was conducted using PubMed and Medline.

Results: 1934 papers were found and abstracts screened. 1898 papers were excluded, and the full text assessed for 36 papers. 28 papers met our inclusion criteria for this writing this paper. Radiation levels varied from ≤ 100 mSv to ≥ 6 mSv. Five papers found that radiation at ≤ 100 mSv level was beneficial to health in high background-radiation areas, and conversely four papers found it was detrimental. The other 19 papers recommended conducting long-term research. Only in one paper was found neurological disorder. Ionizing radiation is a risk factor for Alzheimer's disease.

Conclusion: However, there are still unknown areas with abnormal radiation. The opinion of scientist differs in this issue. Thereby, there is a need for more investigation into the effects of radiation effects.

Key words: natural background radiation, health, cognition, mild cognitive impairment, Alzheimer disease.

Introduction. For the last two decades, the international scientific community has expressed concern about the interaction between the environment and human health. One unknown and disputable theme is the impact of the natural background radiation on human health. In our previous paper, we summarized all essential data about the natural background radiation [1]. The aim of this paper is to add information about the main effects of natural ionizing radiation on the human brain.

The question of the radiation exposure is still under study. The impact of radiation on the organism depends on the radiation dose. Ionizing radiation can be categorized into low (≤ 1 Gy) and high (≥ 1 Gy) doses. There are several areas with High natural Background Radiation, and different populations are exposure to different doses. As for instance in China (Yangjiang province) it corresponds to $5.06\text{mSv}\cdot\text{y}^{-1}$ to $6.86\text{mSv}\cdot\text{y}^{-1}$, in Brazil (Poços de Caldas, Araxà) 7mSv , Iran (Ramsar) ranges between 0.7 and 131mSv with a mean of 6mSv and India (Kerala) considerable range of 1 to about $45\text{mSv}\cdot\text{y}^{-1}$ has also been reported [2]. In terms of the effects induced by the low doses of ionizing radiation, the annual dose varies from 100Gy to 1Gy [3].

Naturally occurring radionuclides such as ^{226}Ra , ^{232}Th and ^{40}K , cosmic rays, mountains and rivers are formed the Natural Background Radiation of any area [4].

The molecular epidemiological study Shibiao Su et.al., revealed that low dose of ionizing radiation induced adaptive response (Hormesis effect) on the cell at the High Background Radiation Area (HBRA) [5]. It is quite interesting result presented in Vinay Jain and Birajalaxmi Das paper. The authors formed four different background dose groups based on the individual dose received annually by them and made transcriptome analysis to 36 respondents. The result showed that individuals exposed to background doses

of $>5\text{mGy/year}$ have shown alteration in expression of many genes involved in important functions or pathways. The results have also shown that, Group II ($<5.0\text{mGy/year}$) has very few significantly differentially expressed genes as compared to Group III and Group IV of high level natural radiation areas ($>5.0\text{mGy/year}$). The plausible explanation could be that individuals belonging to higher background dose groups ($>5.0\text{mGy/year}$) have accumulated larger doses and thus stimulating many genes from different cellular and molecular pathways to maintain genome integrity. Overall analysis has revealed that biological processes such as regulation of transcription, apoptosis, regulation of cell cycle, response to DNA damage, metabolic processes, RNA processing, Immune response, signal transduction, DNA repair, protein transport, histone/chromatin modification, response to oxidative stress, protein ubiquitination are over-represented in higher dose groups (Group III and Group IV) as compared to Group I [6].

Ionizing radiation generates plenty of reactive oxygen species (ROS) which interact with the biomolecules such as DNA, protein, lipids thus producing a variety of oxidative lesions. Majority of oxidative damages include oxidative clustered DNA lesions (OCDLs) [7]. Understanding the risk from the natural background radiation, Vinay Jain et al., the authors studied the repair of DNA double strand breaks (DSBs) in high background radiation area and determined the low dose as $1.51\text{--}5.0\text{mGy/year}$ and high dose as $>5.0\text{mGy/year}$. The results demonstrated that faster repair of DSBs and involvement of non-homologous end joining repair pathway in High level natural radiation area group of individuals was assessed as adaptive response [8]. However, further studies on DNA damage induction and repair kinetics are required for the strong evidence [9, 10].

One of the common opinion is ionizing radiation induced effect, which can increase the risk of cancer incidence. Despite the low value of the effective dose rate, which ranged from 0.06 to 0.38mSv/y , with mean of 0.20mSv/y ; the area was characterized by low background radiation. Therefore, this made clear to the authors that natural radioactivity is probably not directly influencing the increase in cancer incidence in the region. Therefore, the future research is needed to conduct, as doses from internal radiation exposure and analyses of environment such as rocks, soils, as well as food and water for human consumption may contribute to the impact on the human health by ionizing radiation [11, 12]. However, the research, conducted in France from 1990 to 2009 did not reveal any correlation between risk factors for childhood acute leukemia and low doses due to natural background radiation [13]. In Swiss Cohort Study with children under 16 years old, Ben D. Spycher et al., 2015, suggested that background radiation may contribute to the risk of cancer in children, including leukemia and CNS tumors. Furthermore, the authors found the correlation between the cumulative dose and age [14].

There are few papers dedicated to the assessment of ionizing radiation in food. Nasrin Fathabadi et al., identified the radioactivity levels in Iran, Ramsar local foodstuff consumed by residents of the high level natural radiation areas. The results showed the high doses in some products (milk and eggs). Additionally, the radionuclides in the uranium and thorium decay series may also considerably influence on the Ramsar food [15, 16]. Additional sources of natural background radiation exposure might be due to the natural radionuclides. In the paper done by Iwaoka, K. et al., 2017, the ranges of ^{222}Rn mass exhalation rates were almost identical to the natural rocks in Japan. Authors recommended that the risk of inhalation of ^{220}Rn decay products should be considered (as the radiological performance of the products depends on raw material) and the methodology should be further studied [17]. Another sources of exposure due to radionuclides is the contamination of water by ionizing radiation. Terrestrial radionuclides are one of the most important sources of human exposure to radiation due to the emission of radioactive particles (UNSCEAR2008) [18, 19]. Furthermore, chronic exposure to ionizing radiation might be the potential health risk for the population [20]. In terms of terrestrial radionuclides, one of the main contributor to radiation exposure is monazite – rich black sands in Miami Bay, Malaysia. Miami Bay can be listed as a High Background Radiation Areas (HBRA) and considered as a potential risk area for its inhabitants [21]. Also, it is quite interesting research, dedicated to the impact of the natural radioactivity and technical radiation on the soil and as a consequences on the human health. In this term, paper was written by Amira Kasumović et al., 2015 revealed no significant difference in the samples taken from the industrial and from non-industrial areas [22]. Also, in Qureshi A. A. et al. paper, there was no any significant confirmation in supporting hazards due to the usage Mansehra granite as a building materials [23], as well as there was not found the potential risk for health due to the raw ceramics as a material for bulding dwelling houses [24]. Also, Luevano-Gurrola, S. et al., 2015, revealed low annual effective dose of outdoor

radiation that might play non-significant role for producing some health effect, compare with radiation after nuclear accidents [25]. In paper by Krishnamoorthy, N., et al., 2013, the radiological hazard parameters such as indoor gamma dose rate (DIN), is higher than the recommended level whereas the other calculated hazard parameters are within the criterion limit suggested by UNSCEAR. That can be a potential risk for the human health [26].

In Sajad Borzoueisileha et al., 2013, retrospective study of health status of former students in High Natural Background Radiation area (HNBRA). There was no significant difference between students from HNBRA compared with control group. However, the authors recommend continuing the health supervision of this population (from HBRA) in the future [27, 28]. Lehrer, S. et al., 2017 found the strong correlation between natural background radiation and risk of developing Alzheimer Disease [29]. Still, this question is under discussion, as there are might be ecological fallacy.

Thereby, the opinions in terms of natural background radiation impact on the health is debatable. However, we cannot deny possible influence of the chronic low doses of radiation on the human health. Hereby, this theme requires detailed study.

Objective: to search the data about the natural ionizing radiation impact on human health.

Materials and Methods. We searched the PubMed and the Medline databases for English language peer-reviewed articles between 2013 and 2018. Keywords were the following: “Natural background radiation AND health”, “Background ionizing radiation AND health”, “Natural background radiation AND brain”, “Natural background radiation AND mild cognitive impairment”, “Background radiation AND Alzheimer disease”, “Radiation Background AND dementia”. Papers for uranium mining sites, man-made radiation (due to CT scan, X-ray, radiation the rapyetc.) and atomic bombing victims were excluded. We excluded papers available only in the form of abstract, duplicate papers and animal studies.

Results: 6923 titles and abstracts identified through database search. We identified 1934 citations from searches and reviews of reference lists after removal of duplicates and assessed full-text reviews for eligibility. Overall, 28 articles met the inclusion criteria. Radiation levels varied from ≤ 100 mSv/y to ≥ 6 mSv/y. Five papers found that radiation at 0.06 mSv/y level was beneficial to health in high background-radiation areas, and conversely four papers found it was detrimental. The other 19 papers recommended conducting long-term research. Only in one paper was found neurological disorder, such as Alzheimer’s disease (AD) [29]. According to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), there are four main sources, which form the Natural Background Radiation: cosmic rays, terrestrial radiation, intakes of naturally occurring radionuclides through inhalation and ingestion.

We identified 13 papers that fulfilled the criteria of natural background radiation impact on the health over the terrestrial radiation, intakes of naturally occurring radionuclides through inhalation and ingestion [5-7, 12, 13, 16, 17, 19, 21-23, 27, 28]. There are several molecular epidemiological studies that revealed low dose of natural background radiation beneficial for health, as it induce the adaptive response in the DNA damage repair capacity and antioxidant capacity of inhabitants in the high background-radiation area [1-3, 9-11, 15, 18, 25]. There were just four papers, which suspected the adverse effect from natural background radiation on the human health [4, 8, 11, 14, 18, 20]. However, the authors still recommended studying this question, as to be sure that radiation is a dominant risk factor for the health. Additionally, there was no any significant danger to the population health in two papers by Muneer Aziz Salehab et al. and Krishnamoorthy, N. et al. [24, 26].

Discussion. Environmental issues increase interest in all scientific spheres. A huge number of papers published with hazard effect of air pollution, ozone layer depletion, climate changing and natural ionizing radiation.

To our knowledge, this is the first systematic review that evaluated the influence of natural background radiation on human health. There are numerous systemic review in terms of man-made (due to the technic radiation), atomic bomb disaster impact on the human’s health [30-32]. However, there was few studies with strong evidence of hazard effect on human health. One of the reason is difficulties in identifying the true natural ionizing radiation risk, as comorbidities such as diabetes mellitus, cardiovascular disease, metabolic syndrome contribute negative effect to the whole organism as well [33]. Our findings seems to suggest that the first step in identifying clear effect on health due to natural radiation is conducting a good epidemiological study in order to detect an annual effective dose of radiation. The second step should be longitudinal study for identifying the main health issues and possible risk factors.

At the experimental works on the animals, the adverse effect on the animal health was proved. However, the limitation of such kind studies is the artificial radiation exposure [34, 35].

The strengths of our review is that we investigated the association between natural background radiation as source of exposure on human health. We searched two scientific databases. Nevertheless, some potential limitations of the review process exist. Despite intensive searches, relevant publications may have been missed. The strength of our conclusion is limited by the very low quality of evidence available for our research question of interest.

Conclusion: However, there are still unknown areas with abnormal radiation. The opinion of scientist differs in this issue. The specific effects due to radiation (stochastic and deterministic effects) are controversial as there are a huge restriction in terms of study diseases, immune and gene respond to the natural background radiation. Definitely, there is impact on health due to radon gas (one of the source of background radiation) and radionuclides, but there is no approved methodology in order to measure the effects on human health. Furthermore, there is no studies about the radio-resistance and radio-tolerance in human, what can be taken into consideration and become the first step for the future research project idea.

С. Т. Туруспекова, Р. Т. Цой

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ТАБИҒИ РАДИАЦИЯЛЫҚ ФОННЫҢ АДАМ ДЕНСАУЛЫҒЫНА ӘСЕРІ

Аннотация. Табиғи радиациялық фон жаппай, бүкіл Жерде кездеседі. Қазіргі уақытта табиғи радиациялық фонның адам ағзасына әсері салдарынан пайда болатын нәтижелер туралы әртүрлі гипотезалар бар. «Радиацияның адам денсаулығына әсері» атты әдеби деректерде білімнің үлкен олқылықтар орын алған.

Мақсаты. Табиғи радиациялық фонның адам денсаулығына әсер ететін-етпейтіндігін анықтау.

Материалдар мен әдістер. Біз әдеби шолу жасадық. Іздеу 2013 жылдан бастап 2018 жылға дейін PubMed және Medline деректер базасында ағылшын тілінде жүргізілді.

Нәтижелері. 1934 абстракт табылды. 1898 жарияланым шығарылып тасталды. Біз 36 толық мәтінді құжатты зерделедік. Осы әдеби шолуды жазу үшін 28 құжат біздің критерийлерімізге сәйкес келді. Табиғи радиациялық фон ≤ 100 мЗВ-дан ≥ 6 мЗВ-ға дейінгі диапазонда орналасқан. Бес жарияланымда ≤ 100 мЗВ дозадағы табиғи радиациялық әсердің оң әсері анықталды, ал төрт жұмыста авторлар табиғи радиациялық фонның адам денсаулығына зиянды әсері туралы көрсеткен. Он тоғыз жарияланымның авторлары ұзақ уақыт бойы мұқият зерттеу жүргізуді ұсынды. Тек бір жұмыста ғана табиғи радиациялық фонның әсері салдарынан когнитивтік тапшылық туралы, атап айтқанда Альцгеймер ауруының дамуы туралы нәтижелер айтылған.

Қорытынды. Ғалымдардың пікірі табиғи радиациялық фонның адамға әсері мәселесінде әр түрлі. Табиғи радиациялық фонның әсері салдарынан туындайтын әсерлерді анықтау бойынша қосымша зерттеулер жүргізу қажеттілігі бар.

Түйін сөздер: табиғи радиациялық фон, денсаулық, когнитивті функциялар, орташа когнитивті бұзылулар, Альцгеймер ауруы.

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ВЛИЯНИЕ ПРИРОДНОГО РАДИАЦИОННОГО ФОНА НА ЗДОРОВЬЕ ЧЕЛОВЕКА

Аннотация. Природный радиационный фон встречается повсеместно, по всей Земле. На данный момент существуют различные гипотезы об эффектах, возникающих вследствие воздействия природного радиационного фона на организм человека. В литературных данных на тему «Воздействие радиации на здоровье человека» существует огромный пробел в знаниях.

Цель. Выявить влияет ли природный радиационный фон на здоровье человека

Материалы и методы. Нами был проведен литературный обзор. Поиск осуществлялся на английском языке с 2013 по 2018 года в базах данных PubMed и Medline.

Результаты. Было найдено 1934 абстракта. 1898 публикаций были исключены. Мы изучили 36 полнотекстовых документа. 28 документов соответствовали нашим критериям включения для написания данного литературного обзора. Природный радиационный фон находится в диапазоне от ≤ 100 мЗВ до ≥ 6 мЗВ. В пяти публикациях было выявлено положительное влияние природного радиационного в дозе ≤ 100 мЗВ, в то время как в четырех работах авторы указали о пагубном влиянии природного радиационного фона на здоровье человека. Авторы девятнадцати публикаций рекомендовали провести более тщательное исследование с длительным временным промежутком. Только в одной работе были упомянуты результаты о возможном когнитивном дефиците вследствие воздействия природного радиационного фона, а именно, о развитии болезни Альцгеймер.

Вывод. Мнение ученых расходится в вопросе влияния природного радиационного фона на человека. Существует необходимость в проведении дополнительных исследований по выявлению эффектов, возникающих вследствие действия природного радиационного фона.

Ключевые слова: природный радиационный фон, здоровье, когнитивные функции, умеренные когнитивные нарушения, болезнь Альцгеймер.

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NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 11 – 15

<https://doi.org/10.32014/2019.2519-1629.25>

UDC 615.1.4 (175)

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E-mail: kdrakhimov@inbox.ru**STUDIES OF ANTIBLASTOMA NATURAL PRODUCTS
ON THE ORIGINAL AND DRUG-RESISTANT VARIANTS OF TUMORS**

Abstract. Preclinical studies in laboratory animals have shown that polyflavans possess high antitumor activity: 70-92% growth inhibition of Pliss lymphosarcoma, sarcoma 180, Erlich solid tumor, alveolar mucous cancer of the liver PC-1, Guerin carcinoma, sarcoma 45 resistant to sarcolysin and prospidin.

Key words: Pliss lymphosarcoma, Guerin carcinoma, sarcoma 45, P-388 lymphocytic leukemia, breast cancer (BC), antineoplastic drugs.

The antiblastoma effect of many plant extracts under experimental conditions is explained by the presence of dimeric catechins, condensed flavanols, ellagotanins in them [1-3, 6, 8].

A targeted search for anticancer drugs among these groups of compounds is carried out on a large scale in pharmacotherapy at the Kazakh Research Institute of Oncology and Radiology, together with the Department of Chemistry of the Natural Compounds of the al-Farabi Kazakh State University. The researches have revealed some data on the relationship of structure and antitumor activity in a number of different groups of flavanoids, hydrolyzable and condensed tannins [3, 6, 10].

A number of flavanols among monomeric catechins (flavon-3-ol), monomeric (+) - catechin and (-) - epacatechin, when injected intravenously in mice with sarcoma 180 and rats with Walker carcinosarcoma, don't have antitumor action. Dimeric compounds (catechins from Persia gratissima, Ouvatea) inhibit the growth of tumors by up to 50%. More pronounced antitumor activity was found in polymeric flavanols. In works [1, 3, 7, 20, 21] it was shown that monomeric (-) - epicatechin (+) - catechin are low active in antitumor relation, dimeric catechins (from *Coataster vulgaris*, *Larix sibirica* A.) reliably (up to 50-63 %) inhibit the growth of sarcoma 180 and considerable Ehrlich tumor. The condensation products of flavanes with 3', 4', -di-, 3', 4', 5', -triooxy groups with a molecular weight of between 10,000 and 20,000 showed a higher antitumor activity (63-90% of the growth inhibition of a number of transplantable animal tumors). As the authors point out, in this group of polyflavane substances (proanthocyanidins) the degree of their specific activity increases with increasing molecular weight of the polycondensate. In high doses, they exhibit an antitumor effect, in medium doses they are radiosensitizing, and in small doses have an antiradiation effect [1, 3, 5, 6, 19].

Phytopreparations were isolated at the Department of Chemistry of Natural Compounds of the Kazakh State University from various plants - tanning ram (*Polygonum coriarium* grig.), mountain ephedra (*Rumex confertus* Willd.), tatar rhubarb (*Rheum tataricum* L.), siberian larch (*Larix sibirica* A. Ledeb. Tien Shan sorrel, Tien Shan cuff (*Rumex*, *Alchimilla* L. *tianschanicum*), camel thorn (*Alhagi kirgisorum* A. Schrenk.) and others. Leukoefdin from ephedra mountain [21], Alhidin from a camel's thorn [12, 14, 17] was previously recommended by the Laboratory for Experimental Therapy of Tumors of the Kazakh Research Institute of Oncology and Radiology (KazRIOR) for preclinical study.

In the study of the acute toxicity of leukoefdin, it was administered intraperitoneally once as a 2% aqueous solution in doses of 220, 300, 400, 500, 600, 700, 900, 1100 mg / kg. Alhidine in 2% concentration in 0.1% solution of sodium bicarbonate in doses of 600, 1000, 1400, 1800, 2000, 2500 mg / kg.

For male mice, the maximum tolerated dose (MTD) for leucoefdin was 345 mgm / kg, LD₅₀-610 (552 ÷ 668 mg / kg); Alhidin MTD - 510 mg / kg, LD₅₀-840 (710 ÷ 876 mg / kg). After the introduction of drugs, excitation was observed, followed by ruffled coat and depression (within 3-5 hours); in the future, the remaining living mice had these phenomena. Mice died in a state of oppression at 1-5 days after their introduction.

Intolerable single doses of intraperitoneal administration of leucoefidine and alhidine, from which female mice died, the terms of their death from them are close to those of males. Therefore, special titration of single doses on white outbred mice-females was not performed.

At the dissection of the fallen mice, the fullness of the liver and spleen, hyperemia of the abdominal vessels, distention of the intestine are macroscopically noted.

The body weight of the mice in the first two weeks after the administration of leucoefdin in doses exceeding LD₅₀ somewhat decreased and then its recovery occurred. After the introduction of the drug in doses of lower LD₅₀, this indicator increased in accordance with the physiological developmental norms.

The maximum tolerable dose of leucoefdin when administered intraperitoneally for rats was 320 mg / kg, LD₅₀-530 (500 ÷ 560) mg / kg for alhidine 480 mg / kg, LD₅₀ - 690 ÷ 770 mg / kg. In toxic doses (700-1000 mg / kg), leucoefdin after administration caused excitement, then ruffled coat and depression (3-6 hours), rats died 1-5 days after exposure to the drug. At the dissection of dead rats from intolerance to leucoefdin, the same pathological picture was noted as in the case of experiments on mice with a single intraperitoneal injection.

A 10% aqueous solution of lyophilized leucoefdin after a single injection into the bladder at a dose of 250 mg / kg did not cause the death of rats, dysuric events, abnormalities in the pathological and morphological studies of the internal organs and bladder. Single doses of 550 and 890 mg / kg resulted in the death of rats by 40 and 50%. The death of animals from intolerable doses mainly occurred on the 8-10 day after administration, starting from 3-4 days. Toxic effects developed slowly and were caused by a pronounced irritant effect on the bladder mucosa; incomplete bladder content was observed. Common symptoms of intoxication were lethargy, loss of appetite, and general depression. Restoration of these changes in the surviving animals occurred for 15-20 days with the subsequent normalization.

With the introduction of a 10% aqueous solution of leucoefdin in the MPD in the bladder to rats daily for 10 days was 50 mg / kg and for the next 30 days there was no toxic effect of the drug [1, 11, 16].

Alhidine at a 2% concentration in a 0.1% solution of sodium bicarbonate was tested with a single intraperitoneal intravenous (tail vein) of mice and rats.

The MTD was 45 mg / kg, LD₅₀ 90 mg / kg. The therapeutic latitude of alhidine for mice is small: the value of MTD is close to the lower boundary of the confidence interval for LD₅₀. The indicated toxicity parameters in female mice of line F₁ (CBA x C57Bl 6) are identical to the data on white outbred male mice.

The main death of animals from intolerance to doses began after 2-15 minutes and after 1-3 hours (below LD₅₀) and occurred 1-3 days after a single injection of the drug, but individual mice died on 8-12 days of experience [1, 4, 9, 13]. Exceeding the permissible concentration of alhidine (4% versus 2%) did not cause a local irritating action (no infiltration of the subcutaneous tissue of the tail). At the autopsy of rats suffering from intolerance to doses of alhidine, the same pathological-anatomical picture was observed as in the case of experiments on mice with a single injection of the drug.

Parameters of acute toxicity of sea buckthorn polyflavones and cuff grass are of low toxicity.

Chronic toxicity. In experiments on rats with transplantable tumors, the maximum tolerated dose (MTD) of a 2% aqueous solution of leucoefdin with daily intraperitoneal administration for 10 days was 50 mg / kg for mice, 40 mg / kg for rats, oral: 200 mg / kg for mice, 500 mg / kg for rats.

For 2% alhidine in a 0.1% sodium bicarbonate solution with daily intraperitoneal administration for 10 days, a single dose was 70 mg / kg for mice and rats; intravenous was 50 mg / kg for mice, 40 mg / kg for rats.

The MTD of a 2% aqueous solution of sea buckthorn polyflavan with daily intraperitoneal administration for 10 days for mice is 70 mg / kg, for rats it is 90 mg / kg.

With daily intraperitoneal administration for 5 days of a 2% aqueous solution of polyflavane alchemine-1, the MTD was 30 mg / kg, of alchemy II, 40 mg / kg in experiments on mice; 40 mg / kg in rats. In these doses, no marked toxic effects on animals and their death were observed. At autopsy of

animals slaughtered at the end of the experiment, no pathological changes from the internal organs were revealed.

The antitumor activity of polyflavans: leucoefdin, alhidin, alchemina I and II was studied in mice and rats with the original tumor strains, as well as in rats with drug-resistant variants.

It has been established that intraperitoneal and intravenous injections in MTD, leucoefdin and alhidin, have significant antitumor activity in experiments on rats with Pliss lymphosarcoma (LSP), Guerin carcinoma (K.Geren), carcinoma of Walker (KSU), alveolar mucous liver cancer (PC-1) (62-95% growth inhibition, $P < 0.02-0.001$) to a lesser extent - M-1 sarcoma (CM-I), 45 sarcoma (C45) and breast cancer (RMK-1) (26-60%). A reliably pronounced inhibitory effect was obtained in the treatment of these drugs in MTD mice with sarcoma 37 (C37), sarcoma 180 (S180), a considerable Ehrlich tumor (Erlieh tumor), gastric cancer of OZh-5 (OZh-5), adenocarcinoma of the mammary gland (CA) 755, cervical cancer (CCR-5) and Lewis lung carcinoma (LL) (60-84% growth inhibition, $P < 0.01-0.05$). At the same time, an increase in life expectancy (ILE) of the mice with lymphocytic leukemia P-388 (P-388) (by 46-87%) with respect to the control was noted. Lymphoid leukemia L 1210 (L1210) (UPJ - 11-12%) and hepatoma 22a (12-36%) are not very sensitive.

Sea buckthorn polyflavone had a significant inhibitory effect in MTD in experiments on five tumors: breast cancer (RMK-1) and Pliss lymphosarcoma (88 and 60% growth inhibition, respectively), C-180, Ehrlich solid tumor (55 and 49%, respectively), P-388 (UPZh-50%). The remaining tumors of mice and rats were insensitive to this drug.

Alchemine-I had a high antitumor effect in comparison with alchemine-II in MTD on KSU, a solid tumor of Erlich, K.Heren (90-56% growth inhibition, $P < 0.001-0.05$); both alchemine and C 45, LSP growth (72-76%) were equally inhibited. The remaining tumors were insensitive to them.

Thus, polyflavans have a high antitumor activity: 70-92% growth inhibition of Pliss lymphosarcoma, 180 sarcoma, Erlich solid tumor, alveolar mucous liver cancer PC-1, Guerin carcinoma.

Leukoefdin, alhidin and polyflavin from sea buckthorn with intraperitoneal daily use (for 10 days) caused a significant reliable therapeutic effect in relation to the resistance to rubomicin of Pliss lymphosarcoma (59-80% inhibition). As one can see, the initial sensitivity (60-88%) of the given strain to drugs is retained. The substrains of sarcoma 45, resistant to rubomycin and 5-fluorouracil were insensitive to polyflavins. On the contrary, in a comparative study, the tested polyflavans (at doses of 45, 70, 90, and 40 mg / kg, respectively) up to 90% inhibited the growth of sarcoma 45 resistant to prospidine. High sensitivity (up to 83% inhibition) and sarcoma 45 resistant to 5-fluorouracil have been revealed for alhidine [1, 4, 6, 7].

Sarcoma 45, resistant to sarcolysin, showed hypersensitivity to leukoefdin. The drug inhibited the growth of the original strain by 38%, and drug-resistant by 80% ($P < 0.001$). Whereas on this strain, alhidin and polyflavin from sea buckthorn caused cross-resistance.

Similar results were obtained in the treatment of leucoefdin rats with Pliss lymphosarcoma resistant to prospidin. In experiments with this tumor strain, the initial sensitivity (92 and 56%, respectively) was retained when exposed to alhidin and alchemine-I (76 and 74%, respectively).

High antitumor activity was detected when leucoefdin and alhidine were administered (in MTD by intraperitoneal administration) to mice with lymphoid leukemia L 1210, resistant to methotrexate (MTX), nitrosomethylurea (NMU) [15], 6-mercaptopurine (6-MP) 146% ILE in relation to the control. A moderate increase in the life expectancy of the mice was found during treatment with a polyflavin of sea buckthorn and alchemine I (up to 35% ELE).

The studied polyflavans, in addition to tannins (82%), flavanoids (5%), glucose (2.2%), arabinose (1%), contain polysaccharides (1.6%).

Thus, with the use of drug-resistant transplantable rat tumors, Pliss lymphosarcoma and sarcoma 45, resistant to rubomicin and prospidin, were susceptible to polyflavans; sublimes of leukemia L 1210, resistant to 6-mercaptopurine, nitrosomethylurea, methotrexate.

Of the polyflavans used, the more active (on 6-8 strains) were alhidin and leucoefdin. On sarcoma 45, resistant to sarcolysin and prospidin, collateral sensitivity to leucoefdin is manifested, and sarcoma 45, resistant to 5-fluorouracil – to alhidin.

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**ТАБИҒИ ПРЕПАРАТТАРДЫҢ
БІРІНШІЛІКТІ ЖӘНЕ ДӘРІГЕ ТҰРАҚТЫ ҚАТЕРЛІ ІСІКТЕРГЕ
АНТИБЛАСТОМДЫҚ ӘСЕРІН ЗЕРТТЕУ**

Аннотация. Зертханалық жануарларға клиникаға дейінгі зерттеу кезінде полифлавандар қатерлі ісікке қарсы әсері жоғары екені дәлелденді: сарколизинге және проспидинге тұрақты Плисс лимфосаркомасы, саркома 180, Эрлихтың солидті ісігі, бауырдың альвеолярлы сілемейлі ісігі, РС-1, Герен карциномасы, саркомы 45 өсуін 70-92% тежеді.

Түйін сөздер: Плисс лимфосаркомасы, Герен карциномасы, саркома 45, лимфоцитарлы лейкемия Р-388, сүт безі қатерлі ісігі (РМЖ-1), қатерлі ісікке қарсы препараттар.

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**ИССЛЕДОВАНИЯ АНТИБЛАСТОМНЫХ ПРИРОДНЫХ ПРЕПАРАТОВ
НА ИСХОДНЫХ И ЛЕКАРСТВЕННО РЕЗИСТЕНТНЫХ
ВАРИАНТАХ ОПУХОЛЕЙ**

Аннотация. Доклинические исследования на лабораторных животных доказали, что полифлаваны обладают высокой противоопухолевой активностью: 70-92% торможения роста лимфосаркомы Плисса, саркомы 180, солидной опухоли Эрлиха, альвеолярного слизистого рака печени РС-1, карциномы Герена, саркоме 45, резистентной к сарколизину и проспидину.

Ключевые слова: лимфосаркома Плисса, карцинома Герена, саркома 45, лимфоцитарная лейкемия Р-388, рак молочной железы (РМЖ-1), противоопухолевые препараты.

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NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 16 – 19

<https://doi.org/10.32014/2019.2519-1629.26>

UDC 616.379-008.64

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**MORPHOLOGICAL CHANGES OF THE THYMUS DURING ACUTE
INTOXICATION WITH YELLOW PHOSPHORUS**

Abstract. This scientific article discusses the violation of the thymus after acute intoxication with yellow phosphorus. After 6 days, it was found that the volume of the connective tissue capsule and partitions increased in the thymus. Accumulations of mast cells are detected, the cross-sectional area decreases. One month after intoxication in the parenchyma of the lymph nodes, an increase in the plasma cells content in the cortex with a characteristic (in the form of "wheel spokes") arrangement of nuclear chromatin is visually observed. Active plasmation of lymphocytes in these conditions is probably associated with enhanced penetration of antigens into the lymph nodes, and therefore the content of the vascular bed is particularly important. The results confirm the involvement of the immune system in the development of intoxication.

Key words: yellow phosphorus, xenobiotic substances, thymus, intoxication, microscopy.

Introduction. Relevance The production of yellow phosphorus in the Republic of Kazakhstan is one of the factors that pollute the environment with xenobiotic substances, the amount of which significantly exceeds the limit of permissible concentration in the external environment, especially at work and close to it (1.2) Intensive mining, production of phosphorus and that compounds in the cotton-growing areas of Kazakhstan are conducted on the background of ultraviolet insolation and overheating of the body, which aggravates the pathogenic effect of yellow phosphorus and its of the connections. The prolonged effect on the body of even the smallest concentrations of toxic substances contributes to the emergence of hidden, few symptomatic forms of chronic intoxication, which makes it especially necessary to search for new methods of diagnosis and treatment (3,4,5,6,7,8,9,10)

Until now, cytomorphological changes in the thymus, after acute intoxication with yellow phosphorus and its compounds, have not been adequately studied.

However, in the literature studied by us there are no data, the effect of acute phosphorus intoxication and its compounds on the organs, the thymus morphostructure.

Materials and research methods. Experimental studies were performed on 12 semi-mature outbred white male rats with an initial body weight of 120-140 g. The animals were kept in a vivarium at a normal food regime and, before the beginning of the experiment, were quarantined for 12-14 days. Weigh rats once a week. Yellow phosphorus in cotton oil was injected into rats in the stomach daily with a probe at a dose of 1.0 mg / kg body weight. After the end of the experiment, the animals were killed by decapitation under ether anesthesia. For light microscopy, samples were prepared after fixation in a 10-12% solution. formalin on phosphate buffer Paraffin sections were stained with hematoxylin and eosin.

The counting of various forms of erythrocytes was carried out on electron diffraction patterns at a magnification of 4,000 times. At least 1,000 erythrocytes were used for each term. Statistical material processing and graphing were performed on a Pentium 111 computer using the BS-Statistika program, as well as Excel-OfficeMicrosoft-Window's-98 application programs.

Results. 6 days after intoxication, the cortical substance of the thymus lobes is represented by tightly adjacent large blocks of heterochromatin, and a thin rim of poorly differentiated cytoplasm with single

mitochondria. T-lymphocytes tightly adjacent to each other, contacting their plasmolemmas. Sometimes, plasma cells are found among them, a typical feature of which are numerous narrow, concentrically located tanks of the granular endoplasmic reticulum.

Normally, plasma cells do not occur in the thymus, and the identified symptom indicates a violation of the permeability of the hematotomus barrier, which is known to include endothelial cells of the blood capillary wall, their continuous basement membrane, perivascular space, epithelioreticulocyte basement membrane and cytoplasm of the cell and the cytoplasm. cells are characterized by elongated nuclei with scalloped contours, containing predominantly heterochromatin. In their cytoplasm the Golgi complex and the endoplasmic reticulum are moderately developed.

However, especially in the medulla of the thymus lobules, epithelial cells of the stroma are found with a very well developed Golgi complex, which is located in the perinuclear zone and is represented by several dictyosomes, lysosomes and a multitude of vesicles. In such cells there are large, expanded tanks of a granular endoplasmic reticulum with flaky content in the lumen, vacuoles specific for reticuloepitheliocytes are found.

Such uniform vacuoles are characteristic of secretory epithelioreticulocytes, in which hormone-like factors – thymosin, thymopoietin and thymulin – were detected using monoclonal antibodies. This type of stromal cells is characterized by the presence of a large nucleus with diffuse chromatin and 1-2 large nucleoli, represented predominantly by the granular component.

When studying the microvasculature vessels, blood capillaries with altered endothelium were detected. The surface of endotheliocytes, facing the capillary lumen, contains numerous outgrowths and invaginations, and thinning areas are found. There are few organelles in the cytoplasm, micropinocytosis vesicles are visible. The basement membrane in the wall of such capillaries is unstructured, characterized by low electron density. These ultrastructural features suggest an increase in permeability of the blood-brain barrier. Often there are closed capillaries with a nucleating part of the endotheliocyte emanating into the lumen. Pinocytotic vesicles are numerous in the cytoplasm of endothelial cells.

Thus, the ultrastructure of thymus lymphocytes and reticuloepithelial cells at this time of the study is not characterized by gross pathology and the most noticeable change is the presence of plasma cells in the organ parenchyma due to a violation of the permeability of the hematothymus barrier.

The causes and nature of changes in immunocompetent organs in conditions of intoxication are multifaceted. A number of changes are undoubtedly due to the direct alternative effects of intoxication factors (stress, hypoxia, toxemia, etc.) on parenchymal and stromal elements. In addition, in these experimental conditions, the stress of functioning should take place and, accordingly, more intensive wear of immunocompetent cells and components of the stroma of the organs due to the appearance in the body of a significant amount of substances with antigenic and autoantigenic properties.

One month after intoxication in the parenchyma of the lymph nodes, an increase in the plasma cells content in the cortical substance with a characteristic (in the form of "wheel spokes") arrangement of nuclear chromatin, well developed, tightly fitting tanks of granular endoplasmic reticulum, large mitochondria of a rounded or slightly elongated shape is visually observed. with parallel cristae. Active plasmatization of lymphocytes in these conditions is probably associated with enhanced penetration of antigens into the lymph nodes, and therefore the content of the vascular bed is particularly important.

The vessels of the microvasculature look as spasmed; the cells forming their wall show signs of dystrophic changes. The lumen of arterioles appears to be sharply constricted, the endothelial cells protruding into it form a characteristic "jagged" structure. The nuclei of some endotheliocytes show signs of pycnosis; vacuolation of the cytoplasm of individual smooth muscle cells is found. The elastic membrane is sharply winding. In the blood capillaries, vacuolar degeneration of endotheliocytes, sometimes pycnosis of the nuclei, and destruction of the basement membrane is also noted.

The above changes can, in all likelihood, be regarded as evidence of the inclusion of an autoimmune process intoxication in the pathogenesis.

A month later, the cortical substance of the thymus lobules is represented by clusters of lymphocytes in loops formed by the reticuloepithelial stroma. Lymphocytes are characterized by a round heterochromatic nucleus and a thin rim of cytoplasm; In some thymic lymphocytes, changes in the form of perinuclear cysts expansion and signs of apoptosis are found.

The ultrastructure of reticuloepithelial cells is distinguished by polymorphism. Among them are the "light" and "dark" cells, which differ from each other in the electronic density of hyaloplasm; reticuloepithelial cells with signs of destruction and the formation of apoptotic bodies and cell breakdown are found. Along with this many thymus reticuloepitheliocytes are characterized by the presence of a well-developed granular endoplasmic reticulum in the cytoplasm, a large nucleus with a granulated nucleolus.

There are spasmodic capillaries with moderate signs of dystrophy endotheliocytes and destruction of the basement membrane. The reticuloepithelial cells located next to such capillaries showing signs of vacuolization. Reticuloepithelial cells with signs of destruction and apoptosis are detected.

It seems that in the thymus, as in other organs studied under the conditions of this pathology, destructive changes are most pronounced in the parenchymal and stromal elements of the organ, which are located in the immediate vicinity and the walls of the blood capillaries. Taking into account the presence of toxins in plasma intoxication, it can be assumed that these changes are manifestations of a direct cytotoxic damaging effect.

After 6 days in the thymus there is an increase in the volume of the connective tissue capsule and partitions, accumulations of mast cells are found, the cross-sectional area of the thymus and the area of the cortex of its lobules are reduced, i.e. there are changes that essentially reflect the accidental involution of the thymus under intoxication conditions, which is a mandatory component of the onset and development of this pathology.

The results confirm the involvement of the immune system in the development of intoxication. It can be assumed that there are several options for its involvement in the process or a combination of options, namely:

- primary alternative changes in the organs of immune protection of a polyetiological nature, aggravating the course of the main process and participating in the formation of vicious circles;
- stress response due to autoimmune process;
- stress response due to antibacterial immunity in concomitant infectious process.

Thus, in the conditions studied, there is a combination of the primary damaging effects on the immunocompetent organs and the development of a stress response in them.

Submicroscopic changes found in immunocompetent organs in the intermediate and late periods of intoxication are multidirectional in nature and cannot be interpreted unambiguously: in all likelihood, a combination of changes takes place in these circumstances;

- direct damaging effects on parenchymal and stromal elements, factors of developing intoxication (hypoxia stress, toxemia, etc.);
- stress of functioning and accelerated wear of immunocompetent cells under conditions of increased requirements to the organs of immune protection that occur during the development of intoxication.

However, in spite of the presence of both reactive and destructive changes in the organs studied, and in some cases signs of programmed cell death, the infrastructure of the lymph nodes and the thymus seems to be sufficiently safe to be able to realize the immune response. These circumstances dictate the need for a rational correction of the immune status of the body in conditions of intoxication.

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САРЫ ФОСФОРМЕН ЖЕДЕЛ УЛАНТЫРҒАНДА ТИМУСТЫҢ МОРФОЛОГИЯЛЫҚ ӨЗГЕРІСТЕРІ

Аннотация. Тимустың сары фосформен уланғандан соң интоксикациялық өзгерістер болады. 6 тәуліктен соң тимуста дәнекер тіңдер қабығы және тосындардың көлемі үлкейеді. Базал жасушалар саны көбейеді. Интоксикациядан кейін бір айдан соң лимфатикалық тамырлардың паренхимасында плазмациттардың көбейуі байқалады. Лимфоциттардың белсенді плазматизациясы мүмкін, антигендердің лимфатикалық түйіндердің ішіне кіруіне байланысты болып табылды. Алынған нәтижелер иммунитеттік жүйенің интоксикация процессінде қатысуіні дәлелдейді.

Түйін сөздер: сары фосфор, ксенобиотикалық заттар, тимус, интоксикация, микроскопия.

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МОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ ТИМУСА ПРИ ОСТРОЙ ИНТОКСИКАЦИИ ЖЕЛТЫМ ФОСФОРОМ

Аннотация. В этой научной статье рассматриваются нарушения тимуса после острой интоксикации желтым фосфором. Через 6 суток выяснено, что в тимусе увеличился объём соединительнотканной капсулы и перегородок. Обнаруживаются скопления тучных клеток, уменьшается площадь поперечного сечения. Через месяц после интоксикации в паренхиме лимфатических узлов визуально отмечается увеличение содержания плазмоцитов в корковом веществе с характерным (в виде «спиц колеса») расположением ядерного хроматина. Активная плазматизация лимфоцитов в данных условиях связана, вероятно, с усиленным проникновением антигенов в лимфатические узлы, в связи с чем особенно важным представляется содержание сосудистого русла. Полученные результаты подтверждают участие иммунной системы в развитии интоксикации.

Ключевые слова: желтый фосфор, ксенобиотические вещества, тимус, интоксикация, микроскопия.

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NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 20 – 26

<https://doi.org/10.32014/2019.2519-1629.27>

UDC 577.21

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CLUSTERS OF miRNAs BINDING SITES in 3'UTR mRNA OF BREAST CANCER CANDIDATE GENES

Abstract. Breast cancer is the most common disease among women and the development of methods for early diagnosis requires the identification of non-invasive molecular markers of oncogenesis. Associations of miRNAs and breast cancer candidate genes can serve as such markers. Characteristics of the interaction of miRNAs with mRNAs of several genes were predicted using the MirTarget program. It has been established that miRNA binding sites (BS) can be located in the mRNA with overlapping nucleotide sequences, forming clusters of BS. The studied genes contained BS of one or more miRNAs in the 3'UTR mRNA. When the nucleotide sequences of the BS in the cluster overlap, a multiple decrease in the occupied part of mRNA takes place. As a result of the compactization of BS between the miRNAs, there is competition for binding in the cluster. Identified ID00436.3p-miR and ID01030.3p-miR with BS with the overlap of nucleotide sequences in the 3'UTR mRNA containing multiple repeats of the GU and CA dinucleotides of *BACH1*, *CD19*, *CDK6*, *ETS1*, *FGFR3*, *FOXP1*, *IGF2R*, *FOXP1*, *IGF2R*, *IGF2R*, *IGF2R*, *IGF2R*, *SP1*, *ST8SIA1* and *WT1* genes. Established ID00470.5p-miR and ID02299.5p-miR which BS are also located with the overlap of nucleotide sequences in the mRNA of *CARNS1*, *CCND1*, *EFNB1*, *IGF2*, *SMAD4* and *ZEB1* genes. ID01727.5p-miR and ID02882.3p-miR have coinciding sites in the mRNA of *ELK4*, *FOXP1* and *SFN* genes. ID01382.3p-miR has BS in *TGFBI* and *SMAD3* genes consisting of four repeats of GCCCC. The associations of ID00436.3p-miR and ID01030.3p-miR with target genes are proposed for early molecular diagnosis of the disease. These associations include *BACH1*, *CDK6*, *ETS1*, *IGF2*, *SFN*, *SMAD4*, *SP1* and *ST8SIA1* genes. Associations of ID00470.5p-miR and ID02299.5p-miR with *CARNS1*, *CCND1*, *EFNB1*, *IGF2*, *SMAD4* and *ZEB1* genes are recommended to use for early molecular diagnosis of the disease.

Key words: miRNA, mRNA, cluster, target gene, breast cancer.

Introduction. The incidence of breast cancer (BC) has high rates in the world and Kazakhstan [1]. This is due to the insufficiency of preventive measures, such as early diagnosis. Recently, there have been many studies on the diagnosis of BC using miRNA (mRNA-inhibitory RNA), which play a key role in the post-transcriptional regulation of genes involved in proliferation, differentiation, angiogenesis, migration, apoptosis and carcinogenesis [2]. More than 600 genes are involved in the development of BC [3] and it seems important to identify which of them may be targets for miRNAs. Earlier, we studied the interactions of miRNAs from miRBase database with BC candidate genes [3-5] and it was shown that miRNAs can be strong regulators of the expression of many genes and serve as markers for developing methods for early diagnosis of BC [6]. According to the literary data, miRNAs are predominantly bind in the 3'UTR mRNA [7]. Thereby, in this work, we studied interaction characteristics of recently discovered and poorly studied 3707 miRNAs [8] with mRNA of BC candidate genes.

Materials and Methods. The nucleotide (nt) sequences of 19 BC candidate genes were downloaded from GenBank (<http://www.ncbi.nlm.nih.gov>). The nucleotide sequences of 3707 miRNAs were taken from the publication [8]. RPKM values [9] are given in the Human Protein Atlas data (<https://www.proteinatlas.org>). Human Protein Atlas data were used as a quantitative measure of

transcript expression in mammary gland. Recently, computer approaches in biotechnology [10] and biology [11] have been actively used. The miRNAs binding sites (BS) in mRNAs of several genes were predicted using the MirTarget program [10]. This program defines the following features of miRNA binding to mRNA: a) the start of the initiation of miRNA binding to mRNAs; b) the localization of miRNA BS in 5'UTRs, CDSs and 3'UTRs of the mRNAs; c) the free energy of interaction miRNA and the mRNA (ΔG , kJ/mole); d) the schemes of nucleotide interactions between miRNAs and mRNAs. The ratio $\Delta G/\Delta G_m$ (%) was determined for each site (ΔG_m equals the free energy of miRNA binding with its fully complementary nucleotide sequence). The miRNA BS located in mRNAs had $\Delta G/\Delta G_m$ ratios of 87% or more. $\Delta G/\Delta G_m$ ratios were taken on the assumption that the members of the miRNA of one family generally differ by no more than 1-3 nucleotides, that with a miRNA length of 22 nt, the $\Delta G/\Delta G_m$ value was 96% (21 nt/22 nt = 96%) - 87% (19 nt/22 nt = 87%). With a larger difference in the number of mismatched nucleotides, the probability of two or more miRNAs to bind in one site increases, which excludes the natural property of the miRNA to interact selectively with the mRNA of the target gene. The MirTarget program identifies the positions of the BSs on the mRNA, beginning from the first nucleotide of the mRNA's 5'UTR. The numbers of hydrogen bonds in the G-C, A-U, G-U and A-C interactions were found to be 3, 2, 1 and 1, respectively [12-14].

Results and Discussion. The *AKT1* gene is the target of three miRNAs (Table 1). The BSs of these miRNAs are located with the overlap of nucleotide sequences that form the mRNA region named by us as cluster of BSs. The total length of three miRNAs BSs is 64 nt and, due to compactization, they are located in a cluster of 35 nt length. The length of 3'UTR is 992 nt and there is no need to compactized BSs. Probably, the compactization of BSs is intended to limit the dependence of gene expression on three miRNAs simultaneously, since only one miRNA can be bind at a 35 nt cluster. The binding characteristics of the three miRNAs are close (table 1) and miRNA present in greater concentration will have an advantage in interacting with mRNA.

Table 1 – Characteristics of miRNA binding in the 3'UTR mRNA of BC genes

Gene; RPKM	miRNA	Start of site, nt	ΔG , kJ/mole	$\Delta G/\Delta G_m$, %	Length, nt
<i>AKT1</i> ; 33.6	ID00403.3p-miR	2864	-117	93	21
	ID00722.5p-miR	2866	-113	93	20
	ID00843.5p-miR	2875	-119	90	23
<i>BACH1</i> ; 5.6	ID00436.3p-miR (8)	4257÷4279	-104÷-106	89÷91	23
	ID01030.3p-miR (6)	4257÷4267	-108	89	23
<i>BIK</i> ; 3.5	ID00700.5p-miR	546	-117	92	20
	ID02766.3p-miR	548	-123	92	22
	ID02108.3p-miR	553	-113	90	22
<i>CARNS1</i> ; 0.8	ID00470.5p-miR (4)	3225÷3231	-108	89	23
<i>CCND1</i> ; 27.6	ID00470.5p-miR (2)	2595÷2597	-108	89	23
<i>CD19</i> ; 0.1	ID00436.3p-miR(2)	1862÷1864	-104÷-106	89÷91	23
	ID01030.3p-miR	1862	-108	89	23
<i>CDK6</i> ; 2.2	ID00436.3p-miR (9)	1896÷1920	-104÷-106	89÷91	23
	ID01030.3p-miR (7)	1900÷1918	-108÷-115	89÷95	23
	ID02513.5p-miR	1901	-102	91	22
<i>CREB1</i> ; 5.3	ID01332.3p-miR	2780	-113	91	22
	ID03006.5p-miR	2781	-121	89	24
	ID03149.5p-miR	2784	-115	92	22
<i>ELK4</i> ; 0.1	ID02868.3p-miR	8296	-113	90	23
	ID01727.5p-miR	8297	-104	89	23
	ID02882.3p-miR	8302	-110	93	21
<i>EFNB1</i> ; 30.4	ID00470.5p-miR (3)	2526÷2530	-108	89	23
<i>ETSI</i> ; 28.5	ID01030.3p-miR (12)	3875÷3908	-108	89	23
	ID00436.3p-miR (11)	3888÷3908	-104	89	23

Continuation of table 1					
<i>FGFR3</i> ; 2.3	ID00436.3p-miR	2814	-108	93	23
	ID01030.3p-miR	2814	-113	93	23
	ID01727.5p-miR	2819	-104	89	23
<i>FOXPI</i> ; 5.3	ID00436.3p-miR	5952	-104	89	23
	ID01727.5p-miR (2)	5953÷5955	-104÷-106	89÷91	23
	ID02882.3p-miR	5960	-110	93	21
<i>IGF2</i> ; 20.4	D00436.3p-miR	5970	-104	89	23
	D00470.5p-miR (9)	2286÷2463	-108÷-113	89÷93	23
	ID02299.5p-miR (3)	2302÷2458	-100	94	21
	ID00470.5p-miR (3)	2520÷2539	-108	89	23
<i>IGF2R</i> ; 13.5	ID00470.5p-miR (3)	2655÷2672	-108÷-110	89÷91	23
	ID00436.3p-miR(6)	8447÷8457	-104	89	23
	ID01030.3p-miR(5)	8447÷8455	-108	89	23
<i>PAX2</i> ; 0.2	ID02062.3p-miR	3098	-121	90	22
	ID03306.3p-miR	3104	-123	94	21
	ID02781.3p-miR	3105	-117	93	20
	ID00329.3p-miR	3107	-127	92	22
<i>SFN</i> ; 9.4	ID00790.3p-miR	1179	-104	89	23
	ID02868.3p-miR	1188	-113	90	23
	ID00436.3p-miR (7)	1190÷1202	-104	89	23
	ID01030.3p-miR (6)	1190÷1200	-108	89	23
	ID01727.5p-miR	1203	-106	91	23
	ID02882.3p-miR	1210	-108	91	21
<i>SMAD3</i> ; 14.0	ID02822.5p-miR	2070	-127	91	23
	ID00978.5p-miR	2072	-119	90	22
	ID01382.3p-miR	2075	-113	93	20
<i>SMAD4</i> ; 9.8	ID00470.5p-miR (5)	7744÷7752	-108	89	23
	ID02299.5p-miR (6)	7743÷7753	-96	90	21
<i>SOX4</i> ; 13.2	ID01839.3p-miR	2994	-123	89	23
	ID01282.3p-miR	3000	-125	95	23
	ID00101.3p-miR	3001	-115	92	22
	ID03445.3p-miR	3001	-121	89	23
<i>SPI</i> ; 15.5	ID00436.3p-miR (8)	4147÷4161	-104÷-106	89÷91	23
	ID01030.3p-miR (7)	4147÷4159	-108	89	23
<i>ST8SIAL1</i> ; 0.5	ID00790.3p-miR	4531	-104	89	23
	ID00436.3p-miR (14)	4537÷4563	-104÷-106	89÷91	23
	ID01030.3p-miR (12)	4537÷4559	-108	89	23
	ID01727.5p-miR	4562	-106	91	23
<i>TGFBI</i> ; 19.5	ID03306.3p-miR	2060	-123	94	21
	ID01382.3p-miR	2062	-113	93	20
	ID03208.5p-miR	2066	-125	88	24
<i>WT1</i> ; 0.0	ID02513.5p-miR	2698	-104	92	22
	ID00436.3p-miR (8)	2705÷2719	-108	89	23
	ID01030.3p-miR (12)	2705÷2715	-104	89	23
<i>ZEB1</i> ; 11.3	ID00470.5p-miR (10)	3587÷3605	-108	89	23
<i>ZIC1</i> ; 0.1	ID03324.3p-miR	2547	-115	90	22
	ID00849.3p-miR (2)	2551÷2558	-119÷-121	92÷93	22
	ID01545.3p-miR (2)	2552÷2559	-110÷-113	91÷93	21
	ID01911.5p-miR	2553	-127	92	23

In the mRNA of *BACHI* gene, the BSs of two miRNAs are located, which have eight and six arranged sites. The nucleotide sequence of cluster is represented by 17 repeats of GU dinucleotide. With a length of 3'UTR equal to 3315 nt, there is no point in compactizing BSs. By overlapping the miRNA BSs, as in the *AKT1* gene, competition is created between two miRNAs. To date, there is no explanation for the biological function of nucleotide repeats in the 3'UTR. In our work, the value of dinucleotide repeats as miRNA BSs was established for the first time. The mRNA of *CDK6* gene contains BSs of ID00436.3p-miR and ID01030.3p-miR, which have nine and seven arranged BSs, respectively. The 46 nt cluster consists of 23 dinucleotide GU repeats. The length of 3'UTR is equal to 10219 nt, that is, it is much longer than the length of the cluster and there is no need for superposition of these miRNAs BSs. However, there is a competition between these miRNAs for binding in the cluster.

The cluster of ID00436.3p-miR and ID01030.3p-miR BSs in the mRNA of *ETS1* gene contains 11 and 12 BSs of these miRNAs 57 nt long, consisting of 28 repeats of GU dinucleotide. The length of 3'UTR is equal to 3601 nt and the superposition of two miRNAs BSs slightly reduces its length. That is, in this case, there is competition between two miRNAs. The mRNA of *FGFR3* gene has only one BS for ID00436.3p-miR and ID01030.3p-miR, but the nucleotide sequences of their BSs are overlap. The cluster of six miRNAs BSs in the mRNA of *SFN* gene contains seven and six BSs of ID00436.3p-miR and ID01030.3p-miR, respectively. The cluster 67 nt long consists of 33 repeats of GU dinucleotide. 3'UTR includes 498 nt so clustering does not significantly affect the length of 3'UTR, but competition between miRNAs arises. The mRNA of *SPI* gene has eight and seven BSs for ID00436.3p-miR and ID01030.3p-miR. The cluster of BSs 38 nt long consists of 19 GU dinucleotides with a length of 3'UTR equal to 5207 nt.

The mRNA of *ST8SIAL1* gene contains 14 and 12 BSs of ID00436.3p-miR and ID01030.3p-miR, which are included in the cluster of BSs of four miRNAs. The cluster consists of 23 GU dinucleotide repeats, 46 nt long, which is significantly less than the length of 3'UTR equal to 8162 nt. Six and five BSs of ID00436.3p-miR and ID01030.3p-miR, respectively, were identified in the mRNA of *IGF2R* gene. Eight and twelve BSs of ID00436.3p-miR and ID01030.3p-miR, respectively, were identified in the mRNA of *WT1* gene.

In addition to ID00436.3p-miR and ID01030.3p-miR, which have BSs with overlapping nucleotide sequences in mRNA of several genes, we have identified ID00470.5p-miR and ID02299.5p-miR BSs, which are also located with overlapping nucleotide sequences in mRNA of *IGF2* gene. The first cluster is located from 2286 nt to 2486 nt, the second from 2520 nt to 2562 nt and the third from 2655 nt to 2695 nt. All three clusters consist of CA dinucleotide repeats with irregular inserts of C or A nucleotides. The length of 3'UTR is 3871 nt. ID00470.5p-miR and ID02299.5p-miR have five and six sites in *SMAD4* gene, respectively. ID00470.5p-miR has four sites in the mRNA of *CARNS1* and *CCND1* genes, three sites in *EFNB1* mRNA and ten BSs in *ZEB1* mRNA.

The results show that a single gene can be targeted by several alternative miRNAs. One miRNA can interact with several alternative target genes. On the one hand, such links between miRNA and target genes significantly complicate the use of associations of miRNA and genes in the diagnosis of the disease. On the other hand, such associations of miRNA and target genes make diagnosis more reliable, since such associations are not random and more accurately reflect the contribution of each component to the development of the disease.

A feature of the miRNA BSs in the 3'UTR mRNA BC candidate genes is their organization into clusters with the number of sites from two to six. However, in the 3'UTR mRNA of many genes there are clusters consisting of multiple BSs of one or two miRNAs. These miRNAs can significantly affect the translation of mRNA of many BC candidate genes, which increases the probability of their influence on oncogenesis. The associations of ID00436.3p-miR and ID01030.3p-miR with target genes must be used for early molecular diagnosis of the disease. These genes include *BACHI*, *CDK6*, *ETS1*, *IGF2*, *SFN*, *SMAD4*, *SPI* and *ST8SIAL1*, characterized by the RPKM value from 0.5 to 28.5. Consequently, these miRNAs can suppress translation regardless of the rate of target genes expression.

Schemes of interaction of nucleotide sequences of BS of miRNA with mRNA candidate genes of breast cancer in table 2 show how miRNA interacts with mRNA by all miRNA nucleotides. The miRNA and mRNA interaction schemes clearly demonstrate advantages of MirTarget program over the existing programs for predicting miRNA BSs with mRNA target genes.

анықтау керек. миРНК-лар және сүт безінің қатерлі ісік кандидатты гендерінің ассоциациялары мұндай маркерлер ретінде болуы мүмкін. MiTarget бағдарламасы арқылы miRNA-дың және бірнеше гендердің мРНК-мен өзара әрекеттесуінің сипаттамалары анықталды. МиРНК-ның байланысу сайттары мРНК-да нуклеотидтік тізбектердің бүркелуі арқылы кластерлерді құрайтыны анықталды. Зерттелген гендердің мРНК-ның 3'UTR-де бір немесе бірнеше миРНК-дың көптеген байланысу сайттары болды. Кластердегі байланысу сайттардың нуклеотидтік тізбектері қабаттасқанда, миРНК-дың бөлігінің бірнеше есе төмендеуі болады. Байланысу сайттары тығыздалуы нәтижесінде кластерде миРНК-дың арасындағы байланыстыру үшін бәсекелестік пайда болады, өйткені бірнеше миРНК-лар мРНК-ның ұзындығы 25-50 нуклеотидтер кластерінде бір уақытта өзара әрекеттесе алмайды. GU және CA динуклеотидтер бар *CD19*, *CDK6*, *ETS1*, *FGFR3*, *FOXP1*, *IGF2R*, *SFN*, *BACH1* гендерінің мРНК-ның 3'UTR-де ID00436.3p-miR және ID01030.3p-miR миРНК-дың нуклеотидтік тізбектердің бүркеліп орналасқан көптеген байланысу сайттары бар екені белгілі болды. *CARNS1*, *CCND1*, *EFNB1*, *IGF2*, *SMAD4*, *ZEB1* гендерінің мРНК-сында ID00470.5p-miR және ID02299.5p-miR-дың байланысу сайттары қабаттасып орналасқан. Кластердің барлық байланысу сайттары CA динуклеотидті қайтамалардан тұрады. *ELK4*, *FOXP1*, *SFN* гендерінің мРНК-сында ID01727.5p-miR және ID02882.3p-miR байланысу сайттары сәйкес келеді. *TGFBI*, *SMAD3* гендерінде ID01382.3p-miR-ның төрт рет қайталанатын GCCCC пентануклеотидтен тұратын байланысу сайттары бар. Нәтижелер бір ген бірнеше альтернативті миРНК-дың нысанысы болуы мүмкін екендігін көрсетеді. ID00436.3p-miR және ID01030.3p-miR нысана гендерімен ассоциацияларды аурудың алдын ала молекулалық диагностикасы үшін ұсынуға болады. Бұл ассоциацияларға *BACH1*, *CDK6*, *ETS1*, *IGF2*, *SFN*, *SMAD4*, *SPI*, *ST8SIA1* гендер кіреді. *CARNS1*, *CCND1*, *EFNB1*, *IGF2*, *SMAD4*, *ZEB1* нысана гендердің және ID00470.5p-miR мен ID02299.5p-miR асоциацияларды аурудың алдын ала молекулалық диагностика үшін пайдалануға ұсынылады.

Түйін сөздер: miRNA, mRNA, кластер, нысана ген, сүт безінің қатерлі ісігі.

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КЛАСТЕРЫ САЙТОВ СВЯЗЫВАНИЯ miRNA В 3'UTR mRNA КАНДИДАТНЫХ ГЕНОВ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

Аннотация. Рак молочной железы является самым распространенным заболеванием среди женщин и для разработки методов ранней диагностики необходимо выявление неинвазивных молекулярных маркеров онкогенеза. Такими маркерами могут служить ассоциации miRNA и кандидатных генов РМЖ. Характеристики взаимодействия miRNA с mRNA нескольких генов были предсказаны с помощью программы MiTarget. Установлено, что сайты связывания miRNA могут располагаться в mRNA с наложением нуклеотидных последовательностей, образуя кластеры сайтов связывания. Изученные гены содержали в 3'UTR mRNA множественные сайты связывания одной и более miRNA. При наложении нуклеотидных последовательностей сайтов связывания в кластере происходит многократное уменьшение занимаемой ими доли mRNA. В результате компактизации сайтов связывания между miRNA возникает конкуренция за связывание в кластере поскольку несколько miRNA не могут одновременно взаимодействовать с mRNA в кластере длиной 25-50 нуклеотидов. Выявлены ID00436.3p-miR и ID01030.3p-miR, имеющие множественные сайты связывания с наложением нуклеотидных последовательностей в участках 3'UTR mRNA, содержащих множественные повторы динуклеотидов GU и CA генов *BACH1*, *CD19*, *CDK6*, *ETS1*, *FGFR3*, *FOXP1*, *IGF2R*, *SFN*, *SPI*, *ST8SIA1*, *WT1*. Установлены ID00470.5p-miR и ID02299.5p-miR, сайты связывания которых тоже расположены с наложением нуклеотидных последовательностей в mRNA генов *CARNS1*, *CCND1*, *EFNB1*, *IGF2*, *SMAD4*, *ZEB1*. Все сайты связывания кластера состоят из повторов CA динуклеотида. ID01727.5p-miR и ID02882.3p-miR имеют совпадающие сайты связывания в mRNA генов *ELK4*, *FOXP1*, *SFN*. ID01382.3p-miR имеет сайты связывания в генах *TGFBI*, *SMAD3*, состоящие из четырех повторов пентануклеотида GCCCC. Полученные результаты показывают, что один ген может быть мишенью нескольких альтернативных miRNA. А одна miRNA может взаимодействовать с несколькими альтернативными генами мишенями. Ассоциации ID00436.3p-miR и ID01030.3p-miR с генами мишенями предлагается использовать для ранней молекулярной диагностики заболевания. В эти ассоциации входят гены *BACH1*, *CDK6*, *ETS1*, *IGF2*, *SFN*, *SMAD4*, *SPI*, *ST8SIA1*. Ассоциации ID00470.5p-miR и ID02299.5p-miR с генами мишенями *CARNS1*, *CCND1*, *EFNB1*, *IGF2*, *SMAD4*, *ZEB1* рекомендуется использовать для ранней молекулярной диагностики заболевания.

Ключевые слова: miRNA, mRNA, кластер, ген-мишень, рак молочной железы.

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NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 27 – 38

<https://doi.org/10.32014/2019.2519-1629.28>**K. Saparov, S. Aken, A. Aitenova, Zh. Olzhabayeva, D. Turlybekova**

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E-mail: saparov42@mail.ru**ULTRASTRUCTURE OF THE LUNGS OF VERTEBRATES
IN HABITING MOUNTAIN AND STEPPE ZONES**

Abstract. This article describes the features of the ultrastructure of the lungs of vertebrates belonging to different biotopes. Due to the habitat in the fine structure of the lung tendon spines (amphibians, reptiles, small mammals), significant differences were detected by electron and scanning electron microscopy. In the study of light amphibians living in various biotopes, the presence of "living" formations and "mixed" cells was observed. In addition, type I pneumocytes predominate, and type II is rarely common. Amphibians (tailed frog) living in the steppe zone actively excrete mixed cells in the lungs, and in amphibians living in mountainous areas (the Central Asian salamander), such an active secretion does not take place. When studying with the help of electron microscopy of the ultrastructure of light reptiles living in various biotopes, it was observed that the nuclei of the first type of pneumocyte of the oval form and large. Type I of pneumocytes occupies a large number of respiratory epithelium and is involved in the creation of the air-circulating membrane. In reptiles (thyroid snake) living in the steppe zone, there were well observed "bubbles" in type I of pneumocyte. Using electron microscopy of small mammals, I and II types of alveolocytes contained in the respiratory epithelium are distinguished. The form of alveolocytes type II is diverse, the nucleus is hyperchromic, and a complex of surfactants is found. This article presents morphometric studies of the adaptation of animals of different habitats depending on their habitat, thickness of air-blood membranes.

Key words: lungs, pneumocyte, alveolocyte, biotope, electron microscope, scanning electron microscope, vertebrate.

1. Introduction. The ultrastructure of adaptive reactions of the lungs has not yet been studied. In the process, an ultrastructural description of the adaptive reactions of the respiratory part of the lungs when exposed to various external environments is given. The subtle morphofunctional mechanism of the reciprocal-profile reactions found in this work helps to better understand the adaptation of the lungs to various environmental conditions.

Designed to determine the ultrastructure and environmentally established features of structural and functional transformations occurring in the lungs of animals of various environmental specializations, ultrastructures and environmentally defined features of the adaptation of the lungs to various environmental factors of the respiratory part of one mammal and amphibian species. The relationship between the organism and the environment manifests itself in various adaptive reactions of animals, while manifestations of morpho-functional or behavioral flexibility depend not only on the environment, but also on the characteristics of the organization of the animal. With functional load, the degree of morpho-physiological maturity of the organism, organ systems, and organs as a whole is most pronounced. Adaptation reserves of the respiratory organs during an increase in physical activity or hypoxia of representatives not only of different groups of animals, but of the same species, of different age, physical condition, etc., are significantly different. In reptiles, there are primitive air bags that are a continuation of the lungs and contribute to easier conversion of gases. The sharp growth of the respiratory surface due to the formation of many small bronchioles, alveolar sacs and alveoli, the improvement of respiratory motility, especially during flight, dramatically increases the intensity of gas exchange in birds and is an aromatic transformation.

The energy supply of living organisms is due to the combination of oxidation reactions occurring in all living cells. Animals belonging to aerobic organisms use free oxygen for breathing. The free source of oxygen is air and water. Oxygen in the air is used by animals living on land. In connection with the adaptation-regulatory mechanisms of animals living on land, the habitat is diverse, and there are structural features of the organs, thanks to adaptation to the habitat. For example, due to insufficient oxygen content in animals living in mountainous areas, the ultrastructure of the lungs has ultrastructural differences compared to the lungs of animals living in the steppe zone.

2. Materials and research methods. To study the ultrastructure of lungs of vertebrates belonging to different biotopes on land, the following animal representatives were taken. The tailed frog, the Danatin's toad, the Central Asian salamander were taken from amphibians, the Gloydus halys, fast lizard, the viper, the Ablepharus from the reptiles, and the northern red-backed vole, the rabbit from small mammals. To study the ultrastructure of cells using electron microscopy, a very thin piece of material is produced. Initially, the material is fixed, dehydrated, injected liquid polymers and cut through ultratome. To obtain thin pieces of tissue are fixed in two stages in a volume of 1.0-1.5 ml. Initially contained in 0.15 M phosphate buffer in a 2.5% glutaraldehyde solution and kept in phosphate buffer in a 1% OsO₄ solution in a refrigerator at + 40 °C. The material is washed from phosphate fixative in buffer, dried in the refrigerator for 20 minutes at concentrations of 50-96% alcohol, followed by drying, and drying in 100% alcohol at room temperature for 20 minutes. To obtain rigid and elastic pieces (block) for cutting on an ultratome, polymer epoxy resin (Araldite, Epon) or water-soluble mixtures are used. The process of filling the material in epoxy resin takes 1-2 days. The polymerisation of the blocks is maintained in a thermostat of 600 °C for 48 hours. The end of the block is honed in the form of a pyramid. From the tip of the pyramid on the ultratome very thin segments are obtained with the help of a glass knife. Cuts 300-350 Å are placed in electroplating grids covered with porcelain film [25].

For research at a comparative morphological level, lungs of amphibians, reptiles, and mammals living in various biotopes were selected. The animals were kept in the steppe and mountainous areas of the Almaty region (Balkhash, Raiymbek areas, Mountain Turgen valley at an altitude of 2800 m above sea level). For the study of the lungs by histological methods, small particles are placed in the whole attachment. 10% neutral formalin was used as a fixative. After separation of the segments with a thickness of 3-5 µm from the paraffin, hemotoxylin-eosin and van gieson are painted. To study the lung sections using an electron microscope, they were fixed for 2.5 hours in 2.5% glutaraldehyde (pH 7.4 - 7.6) and 2 hours in 1% osmic acid solutions. Then treated with ethanol and acetone and poured into epon (812). Morphometric studies were carried out from electron diffraction patterns, statistical processing was carried out using Student's method (G. Lakin, 1990). Delicate cuts were treated with uranyl acetate and lead citrate (Reynolds method). Thin sections were investigated and photographed on an electron microscope computer-100L. For a scanning electron microscope study, pieces of the lungs (5x3x3 mm) were processed through alcohols and acetone with dehydration, then dried. The pieces were studied in the raster mode of the Super - probe 733 instrument of an accelerated gold electronic microanalyzer. Samples were enlarged to 800-4000x and photographed [3].

3. Research results and discussion. In the study of the respiratory epithelium of caudate amphibians (*Amphibia*), including the tailed frog (*Listotritonn vulgaris*) living in the steppe zone, under an electron microscope, hyperplasia of very rare mucous cells is observed in its structure. Such cells have a large volume, a pronounced layer of the nucleus, and chromatin in large quantities occupies the outermost layer of the nucleus. The central and extreme parts of these cells are filled with dense electronic small mucous membranes. In addition, there are "mixed" cells, rich in many mucous granules and having single osmiophil bodies. The granules are synthesized, in addition to the perikaryon zone, and in the peripheral parts of the cell. Membranes of the endothelium and epithelium are not connected in the air-blood (air-hem) zones. The thickness of the air-circulatory system is quite significant.

Thanks to the research conducted using a scanning electron microscope, an active tapping of mucous cells was detected. A smooth spherical structure appears on the upper surface of the central and peripheral sides of the pneumocytes. Most of the "mixed" cells indicate that the juice is actively secreted, which indicates a multitude of formations on its upper surface. It was shown that in many secret cells there existed the last phase of juice extraction.

A representative of caudate amphibians of the Central Asian salamander (*Ranodon sibiricus*) living in mountainous areas, living under hypoxia and water temperature (+8 – + 12°C) and air temperature (+12 – + 20°C), the volume of the respiratory part of the lung is greater than that of the tailed frog, and the air-blood membrane, which facilitates the diffusion of gases, is much thinner. The reason for this is a combination of the main membranes of the endothelium and epithelium in some parts of the air-circulatory system. Type II pneumocyte and the number of mucous cells is seen very little compared with the tailed frog. In the respiratory part of the lungs of the Danatin's toad, dwelling in the steppe zones, sets of imperfect pneumocytes of type II were observed, which are closely spaced to each other. The nuclei of these cells are large, long, and the shell of the nucleus is smooth, sometimes cut, and the collected chromatins are located on its edges (figure 1 – the Danatin's toad (mountain zone)).



Figure 1 – Danatin's toad (mountain population).
The shell structure of the surfactant (SF) in the area of respiration of the lungs. X 1600

Cytoplasm of II type of well mature pneumocytes is filled with large osmophilic layered bodies and evenly layered substances. Due to the fact that some of them are free, they are also electron-transparent. In dense electron cytoplasm, many mitochondrial edemas are filled with obscure endoplasmic reticulum tubes that are little-known, and tightly packed with membranes.

In the study with a scanning electron microscope, a large number of small cones were observed on the upper (terminal) surfaces of types II and type I of pneumocytes. Small bumps help maintain a yurt-shaped surfactant structure in the respiratory part of the lungs.

There are type II pneumocytes with imperfections and release of active juices on the upper surface. Studies using an electron microscope showed that a slight manifestation of type II pneumocytes is observed in the mountainous area in the respiratory part of the lungs of the Danatin's toad. In the cytoplasm of these cells there is a small number of osmiophil bodies containing homogeneous compaction substances. The dense electron cytoplasm contains numerous tubes and ribosomes of the granular endoplasmic reticulum. Matrix mitochondria with low electron density are located under the nucleus.

As part of the respiratory epithelium of reptiles living in the steppe zone, including the fast lizard (*Eremias velox*), it is clear that type II pneumocytes, which synthesize the surfactant complex, are significantly concentrated. Euchromatin, which has a layer of nucleus type II pneumocytes, has a large volume. In addition to osmiophil layered bodies, the cytoplasm contains tubes of the endoplasmic reticulum, dense matrix mitochondria of oval origin, a well-mature Golgi complex, free ribosomes and poly-ribosomes. The main membrane of the air-blood system consists of homogeneous fibrous components, as in combination with a combination of epithelium and endothelium.

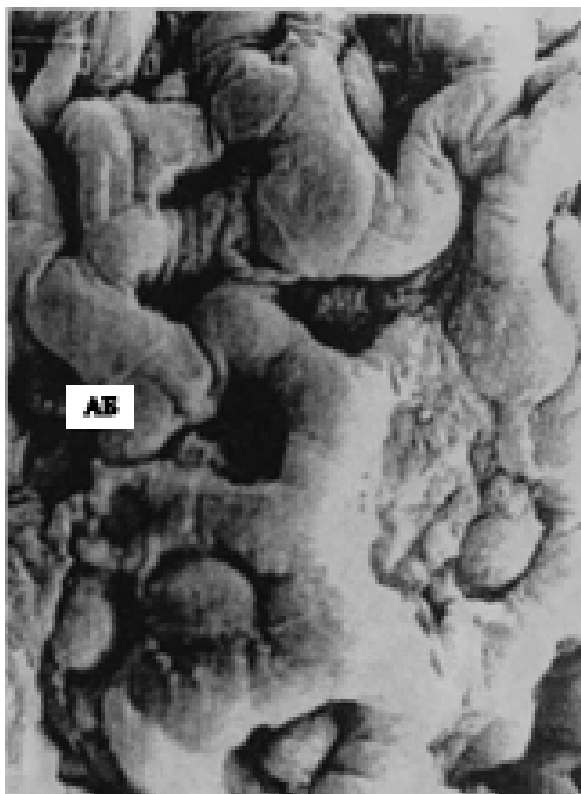


Figure 2 – Danatin's toad (mountain population). Flat and convex apical surface of pneumocytes type I.X 1600

It is noted that high-speed necks are "layer" networks, which reduce the length of the air-blood barrier and therefore reduce the loss of moisture in the respiratory part of the lungs. There were observed small pinocytosis vesicles involved in the transudation of gases and fluids of epithelial cells of the respiratory surface and vascular endothelium cells.

When studying using the electron microscope of the steppe viper and the thyroid snake (*Gloydius halys*) living in the steppe zone, hypertrophy of surfactant kecheen was observed. In this case, there is a large number of "mixed" cells, forming a fragile structure, similar to type II pneumocytes and mucous cells. These cells have a different shape of the nucleus, an increased content of chromatin, the dismemberment of the perinuclear space, a large number of ribosomes are observed in the inner membrane of the nucleus. Among the large osmiophil bodies there are electron dense mucous granules. Small osmiophilic matrix mitochondria are observed in the cytoplasm. It is believed that under conditions of moisture preservation in the respiratory part, the mucoïd structure can enhance the synthesis of surfactant. In the cytoplasm of epithelium cells and the endothelium of the blood necks, small pinocytosis vesicles and layers of the air-circulatory system are observed.

Microscopic examination of the respiratory epithelium of the *Ablepharus alaicus* (*Ablepharus alaicus*) living in the mountainous regions did not show a decrease in type II pneumocytes. However, due to the fusion of the main membrane of the respiratory epithelium and the membrane of the endothelium, a thinning of the air-vascular membrane was observed and an increase in the length of the respiratory surface was observed due to the swelling of the loop of throat grids.

A small number of type II pneumocytes and “mixed” cells were observed in the respiratory epithelium of the shield-mord, belonging to the order of snakes living in highlands. In the cytoplasm of type II pneumocytes, there are very few osmiophilic layered bodies (figure 3 – a thyroid snake (mountainous region)). In the lower part of the nucleus, such bodies are located above the main membrane. In the cytoplasm of “mixed” epithelium cells, small osmiophilic puffed bodies and mucous granules were observed.

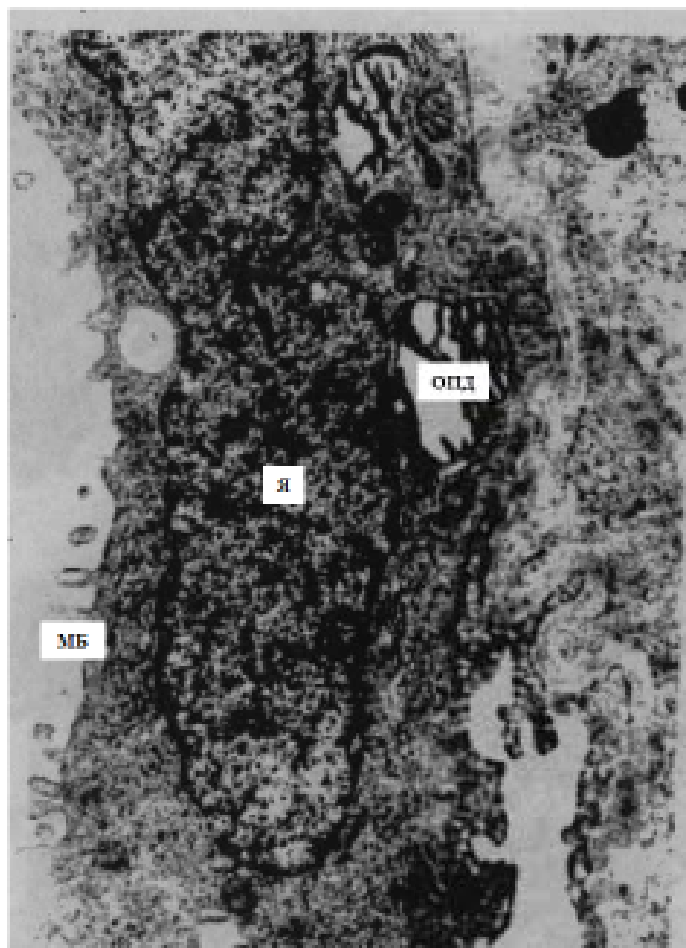


Figure 3 – A thyroid snake (mountainous region).
The second type of pneumocytes with single osmiophilic bodies. X7000

At the end of the bronchi, opposite to the mammalian alveoli, the structures in which gas exchange takes place and called the alveoli, open into the air cavity of the lungs. On close inspection, the lung structure is determined by internal protuberances and partitions resembling a sponge in cross section. Of great importance is the general anatomy of the turtle's lower respiratory tract.

Gas exchange in turtles occurs through various ways of passing gases through breathing. It depends on the type of differences, as well as on whether it is an aquatic or terrestrial turtle. Inhalation and exhalation are generally active processes [5].

Studies using a scanning electron microscope revealed a cluster of yurt-shaped surfactant as part of the respiratory part of reptiles (fast lizard, viper, thyroid snake) living in steppe zones. In addition to the secretion of the surfactant, the mucous secretion of the small mucous membrane was observed on the cell surface. The peculiarity of the respiratory part of the lungs is the presence of “layers” in its composition, which reduce the length of the air-blood barrier of throat grids (figure 4 – the thyroid snake (steppe zone)).



Figure 4 – The thyroid snake (steppe zone).
The network of "folded" capillaries. Respiratory department. X200

In the study of the pulmonary epithelium of reptiles living in mountainous areas with a scanning electron microscope, a small surfactant structure was observed. In the sets of pneumocytes, activity of the secret was not observed. All surfaces of type II pneumocytes are covered with small bumps. One of the features of the respiratory epithelium is swelling in the form of "leaflets" of the shape of hooks of capillary networks. The narrowing of the air-blood barrier allows you to separate the contours of red blood cells inside blood vessels. All of these structures increase the volume of the respiratory surface of reptiles.

Studies performed with an electron microscope have shown that the nucleus of the first type of alveolocytes contained in the respiratory epithelium of small mammals has a large contour of the shell of the nucleus. Completed chromatins are grouped in the envelope of the nucleus and karyoplasm. In the electron dense cytoplasm, small osmiophil mitochondria, endoplasmic mesh tubes, free ribosomes and polyribosomes are located.

The general division of alveolocytes occupies a large number of respiratory epithelium.

The form of alveolocytes type II is diverse, the nucleus is hyperchromic. Perinuclear space is cramped. In the cytoplasm of the tube, the granular endoplasmic reticulum and matrix are large white mitochondria and many osmiophilic layered bodies are free, some are filled with osmiophilic substances. Small vesicles were observed, such as bubble vesicles covered with membranes. The central and peripheral compartments of the alveolocytes are covered with many small buds. Endothelium blood cells have a large nucleus, one occurs, sometimes two nuclei. Completed chromatins are located on the edges of the nuclei. The core of the nucleus is a zigzag, deep invagination of the karyoplasm. The endothelium of the blood vessels has a large number of small pinocytosis vesicles. The core of the alveoli macrophage has a different shape. From their cytoplasm, it is possible to determine secondary, sometimes the first types of lysosomes involved in the process of decomposition of osmiophil granular substances.

According to the data of comparative studies of small mammals living in steppe zones carried out with the help of electron microscopes, hypertrophy of surfactant was observed in this connection. The whole cytoplasm of alveolocytes of the common vole (*Microtus arvalis* Pallas), inhabiting the steppe zone, is filled with large and small osmiophilic folded bodies containing osmiophil substances (figure 5 is the common vole). The peculiarity of the respiratory part of the lungs of mammals living in the steppe is the “folding” of their networks of capillaries, in connection with this slowing down of some cells (alveoli) and reducing the process of evaporation of moisture through the respiratory surfaces of the lungs.



Figure 5 – Common vole. Type II alveolocytes with osmiophilic plates (OPD).X 14000

The absence of hypertrophy of the surfactant complex – the difference of mammals in the steppe zones (common vole) from type II alveolocytes in the respiratory part of the lungs of the Tien Shan ordinary vole (*Clethrionomys centralis* Miller), living in the mountainous area. In addition, the main difference in the study of submicroscopy is a narrowing of the air-blood barrier and an increase in the volume of respiratory surfaces. The connection of the main membranes of the endothelium and epithelium among themselves. Epithelial cells of the blood necks are devoid of organs, turned into a dense electron table (figure 6 – Tian-Shan vole).

Morphometric studies have shown that the thickness of the air-blood membrane of animals living in various biotopes depends on their habitat (table 1 – thickness of the air-blood (aeroHEME) membrane of some vertebrates (nm)).



Figure 6 – Tien-Shan vole.
Toned aerohematomatic membrane system (AGMS).
Fusion of capillary endothelium with epithelial basement membranes. X 9000

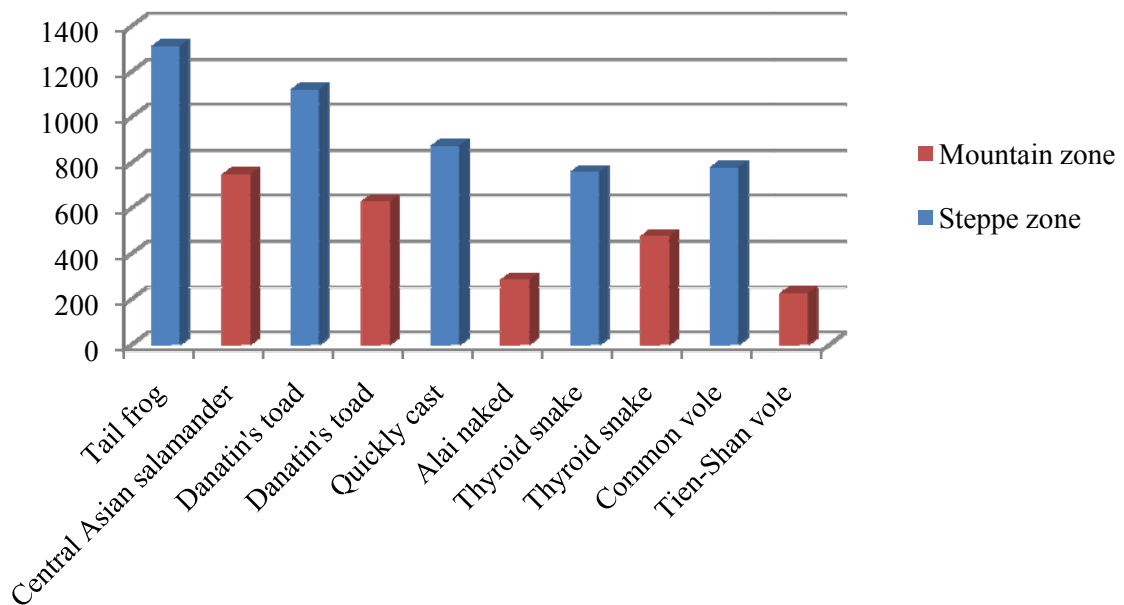


Table 1 – The thickness of the air duct (airgel) of some vertebrates (nm)

In the study of the respiratory part of the lung of rabbits with limited movement, an I type of alveolocytes with serpented envelope of the nucleus and a hyperchromic nucleus was observed under an electron microscope. The cytoplasm contains short tubes of the endoplasmic reticulum, small mitochondria, ribosomes, and narrow fibers. The surface of type I alveolocytes is not smooth. In the peripheral part there are small organelles and ribosomes. The main membrane is relaxed and in some compartments they are connected to the main membranes of the endothelial cells. However, it is not noticeable that the clearly marked air-rod barrier has thinned. In most cases, longitudinal fibroblasts are located between the epithelium and the endothelium of the blood inlets. The nucleus of type II alveolocytes is large, it contains a large number of chromins, the shape of the shell of the nucleus is zigzagged. Cytoplasm is often rich in dense matrices and crystals, elongated mitochondria, granular endoplasmic mesh tubes, empty ribosomes and polyribosomes. Not so many osmiophilic layered bodies. In the cytoplasm of macrophages in the alveoli, in addition to small first lysosomes, there is a second type of lysosome with osmiophilic layered substances.

When studying the respiratory compartment of Desert hare's lung that is in constant motion with the electron microscope, it has been found that the compartment contains type I of large nuclear alveolocytes, which occupy most of the perikaryon cytoplasm zone. There are chromatins collected along the edges of thin nuclear envelope, and euchromatins are found in large quantities. The invagination of nuclear envelope has been observed, the perinuclear space is narrow. On the cytoplasm tubes of the rough endoplasmic reticulum filled with cotton fibers, and numerous ribosomes are located. Elongated cytoplasmic formations are observed on the surface of the plasmalemma's terminal parts. The main membrane of alveolar type I cells is connected to the main membrane of the endothelium. The nucleus of type II alveolocytes is not in the correct form, and chromatin is densely located. In the cytoplasm large mitochondria are observed, in which there are often electron dense crystals of the matrix. Most of the cytoplasm is filled with an osmiophilic layered structure containing electronic transparent substances. Some layered structures are osmiophilic and homogeneous. The location of these bodies on the terminal and main surfaces of the plasma membrane shows that the secretion process is actively going into the space of the alveoli, as well as into the space of the blood capillaries. Active synthesis of surfactant indicates the presence of phagocytic osmiophilic layered bodies in large quantities in the alveolar macrophage's cytoplasm.

The endothelial cells of the blood capillaries of type II alveolocytes' main membrane have a large nucleus, in the cytoplasm ribosomes in large quantities and their connection with the alveoli's surfaces are observed. The interstitial space is narrow.

These studies have shown that adaptive responses of animals – amphibians, reptiles, mammals, belonging to different species or one species, living in different biotopes, are associated with their habitat. It has been proved that the adaptive reaction is associated with the harmonious flow of surfactant synthesis and the structure of pulmonary capillaries.

4. Conclusion. When viewing adaptation reactions of caudate amphibians' representative – the tailed frog living in the steppe zones, at the ultrastructural level, it has been found that the presence of mucous cells and hyperplasia of "mixed" cells similar in structure to type II pneumocytes and mucous cells prevent the disappearance of moisture. Many small buds were observed on the upper surface of the cell. Acceleration of secretion formation from the mucous and "mixed" cells has been proved by scanning electron microscope.

The complex of surfactants and the synthesis of mucus of pneumocytes of type II, contained in the epithelium of the Danatin's toad dwelling in the steppe zones, manifests the effects of adaptation reactions. In addition, an increase in the "folds" of blood capillaries helps to reduce the loss of endogenous liquid substances from the respiratory part of the lungs.

A decrease in the number of pneumocytes of type II of the Danatin's toad living in the mountain zone is observed. In addition, an insignificant amount of osmophilic layered substances was observed in the cytoplasm of these cells. The air-blood system has become thinner. Its thickness at the Danatin's mountain toad is narrow compared to the Danatin's toad living in the steppe zone (628.4 ± 11.5 and 1120.2 ± 20.5 nm, respectively, $P < 0.001$).

The peculiarities of the adaptation of the lungs of reptiles of the steppe zones to the external environment are the main factors due to the absence of moisture loss of the respiratory surfaces of the lungs and the powerful synthesis of surfactant. In addition, hypersecretion of the mucous components of "mixed"

cells and an increase in the interstitial layers of the vascular network, reducing the length of the respiratory surfaces contributes to the preservation of endogenous fluid. In addition to reducing the production of surfactant reptiles in the highlands, we are seeing a narrowing of the air-circulatory system and an increase in the respiratory surfaces of the lungs. For example, it has been established that the air-circulatory membrane system of a shield-mord living in a mountainous area is narrowed in comparison with a shield-ear of a steppe zone (475.4 ± 8.7 and 757.8 ± 14.14 nm, respectively, $P < 0.001$).

The peculiarities of ultrastructure of the lungs of vertebrates belonging to different biotopes are determined by their habitat, which is confirmed by electron microscopy and scanning electron microscopy. During the study of light amphibians living in various biotopes, "fence" structures and "mixed" cells, numerous type I pneumocytes and number II type pneumocytes were found. In addition, it is known that mixed cells of the tailed frog living in the steppe zone secrete secretion, while such secretion is absent in the Central Asian salamander living in the highlands.

In the study of ultrastructure of the lungs of reptiles using electron microscopy, it was observed that the nucleus of a type I pneumocyte are oval in shape, they are large. In the lungs of the thyroid snake living in the steppe zone, the phenomenon of "foaming" was well observed. Using electron microscopy of small mammals, I and II types of alveolocytes contained in the respiratory epithelium are distinguished. Type II alveolocytes have a diverse form, the nucleus is hyperchromic and there is a complex of surfactants. In this article, morphometric studies are clearly expressed, which show that the thickness of the air-blood membrane of animals with different habitats depends on their habitat.

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ТАУЛЫ ЖӘНЕ ДАЛА АЙМАҒЫНДА ТІРШЛІК ЕТЕТІН ОМЫРТҚАЛЫЛАРДЫҢ ӨКПЕЛЕРІНІҢ УЛЬТРАҚҰРЫЛЫМЫ

Аннотация. Берілген мақалада әр түрлі биотопқа жататын омыртқалылардың өкпелерінің ультрақұрылымдарының ерекшеліктері жайлы жазылған. Тіршілік ету ортасына байланысты құрғақтағы омыртқалылардың (амфибиялар, бауырмен жорғалаушылар, ұсақ сүтқоректілер) өкпелерінің нәзік құрылымында айтарлықтай өзгешеліктер электронды және сканды электронды микроскопия арқылы анықталған. Әр түрлі биотоптарда мекендейтін амфибиялардың өкпелерін зерттеу барысында «шарбақ» тәрізді құрылымдар мен «аралас» клеткалардың кездесетіндігі байқалды. Сонымен қатар, пневмоциттердің I түрі басым, ал II түрі сирек таралған. Далалы аймақта мекендейтін амфибиялар (құйрықты бақа) өкпелерінде аралас клеткалар белсенді түрде секрет бөледі, ал таулы аймақтарда мекендейтін амфибияларда (Жетісу аяқты балығы) бұндай белсенді секреция орын алмайды. Әр түрлі биотоптарда мекендейтін бауырмен жорғалаушылардың өкпелерінің ультрақұрылымдарын электронды микроскопия арқылы зерттегенде пневмоциттің I түрінің ядроларының сопақша пішінді, ірі екендігі байқалды. Пневмоциттердің I түрі тыныс эпителийінің үлкен көлемін алып жатады және ауа-қан жарғақшасын құруға қатысады. Далалы аймақта мекендейтін бауырмен жорғалаушыларда (калқантұмсық жылан) пневмоциттің I түрінде «көпіршіктену» жақсы байқалды. Ұсақ сүтқоректілердің электронды микроскопия көмегімен тыныс эпителийінің құрамындағы альвеолоциттердің I және II түрі ажыратылған. Альвеолоциттердің II түрінің пішіні әр түрлі, ядросы гиперхромды болып келген және сурфактант кешені табылған. Бұл мақалада тіршілік ортасы әр түрлі жануарлардың ауа-қан жарғақшасының қалыңдығы олардың өмір сүру ортасына байланысты бейімделуін морфометриялық зерттеулер көрсетті.

Түйін сөздер: өкпе, пневмоцит, альвеолоцит, биотоп, электронды микроскоп, сканды электронды микроскоп, омыртқалы.

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УЛЬТРАСТРУКТУРЫ ЛЕГКИХ ПОЗВОНОЧНЫХ, ОБИТАЮЩИХ В ГОРНЫХ И СТЕПНЫХ БИОТОПАХ

Аннотация. В статье рассматриваются особенности ультраструктуры легких наземных позвоночных. С помощью электронной микроскопии, сканэлектронной микроскопии были выявлены характерные отличия ультраструктуры легких наземных позвоночных (амфибии, рептилии, мелкие млекопитающие) в связи с местом их обитания. Исследования легких амфибии, обитающих в разных биотопах показали структуры в виде «решеточек» и клетки «смешанного» типа. Вместе с тем, отмечилось большое количество пневмоцитов I типа, и незначительное количество пневмоцитов II типа. У амфибий, обитающих в степной зоне (хвостатая лягушка), клетки смешанного типа активно выделяют секрет, а у амфибий, обитающих в горной зоне (семиреченский лягушкозуб), такая активная секреция не наблюдается. Электронномикроскопические исследования ультраструктуры легких пресмыкающихся показали, что ядра пневмоцитов I типа имеют овальную крупную форму. Пневмоциты I типа занимают большую часть дыхательного эпителия и участвуют в формировании аэрогемотических мембран в цитоплазме. У пресмыкающихся, обитающих в степной зоне (гладкий щитомордник), обнаружилось «вспенивание». При исследовании легких мелких млекопитающих с помощью электронной микроскопии были выделены в дыхательном эпителии альвеолоциты I и II типов. Альвеолоциты II типа разной формы с гиперхромным ядром, также обнаружился комплекс сурфактанта. В этой статье морфометрические исследования показали, что у животных, обитающих в разных зонах, имеется разная толщина аэрогемотических мембран в связи с их местом обитания и приспособлением к окружающей среде.

Ключевые слова: легкие, пневмоцит, альвеолоцит, биотоп, электронная микроскопия, скан-электронная микроскопия, позвоночные.

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NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 39 – 47

<https://doi.org/10.32014/2019.2519-1629.29>

UDC 34.27.51; 34.33.33

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STUDY OF THE INFLUENCE OF BIOLOGICALLY ACTIVE ADDITIVE USING MICROALGAE ON THE GROWTH AND MICROFLORA OF RAINBOW TROUT

Abstract. The aim of this work was to study the effect of biologically active feed additive based on microalgae on the growth parameters and microflora of fish. It was found that the growth rate of fish is directly depended on the amount of chlorella suspension in the feed. Higher length and weight measurements of trout were observed in the variant with the addition of a chlorella suspension in the volume of 10 ml/kg compared to the other variants of our experiment. The variant grown with the addition of chlorella suspension in the amount of 10 ml/kg, had greater increase in weight by 112.7, than the control and experimental variants grown with the addition of chlorella suspension in the amount of 5 and 15 ml/kg, showing indicators of 98.2, 97.5, and 99.6, respectively. The survival of fish during the study period remained at a high level (100 %) in the second experimental variant. Survival rate in the control group was reported 97 % and the first variant showed 97.7 %. Despite a significantly high growth rate, the survival rate of fish was amounted to 96.5% in the third variant, Perhaps this is due to the fact that in conditions of excessive intake of chlorella suspension into the environment and with its incomplete assimilation by fish, there is a high reproduction of microalgae in the aquatic environment. Quantitative and qualitative analysis of rainbow trout microflora was carried out in control and experimental variants. The calculation of TMC (full abbreviation) in the bodies of trout in the control variant showed that the number of bacteria ranging from $2,1 \times 10^5$ to $3,8 \times 10^5$ CFU/g in the intestine. Bacterial contamination of the liver was insignificant, and the omch (full abbreviation) index is not more than 1×10^2 KOECFU/g wet weight. Gill contamination ranged from $2,1 \times 10^4$ to 3×10^5 CFU/g. In the experimental variants with the addition of *Chlorella vulgaris* suspension, the omch indices of different trout organs did not differ significantly from those of the control variant. In the intestine, the number of bacteria ranges from $3,1 \times 10^5$ to $3,8 \times 10^5$ CFU /g, in the liver no more than $2,6 \times 10^2$ CFU /g wet weight. The insemination of gills was reported from 3×10^5 to 5×10^5 CFU /g. The selected associations of microorganisms consist of both saprophytic and opportunistic bacteria. The studies found that the qualitative composition of the microbiocenosis of trout in both control and experimental versions/variants is represented by 4 main genera *Lactobacillus*, *Aeromonas*, *Pseudomonas* and *Acinetobacter*. But the numerical ratio of the bacterium of the genus *Lactobacillus* was much higher in the experimental variants, in particular in the second variant of the experiment, compared with the control and other variants of the experiment. In addition to the representatives of these genera, representatives of the genera *Micrococcus*, *Sarcina*, *Bacillus*, *Enterobacter*, *Escherichia*, *Serratia*, *Proteus* and *Vibrio* were also found in different proportions in the trout microflora. The results obtained in the course of the studies allow us to recommend the introduction/addition of feed additives based on microalgae *Chlorella vulgaris* to the composition of feed for trout fish, which allows to increase the growth rates and maintain the physiological state of fish at the appropriate level.

Key words: *Chlorella vulgaris*, rainbow trout, biological active additive, microflora.

Nutrition is the basis of life of fish and any other organism. It is known that fish feed with a large variety should be available both from biological and physiological position [1]. From a biological point of view, food should be available structurally and spatially so that fish can consume it without excessive

energy consumption. From a physiological point of view, the food should be acceptable in taste and smell, easily digested and provide all the energy and plastic needs of the body.

High productivity and rational use of feed are possible only when fish farming facilities are fully provided with the necessary amount of protein, fat, carbohydrates, minerals and vitamins and receive enough energy to carry out their vital functions. Abundant and complete feeding, especially at a young age, contributes to an increase in weight, more rapid achievement of puberty, a clear manifestation of the signs of the exterior. Studies have shown that, providing optimal conditions for metabolic processes in the body of fish, you can achieve an increase in their growth rate with a decrease in 2-3 times the feed consumption. Such results can be obtained through proper feeding, which involves the use of diets containing all the necessary substances for the animal body [1].

Currently, the domestic feed industry is experiencing an acute shortage of quality feedstock. To overcome the crisis in domestic feed production, a number of issues are considered, the main of which are: improving feed formulations with the addition of various natural biologically active substances. At the same time, the use of natural biologically active substances is promising, which provide correction of the standard feed diet and composition of the resulting fish products for the missing nutrients [2]. Currently, the use of various microalgae as biologically active additives to feed is of great interest. It is known that microalgae have a unique biochemical composition, contains a wide range of biologically active substances – vitamins, macro- and microelements, amino acids and functional pigments [3]. In this regard, the search for new, non-traditional sources of biologically active substances for feeding fish is one of the most urgent problems of today.

In this regard, the aim of this work was to study the effect of biologically active feed additives based on microalgae on the growth and microflora of fish. Rainbow trout (*Oncorhynchus mykiss*) is selected as the object- the type that is attributed currently to the genus of Pacific salmon (*Oncorhynchus*) of the salmon family (*Salmonidae*). Rainbow trout meat is provided with easily digestible proteins, unsaturated fatty acids, trace elements and vitamins that are important for human nutrition. Rainbow trout is one of the first places in the world fish market.

Materials and methods of research. The study was conducted on the basis of Turgen trout farm, located in Almaty region, Enbekshikazakh district, Turgen village. For the experiment in the aquarium installation, rainbow trout fry were selected, the average mass of which at the beginning of the experiment was about 50 – 54.1 g. [1, 7]. The control and 3 experimental groups of 10 individuals each were formed by the method of analogues. The juveniles were grown in aquariums with a capacity of 250 l. the duration of the experiment was 10 weeks. The control group received a complete feed Aller silver (Poland). The composition of the feed included: vitamins, premixes and minerals, corn gluten, poultry flour, feather flour, sunflower protein, blood products, wheat gluten, canola, rapeseed oil, fish oil, fish flour, soy protein, soy. The nutritional value of this feed was: crude protein – 45 %, fat – 22 %, carbohydrates -20%, fiber-2%, phosphorus 1%, energy value - 22.3 MJ. As a biologically active additive, *Chlorella vulgaris* suspension and juveniles of the 1st, 2nd and 3rd experimental groups were used, the same compound feed enriched with an additional suspension of *Chlorella vulgaris* microalgae was obtained at the rate of 5, 10 and 15 ml per 1 kg of fish weight, respectively. *Chlorella vulgaris* suspension in 1 ml contained 3 million/s. Feeding rainbow trout during the experiment period was performed 6 times a day, in the daytime at regular intervals. Weekly studies were conducted on the growth and development of rainbow trout on the basis of the results of control catches. The weight method was used. According to the results of weighing, the value of the absolute growth of juveniles was calculated. The absolute increase is calculated by the difference between the initial and final weight of the fish for the period. The relative increase was calculated by the formula: (1) where M_0 , M_P – the average weight of fish at the beginning and end of the period, respectively. To characterize the intensity of growth, indicators of fish fatness coefficient were used [3]. At the end of the experiment, control and experimental groups of trout fish planting material were collected for microbiological studies. Microbiological studies of gills, liver and intestines of control and experimental groups of fish planting material were carried out. 3 fish specimens from each variant of the experiment and control were selected for the autopsy. From selected samples made the seeding of the environment General purpose and selective nutrient medium with three replications to determine KMAFAnM and the number of conditionally pathogenic bacteria. To determine the total bacterial contamination of fish organs, primary bacteriological crops were carried out on fish-peptonic and meat-

peptonic agar media. Enterobacteriaceae bacteria were determined by fermentation in a storage medium and were detected by incubation in an Endo medium at a temperature of 37 °C [4]. The study of morphological, cultural, biochemical properties of the isolated microorganisms was carried out according to the General requirements and recommendations for microbiological studies GOST ISO 7218-2011 [5]. The isolated bacteria were screened out for 1 % of simple agar in test tubes, assigned an individual culture code, and then identified to the genus by conducting and determining the morphological, tinctorial, some biochemical properties of the isolated microorganisms. Spent crops on differential nutrient media: Endo, YSA. To determine the number of lactic acid microorganisms in the intestine of fish, the method of deep sowing of the selected sample for cabbage agar was used. The crops were incubated for 5 days at a temperature of 30 °C. The Number of microorganisms was determined from calculations for 1 g. Identification to the genus was carried out by gram staining followed by microscopy, determination of the ability to capsule and sporulation, tests for oxidase and catalase activity and mobility. At the same time, the isolated microorganisms were identified by determinants [7,8]. Tests for oxidase and catalase activity were performed in accordance with GOST 18963-73. Drinking water was used. Methods of sanitary – bacteriological analysis. The resulting digital material was statistically processed using the program Statistica 6.0.

Research results and discussion. As it is known, the rapid growth of fish and high productivity are achieved only if the fish are provided with the necessary amount of nutrients –protein, fat, carbohydrates, minerals, vitamins – and get enough energy to carry out vital functions [9]. Growth processes in hydrobionts depend on a whole complex of external and internal factors, among which one of the most important is trophic, since the composition of food and the degree of its availability largely determine the linear-weight characteristic of fish [10]. In terms of aquaculture, trout are grown on artificial animal feed, the raw material for the production of which should best match the natural food of fish. Introduction of rainbow trout components uncharacteristic for natural nutrition into the feed composition can have a significant impact on fish metabolism and, as a result, lead to changes in their physiological state and growth processes [11]. The study of the dynamics of the mass of rainbow trout fry in our experience showed that the initial mass of the sample of juveniles in all groups was the same about 55.3–56.7 g. Observations of the process of feed intake by rainbow trout showed that when feeding fish in control and experimental containers, the time of feed intake was different. In General, the eating time of both control and experimental fish ranged from 5 to 20 minutes.

According to the study of feeding rainbow trout feed with the addition of suspension of microalgae *Chlorella vulgaris* found that the growth rate of fish was similar in the control and experimental versions with a tendency to increase absolute growth (table 1).

However, between the experimental groups of fish, the weight gain and growth of rainbow trout differed and depended primarily on the composition of the feed, since the other conditions of trout cultivation were the same. It was found that the growth rate of fish directly depended on the amount of *Chlorella* suspension in the feed. A high increase in the length and weight of the trout was observed in the second variant compared to the other variants of our experiment. At the end of the experiment in the variant with the addition of *Chlorella* suspension in the amount of 10 ml/kg, the trout weight gain was 112.7, and in the control and experimental variants with the addition of *Chlorella* suspension in the amount of 5 and 15 ml/kg, these indicators were 98.2, 97.5, and 99.6, respectively. It is shown that in the second variant there is 12.7% more weight gain compared to other variants.

There are a number of indicators to characterize the physiological state of fish. The most common among them are: Fulton fatness coefficient. This indicator makes it possible to determine the effect of feed used on metabolism and to identify the causes of its positive or negative action [3]. During the research period, the determination of the Fulton fatness coefficient, reflecting the relationship between the weight and length of fish, allowed to analyze the physiological state of rainbow trout (table 2).

The analysis of the obtained results shows that the feed enriched with *Chlorella* suspension used in feeding did not have a negative impact on the physiological state of rainbow trout, which does not contradict the data of other studies [12]. Moreover, it should be noted that the coefficient of fatness of trout increased on average from 3 to 3.2 in the experimental versions.

Table 1 – Growth parameters of rainbow trout

Week	Experiment variant	Weight, g	Length, sm	Increase of weight, g	Increase of length, sm
1	Control	52,3±1,5	10,2	–	–
	1 variant	53,4±1,3	10,1	–	–
	2 variant	51,7±1,2	10,2	–	–
	3 variant	54,1±1,1	10,4	–	–
2	Control	58,1±1,4	11,8	11	15,6
	1 variant	60,2±1,2	11	12,7	8,9
	2 variant	58,6±1,2	11,6	13,3	13,7
	3 variant	60,1±1,1	11,1	11	6,7
4	Control	67,1±2	12,5	28,2	22,5
	1 variant	68,0±1,2	12,5	27,3	23,7
	2 variant	69,1±1,3	12,6	33,6	23,5
	3 variant	69,8±1,1	12,5	29	20,1
6	Control	78,7±1,2	13	50,4	27,4
	1 variant	81,5±1,3	12,8	52,6	26,7
	2 variant	82±1,2	13,2	58,6	29,4
	3 variant	83±2,4	13	53,4	25
8	Control	95±1,3	14,1	81,6	38,2
	1 variant	95,8±1,2	13,8	79,4	36,6
	2 variant	98±1,3	14,2	89,5	39,2
	3 variant	97±1,2	14,4	79,2	38,4
10	Control	103,7±1,2	15,2	98,2	48
	1 variant	105,5±1,3	15	97,5	48,5
	2 variant	110±1,2	15.1	112,7	49
	3 variant	108±2,4	15,1	99,6	45,1

Table 2 – Morpho-physiological characteristics of rainbow trout

Indicators	Control (feed)	Feed+ <i>Chlorellavulgaris</i> 5 ml	Feed+ <i>Chlorellavulgaris</i> 10 ml	Feed+ <i>Chlorellavulgaris</i> 15 ml
Weight, g	103,7±1,2	105,5±1,3	110±1,2	108±2,4
Length, sm	15,2	15	15.1	15,1
Fatness coefficient	2,9	3,1	3.2	3,1

Thus, according to the results of studies, there was a significant positive effect of the *Chlorella* suspension Supplement on the morpho-physiological parameters of rainbow trout growth and development. It was found that the most effective was the feed with the addition of *Chlorella* suspension in the amount of 10 ml/kg. These data indicate a positive effect of feed additive in the form of *Chlorella vulgaris* suspension on the growth of rainbow trout.

Survival of fish during the study period remained at a high level in the second experimental version was 100 %. Survival in the control group was 97 % and in the first variant 97.7 %. In the third variant of the experiment, despite a significantly high growth rate, the survival rate of fish was 96.5%. Perhaps this is due to the fact that in conditions of excessive intake of *Chlorella* suspension into the environment and with its incomplete assimilation by fish, there is a high reproduction of microalgae in the aquatic environment. As you know, their excessive reproduction in the aquarium can lead to a deterioration in the conditions of growing fish, which can thereby affect their survival [12].

As it is known, the state of the microflora of any living organism, including fish, is a determining factor in the normal functioning of the entire immune system as a whole. The microflora of fish is concentrated mainly in the mucus on the scales, on the surface of the gills and in the digestive tract. At the same time, the digestive system is of the greatest interest, since it is a kind of protective barrier between the internal environment of the body and the foreign environment, a special role in which belongs to the normal intestinal microflora, as well as the liver, where the toxic substances of food are detoxified, not neutralized by its enzymatic cleavage.

In this regard, at the next stage of the study of the effect of biologically active feed additives on the growth and development of fish, the study of the state of the microflora of rainbow trout when feeding feeds enriched with suspension of *Chlorella vulgaris* microalgae.

Quantitative and qualitative analysis of rainbow trout microflora in control and experimental variants was carried out. The calculation of TMN in trout organs in the control variant showed that the number of bacteria in the intestine varies from $2,1 \times 10^5$ to $3,8 \times 10^5$ CFU /g. Bacterial contamination of the liver was insignificant, the TMN index is not more than 1×10^2 CFU/g of wet weight. The insemination of gills was from $2,1 \times 10^4$ to 3×10^5 CFU /g.

In the experimental variants with the addition of *Chlorella vulgaris* suspension, the TMN values of different trout organs do not differ significantly from those of the control variant. So in the intestine the number of bacteria varies from $3,1 \times 10^5$ to $3,8 \times 10^5$ CFU /g, in the liver no more than $2,6 \times 10^2$ CFU /g of wet weight. The insemination of gills was from 3×10^5 to 5×10^5 CFU /g.

According to the literature, the microbial number on the gills can vary widely from 6×10^2 to $2,2 \times 10^6$ CFU /g. [13]. It is known that the composition of the microflora of the outer covers is closely related to the conditions of fish [14]. In case of unsatisfactory water condition due to the measures taken to intensify production or damage to the tissues of the Gill epithelium, the level of bacterial contamination in fish increases.

The total number of bacteria in the intestine according to some authors, varies in different species of fish within 10^2 to 10^{12} cl. per 1 gram wet weight. However, most authors point to the $10^5 - 10^8$ cl/g [15]. This variation seems to be related not only to the species diversity of the fish studied, their habitat and physiology, but also to the methods of counting bacteria used by different researchers. After all, it should be noted that the methods for studying the attached intestinal microflora of fish are mainly based on the homogenization of the intestine and subsequent crops of homogenates on various selective media, which, as is known, can detect only microorganisms that can grow on specific environments. The intestine also contains anaerobic bacteria, many of which are known to be resistant to cultivation in the laboratory. In this connection, it is possible and there is a slight underestimation of the population of bacteria.

At the end of incubation of cups with crops from various organs of fish in general, 12 isolates of bacteria with different morphotypes of colonies, from trout organs were isolated into a pure culture.

Morphological characters were studied in 12 selected isolates of bacteria (shape, motility, presence of capsule and the ability to spore formation), identified by their Gram – and has explored some of the cultural (the growth pattern of the selected cultures on solid and liquid media) and biochemical properties.

The study of cultural and morphological properties of the detected and isolated cultures of bacteria found that the trout microflora is represented by mobile and non-mobile, gram-positive and gram-negative cocci and sticks. At the same time, it should be noted the dominance of mobile gram-negative bacteria (sticks) in the control variant, which is 67 % of all isolated microorganisms in trout. During the test to determine the oxidase activity revealed 5 oxidase-positive, 5 oxidase-negative strains and 2 cultures with questionable results in trout. The test for catalase activity of bacterial cultures isolated from trout showed 2 catalase-negative, 8 catalase-positive strains and 2 strains showed ambiguous results (table 3).

Bacteriological study of various organs of fish in experimental variants showed that gram-positive sticks and cocci dominated in all variants of the experiment in the incidence.

Determination of isolated isolates of bacteria was carried out before the genus and, in some cases, before the family. Selected association of micro-organisms are composed of both saprophytic and opportunistic bacteria.

Table 3 – Numerical ratio of belonging to the genera of selected microorganisms, %

Taxon (kind)	Numerical ratio of belonging to the genera of selected microorganisms, %			
	Control (feed)	Feed+Chlorellavulgaris 5 ml	Feed+ Chlorellavulgaris 10 ml	Feed+Chlorellavulgaris 15 ml
<i>Sarcina</i>	6 ± 0,5	5 ± 0,5	5,5± 0,5	5 ± 0,5
<i>Micrococcus</i>	5 ± 0,5	6 ± 0,5	5± 0,5	6 ± 0,3
<i>Aeromonas</i>	16 ± 1	12±1,5	11±1,5	12± 1
<i>Vibrio</i>	8 ± 0,5	8± 0,5	7±1	8± 0,5
<i>Acinetobacter</i>	10 ± 0,5	9 ± 0,5	10 ± 0,2	10± 0,3
<i>Pseudomonas</i>	12 ± 1	11 ± 1	10± 1	12± 1
<i>Enterobacter</i>	6 ± 0,5	5±1	4 ± 0,5	5± 0,5
<i>Escherichia</i>	7± 1	5 ± 0,5	4 ± 0,5	5± 0,5
<i>Serratia</i>	6 ± 1	7 ± 0,5	3 ± 0,5	5 ± 0,5
<i>Bacillus</i>	3± 0,5	3± 0,5	3± 0,5	3± 1
<i>Lactobacillus</i>	11±2,5	18± 2	22± 2,5	17± 1
<i>Proteus</i>	8± 0,5	6± 1	4± 0,5	5 ± 0,5

During researches it is established that the qualitative composition of the microflora of trout in the control and experimental variants are represented by 4 major branches: *Lactobacillus*, *Aeromonas*, *Pseudomonas* and *Acinetobacter*. But the numerical ratio of the bacterium of the genus *Lactobacillus* was much higher in the experimental variants, in particular in the second variant of the experiment, compared with the control and other variants of the experiment. According to literature sources, it is known that the bacteria of the genus *Lactobacillus* are very demanding on food sources and do not grow on simple media. Most bacteria in this family need "arginine, cysteine, glutamic acid, leucine, phenylalanine, tryptophan, tyrosine, valine". The suspension of *Chlorella* is rich in these substances and getting into the gastrointestinal tract of the macroorganism, first of all, becomes the optimal nutrient medium on which lactic acid bacteria develop rapidly [16]. In addition to representatives of these genera in the microflora of trout in different proportions were also representatives of the genera: *Micrococcus*, *Sarcina*, *Bacillus*, *Enterobacter*, *Escherichia*, *Serratia*, *Proteus* and *Vibrio*.

Despite the fact that *Pseudomonas*, *Vibrio* and aeromonad as opportunistic microorganisms under certain conditions, can cause epizootics, they are representatives of normal microflora of fish.

In General, the results correspond to what is known from the literature. According to some authors in the composition of the microflora of the fish in the norm encountered opportunistic microorganisms, among which the representatives of families: *Pseudomonadaceae* (*Pseudomonas* kind), *Vibrionaceae* (*Aeromonas* kind) and *Enterobacteriaceae* [17]. On the skin and gills are common bacteria of the genera: *Aeromonas*, *Pseudomonas*, *Citrobacter*, *Proteus*, *Enterobacter*, *Escherichia*, *Cytophaga*, *Flavobacterium*, *Micrococcus*, *Staphylococcus*, *Enterococcus* [18].

A balanced diet of fish is an important factor in ensuring their normal functioning and proper metabolism. The correct organization of biologically complete feeding of fish contributes to the maximum manifestation of their genetic potential. The data obtained allow us to conclude about the positive effect of biological feed additives based on microalgae *Chlorella vulgaris* on fish microflora, morphophysiological indicators of growth and development of rainbow trout, with the most effective volume of the Supplement is 10 ml per 1 kg of live weight of fish.

As is known, *Chlorella* suspension is not only a source of proteins, vitamins, macro- and micro-elements, but also a source of biologically active substances with a high antagonistic effect in relation to opportunistic microorganisms [19]. It is known that the normal functioning of many systems and organs of animals, including fish, largely depends on the species composition and inter-species ratio of microorganisms that inhabit their intestines. The obtained positive effect of the Supplement on the growth and development of fish can be explained by the fact that the use of feed supplements based on microalgae *Chlorella vulgaris* in the feed for trout increases the contamination of their intestines lactic acid

bacteria, which, in turn, have an antagonistic effect on a wide range of pathogenic and opportunistic microorganisms. Thus, the restoration of the microbiocenosis of the gastrointestinal tract allows to increase the resistance of fish to adverse factors, increase growth rates, improve metabolism, increase the digestibility of nutrients in the diet and increase the survival of fish by stimulating their growth and development [20].

The results obtained in the course of the studies allow us to recommend the introduction of feed additives based on microalgae *Chlorella vulgaris* to the composition of feed for trout fish, which allows to increase growth rates and maintain the physiological state of fish at the appropriate level.

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МИКРОБАЛДЫРЛАР НЕГІЗІНДЕГІ БИОЛОГИЯЛЫҚ БЕЛСЕНДІ ҚОСПАЛАРДЫҢ ҚҰБЫЛМАЛЫ БАХТАХТЫҢ ӨСУІНЕ ЖӘНЕ МИКРОФЛОРАСЫНА ӘСЕРІН ЗЕРТТЕУ

Аннотация. Жұмыстың мақсаты микробалдырлар негізінде алынған биологиялық белсенді коектік қоспалардың балықтардың микрофлорасы мен өсу параметрлеріне әсерін зерттеу болып табылды. Балықтардың өсу қарқындылығы жемдегі хлорелла суспензиясының мөлшеріне тікелей байланысты екендігі анықталды. Бахтахтың ұзындығы мен массасының өсуінің жоғарғы көрсеткіші экспериментіміздің басқа нұсқаларымен салыстырғанда құрамында 10 мл/кг мөлшерінде хлорелла суспензиясы қосылған нұсқада байқалды. Тәжірибе соңында 10 мл/кг мөлшеріндегі хлорелла суспензиясы қосылған нұсқада бахтах салмағының өсімі 112,7 құрады, ал мөлшері 5 және 15 мл/кг хлорелланың суспензиясы қосылған бақылау және тәжірибелік нұсқаларда бұл көрсеткіштер тиісінше 98,2, 97,5 және 99,6 құрады. Зерттеу кезінде балықтардың өміршеңдігі екінші тәжірибелік нұсқада жоғары деңгейде сақталып, 100% құрады. Бақылау нұсқасында өміршеңдік 97% және бірінші нұсқада 97,7% құрады. Тәжірибенің үшінші нұсқасында өсудің айтарлықтай жоғары көрсеткішіне қарамастан, балықтардың өміршеңдігі 96,5% - ды құрады. Бұл хлорелла суспензиясының балықтар мекендейтін ортаға артық мөлшерде түсіп, оны балықтардың толық игере алмағандығынан микробалдырлардың сулы ортада жаппай көбеюімен байланысты болуы мүмкін. Бақылау және тәжірибелік нұсқаларда құбылмалы бахтахтың микрофлорасының сандық және сапалық талдауы жүргізілді. Бахтах органдарында ЖМК есептеу бақылау нұсқасында ішек бактерияларының саны $2,1 \times 10^5$ пен $3,8 \times 10^5$ КТБ /г аралығында ауытқығанын көрсетті. Бауырдың бактериялық тұқымдылығы шамалы, ЖМК көрсеткіші ылғалды салмағының 1×10^2 КТБ бірл./г тең болды. Желбезектеріндегі тұқымдылығы $2,1 \times 10^4$ мен 3×10^5 КТБ /г. аралығын қамтыды. *Chlorella vulgaris* суспензиясы қосылған тәжірибелі нұсқаларда бахтахтың әр түрлі органдарының ЖМК көрсеткіштері бақылау нұсқасынан айтарлықтай айырмашылығы болмады. Ішегінде бактерия саны $3,1 \times 10^5$ мен $3,8 \times 10^5$ КТБ /г аралығында ауытқыса, бауырында ылғалды салмағынан $2,6 \times 10^2$ КТБ /г-нан асқан жоқ. Желбезектеріндегі бактериялардың тұқымдылығы 3×10^5 пен 5×10^5 КТБ/г. аралығын құрады. Микроорганизмдердің бөлінген ассоциациялары сапрофитті және шартты патогенді бактериялардан тұрады. Зерттеу барысында бахтах микроиоценозының сапалық құрамы бақылау және тәжірибелік нұсқаларда *Lactobacillus*, *Aeromonas*, *Pseudomonas* және *Acinetobacter* негізгі 4 туысынан құралғаны анықталды. Бірақ *Lactobacillus* туысының бактерияларының сандық арақатынасы тәжірибелік нұсқаларда, атап айтқанда тәжірибенің екінші нұсқасында, бақылаумен және тәжірибенің басқа нұсқаларымен салыстырғанда әлдеқайда жоғары болды. Бахтах микрофлорасында аталған туыс өкілдерінен басқа *Micrococcus*, *Sarcina*, *Bacillus*, *Enterobacter*, *Escherichia*, *Serratia*, *Proteus* және *Vibrio* туыс өкілдері де әртүрлі қатынаста кездесті. Жүргізілген зерттеулер барысында алынған нәтижелер өсу көрсеткіштерін арттыруға және балықтардың физиологиялық жағдайын тиісті деңгейде ұстауға мүмкіндік беретін *Chlorella vulgaris* микробалдырлар негізінде бахтах балықтары үшін құрама жем құрамына жемдік қоспа ретінде енгізуді ұсынуға мүмкіндік береді.

Түйін сөздер: *Chlorella vulgaris*, құбылмалы бахтах, биологиялық белсенді қоспа, микрофлора.

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ИССЛЕДОВАНИЕ ВЛИЯНИЯ БИОЛОГИЧЕСКИ АКТИВНОЙ ДОБАВКИ НА ОСНОВЕ МИКРОВОДОРОСЛЕЙ НА РОСТ И МИКРОФЛОРУ РАДУЖНОЙ ФОРЕЛИ

Аннотация. Целью настоящей работы явилось изучение влияния биологически активной кормовой добавки на основе микроводорослей на параметры роста и микрофлору рыб. Выявлено, что темпы роста рыб напрямую зависели от количества суспензии хлореллы в корме. Высокий прирост длины и массы форели наблюдался в варианте с добавлением суспензии хлореллы в объеме 10 мл/кг по сравнению с остальными вариантами нашего эксперимента. В конце опыта в варианте с добавлением суспензии хлореллы в количестве 10 мл/кг прирост массы форели составил 112,7, а в контрольном и в опытных вариантах с добавлением суспензии хлореллы в объеме 5 и 15 мл/кг, эти показатели составили соответственно 98,2, 97,5, и 99,6. Выживаемость рыб в период исследований сохранялась на высоком уровне во втором опытном варианте и составила 100 %. Выживаемость в контрольной группе составила 97 % и в первом варианте – 97,7 %. В третьем варианте опыта, несмотря на значительно высокий прирост роста, выживаемость рыб составила 96,5%. Возможно это связано, с тем что в условиях избыточного поступления суспензии хлореллы в среду обитания и при не полном ее усвоении рыбами наблюдается высокое размножение микроводорослей в водной среде. Проведен количественный и качественный анализ микрофлоры радужной форели в контрольном и опытных вариантах. Подсчет ОМЧ в органах форели в контрольном варианте показал, что в кишечнике количество бактерий колеблется от $2,1 \times 10^5$ до $3,8 \times 10^5$ КОЕ /г. Бактериальная обсемененность печени была незначительной, показатель ОМЧ равен не более чем 1×10^2 КОЕ ед/г влажного веса. Обсемененность жабр составила от $2,1 \times 10^4$ до 3×10^5 КОЕ /г. В опытных вариантах с добавлением суспензии *Chlorellavulgaris* показатели ОМЧ различных органов форели не существенно отличаются от таковых контрольного варианта. В кишечнике количество бактерий колеблется от $3,1 \times 10^5$ до $3,8 \times 10^5$ КОЕ /г, в печени не более чем $2,6 \times 10^2$ КОЕ /г влажного веса. Обсемененность жабр составила от 3×10^5 до 5×10^5 КОЕ/г. Выделенные ассоциации микроорганизмов состоят как из сапрофитных, так и из условно-патогенных бактерий. В ходе исследований установлено, что качественный состав микробиоценоза форели как в контрольном, так и в опытных вариантах представлен 4 основными родами *Lactobacillus*, *Aeromonas*, *Pseudomonas* и *Acinetobacter*. Но численное соотношение бактерии рода *Lactobacillus* было намного выше в опытных вариантах, в частности во втором варианте опыта, по сравнению с контролем и остальными вариантами опыта. Кроме перечисленных родов, в микрофлоре форели в разном соотношении встречались также представители родов *Micrococcus*, *Sarcina*, *Bacillus*, *Enterobacter*, *Escherichia*, *Serratia*, *Proteusi* *Vibrio*. Полученные в ходе проведенных исследований результаты позволяют рекомендовать введение в состав комбикормов для форелевых рыб кормовой добавки на основе микроводорослей *Chlorellavulgaris*, позволяющей повысить показатели роста и поддерживать физиологическое состояние рыб на соответствующем нормам уровне.

Ключевые слова: *Chlorella vulgaris*, радужная форель, биологическая активная добавка, микрофлора.

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NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 48 – 55

<https://doi.org/10.32014/2019.2519-1629.30>

UDC 633.18

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RICE VARIETIES' AGROCOENOSIS FORMATION AND GRAIN CROPPING CAPACITY DEPENDING ON FERTILIZER QUANTITY

Abstract. Plant density in agrocenosis and the number of productive stems have significant effect on formation of a high grain yield of rice varieties and samples differing in height and architectonics. Thus, when an optimum fertilizer dosage (N180P120 kg/ha a.v.) is added, high grain yield is formed under the following conditions: 1) a high grain yield of a medium growth variety with narrow, vertically arranged leaves (Kuban 3, Krasnodar 424 and Dubovsky 129 varieties) is formed for the density of rice standing on the shoots of 320-400 pcs/m², before harvesting - 250-350 pcs/m², with a feed area of one plant of 22-30 cm², in the period of sweeping - 25-38 cm². In such an agrocenosis, the number of productive stems is 550-650 pcs/m², or 5.5-6.5 million panicles per hectare. 2) A high grain yield in medium-sized, large-leaved varieties (Marzhan, Aral 202, Togusken 1) is formed on highly productive crops, with a standing density of 280-350 pcs/m², before harvesting - 220-250 pcs/m², with 460-580 pcs./m² of productive stalks, or 4.6-5.8 million panicles per hectare. 3) In stunted, with large and wide leaves of varieties (Estuary) and rice samples (ECM), high grain yield is formed with a standing density of 280-380 pcs/m², before harvesting 220-310 pcs/m², with formations 550-650 pcs/m² of productive stems, or 5.5-6.5 million panicles.

Key words: rice, variety, effect of fertilizers on agrocenosis structure, rice varieties yield dependence on fertilizers' dosages.

In rice agrocenosis, formation of the number of productive stems changes during the growing season and, as an integral indicator, depends on many factors: the number and quality of sown seeds, the number of germinated seedlings, their rooting and preservation, tillering intensity, growth and productivity of side shoots. The number of these indicators, the intensity of growth and development of lateral shoots are significantly influenced by doses and methods of applying mineral fertilizers. The influence of the seeding rate and plant stand density in crops on the yield of rice grain has been studied in many studies and experimental results have been accumulated. In these works, the optimal plant stand density in crops is considered as one of the main factors that have a significant impact on the formation of high yields [1-3]. Currently, in Asian countries they intensify the technology of this valuable culture cultivation in order to provide their population with rice. Thus, according to scientists and specialists from China [4], Indonesia [5], Korea [6] and Vietnam [7], the highest and high-quality grains of rice are formed on crops with optimal plant density, balanced nutrients, and optimal doses and methods of mineral fertilizer application and with timely and high-quality carrying out of all agrotechnical techniques. The influence of the seeding rate and plant stand density on the yield of rice grain has been studied in many studies and experimental results have been accumulated. In these works, the optimum plant stand density is considered as one of the main factors that have a significant impact on the formation of high yields [1-3, 8].

Methods and objects of research. Small-plot and large-field field experiments were carried out on the saline soils of the Kazakhstan Aral Sea area in 2012-2017 to determine the favorable structure of agrocenosis of rice varieties and the optimum dosage of nitrogen fertilizer. Medium-height, narrow-leaved, early-ripe varieties such as Kuban 6 and Dubovsky 129, middle-ripe Krasnodar 424 variety, medium-tall, large-leaved samples 4-15, Kyzylorda 5, KzROS 356, Marzhan variety, low-growing, broad-leaved Firth were studied. In small-scale experiments, the seeding rate was 100, 300, 500, 700, 900 kg/m²;

the dosage of fertilizers N90P90, N180P120 kg/ha a.v., were repeated three times. In large-scale experiments, the seeding rate for Kuban 3 and Liman varieties was 100 kg/ha (3 million viable seeds per hectare), 200 kg/ha (6 million), 250 kg/ha (7.5 million), 300 kg/ha (9.5 million viable seeds per hectare). Seeds of Marzhan variety are larger and spinous, therefore they sowed 130 kg/ha (3 million viable seeds), 230 kg/ha (6 million), 280 kg/ha (7.5 million) and 330 kg/ha (9.5 million viable seeds) using a seeder. Pilot crops were flooded on May 18-20. Mineral fertilizers (ammonium sulfate, granulated superphosphate) were added: N0P0, N90P90, N120P120, N150P120, N180P120, N240P120 kg/ha ae. The area of the plots was 150 m², the number of replications - four.

Results of research and discussion. *The main indicators of the structure of rice agroecosystem* include the optimum plant standing density, the number and productivity of main and lateral shoots and tillering intensity. These indicators vary significantly depending on the area of nutrition and doses and methods of mineral fertilizer application. Thus, in model experiments (plot area - 5 m²), the greatest germination of seeds was observed when 100, 300 seeds were sown per m². With an increase in the number of sown seeds (i.e. with a decrease in the area of nutrition), field germination of seeds decreased. For example, the germination of seeds of narrow-leaved rice varieties Kuban 3, Krasnodarskiy 424 and Dubovskiy 129 decreased from 76.0-79.3% to 48.2-57.4%. The same patterns were observed with crops of large-leaved varieties Marzhan and samples 4-15, Kyzylorda 5, KSROC 356. However, with an increase in the seeding rate, more sprouting rice plants and the productive stems remained till harvesting (Fig. 1). Rice is an intensely bushy plant. With increase in area of nutrition and increase of fertilizers dosages, the number of the 2nd, 3rd and other side shoots increased significantly. However, with a decrease in the area of nutrition and the emergence of optimally dense shoots, tillering of rice decreases, shoots of the first and second order appear, which grow and develop synchronously, not lagging behind the main stem. This is one of the main conditions for obtaining high grain yields. But, with very thickened crops, the leaves located on the lower and middle levels are mutually strongly shadowed, tillering lingers, shoots appear without panicle, which leads to a decrease in grain yield [1-3].

When an optimum fertilizer dosage is added (N180/P120 kg/ha) and with highly productive agroecosystem (i.e. at the optimally crowded cultures) tillering increases and the number of productive stalks and side shoots (stalks with heads) (figure). Thus, when 300, 500, 700 pcs of germinating seeds per a m² and adding fertiliser at the rate of N180P120 kg/ha number of productive stalks of the pilot sowings of large-leaf varieties was 452-567, 469-613, 479-634 pcs/m², correspondingly. As for the narrow-leaf rice varieties with vertical leaf position, such as Kuban 3, Krasnodarskiy 424, the number of productive stalks was 487-686, 569-667 pcs/m², i.e. 8.8-21.0% more. At the optimum fertilizer dosage, such an increase in the number of productive stalks is the main condition of high grain yield formation (figure).

When an optimum fertilizer dosage is added to the rice varieties with narrow vertically arranged leaves such as Kuban 3 and Krasnodarskiy 424, the best yield was achieved when 500, 700 pcs/m² of germinating seeds had been sown and at the density of plants growing of 320-430 pcs/m², prior to harvest - 250-280 pcs./m², at the area of one plant feed of 22-30 cm, during the period of ear formation - 25-38 cm², at the number of productive stalks of 550-650 pcs/m², i.e. when 5.5-6.5 mln. heads are formed per a hectare.

As regards the crops of large-leaved varieties and samples of rice, a high grain yield is formed when sowing 300, 500 pcs / m² of viable seeds and with formations of plant standing on shoots of 230-350 pcs/m², in the period of sprouting 220-300 pcs / m², with one feed area plants shoots 28-45 cm², in the period of sweeping - 31-50 cm². Under such conditions, the optimal number of productive stems was 460-580 pcs / m², i.e. 4.6-5.8 million ears of corn were formed on one hectare. Such crops are called by us highly productive agroecosystem [1-3].

Rice crops - dynamic agroecosystem. With the introduction of the optimal dose of fertilizers and depending on the density of standing and feeding area, the mutual influence of neighboring rice plants in crops during the growing season changes. These changes depend on the architectonics, morphophysiological and genetic characteristics of rice varieties. In rice crops, photosynthetic activity and plant growth processes have a significant impact on the level of yield and grain quality depending on standing density. In this regard, the rice crops are subdivided as follows: thinned, moderate, highly productive and highly thickened agroecosystem. The yield of such crops vary [1-3].

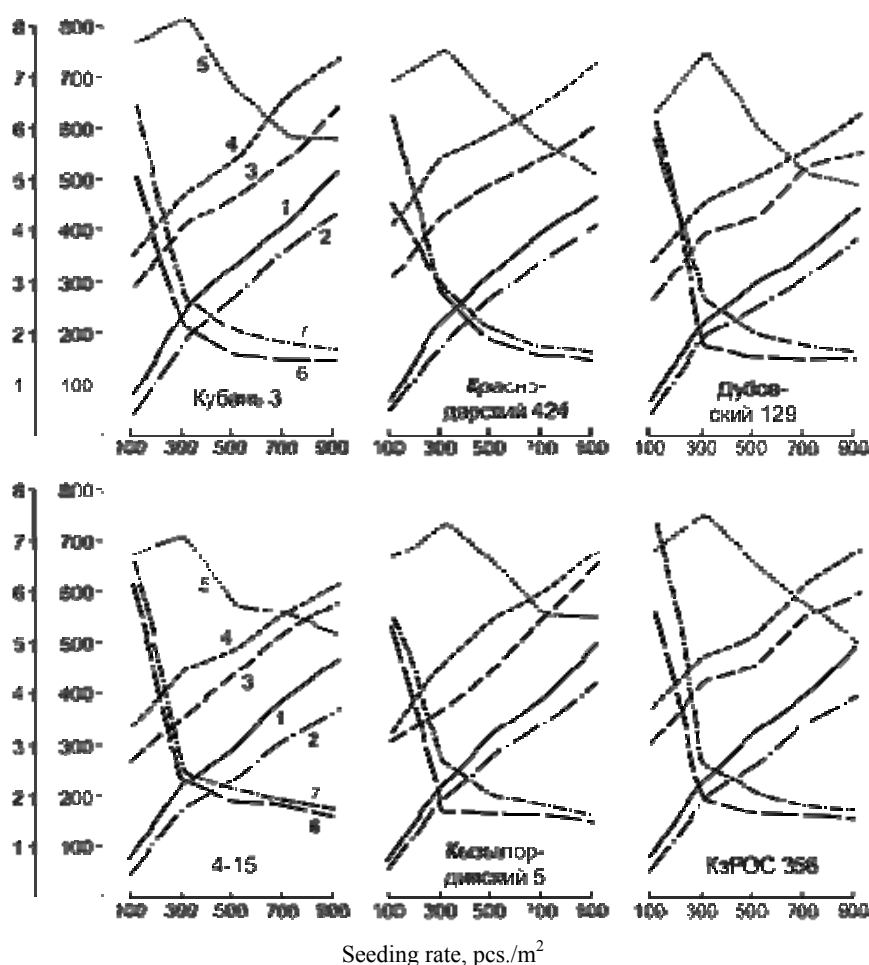


Figure 1 – Formation of agroecological structure of rice medium-growth varieties and samples differing by the architectonic depending on fertilisers’ dosages and coverage area.

Conventional designation: 1 – number of springing rice sprouts, pcs./m²; 2 – number of plants before harvesting, pcs./m²; 3 – number of productive rice stalks at the fertilizer dosage of N90P90kg/ha; 4 – number of productive rice stalks at the dosage of N180P120 kg/ha; 5 – field germination rate %; 6 – rice tillering capacity at the fertilizer dosage of N90P90 kg/ha; 7 – rice tillering capacity at the fertilizer dosage of N180P120 kg/ha.

On all the different soils of the CIS territories, rice is responsive to the doses and methods of applying nitrogen fertilizers compared to phosphate fertilizers. However, with the joint application of nitrogen and phosphate fertilizers, rice forms the highest grain yield [1-3]. In this regard, the effect of nutrition area and doses of nitrogen-phosphate fertilizers on the formation of the structure and yield of agroecological structure of rice varieties (table) was studied.

Germinating ability of seeds and survival ability of sprouts. There is a positive correlative relationship between field seed germination, the number of preserved plants, the density of standing productive stalks and grain yield of rice crops [1-3]. Thus, when sowing 100, 300 seeds per a m² within the framework of the on model experiments (plot area 5 m²), field seed germination was high. With an increase in the number of seeds sown (i.e. with a decrease in the nutrition area), field germination decreased. For example, field germination of seed varieties Kuban 3, Krasnodar 424, Marzhan decreased from 74-82% to 51.3-53.7%. Despite this, with an increase in the seeding rate, seedlings sprouted thick, the number of plants on crops increased and remained until harvest. Such patterns were preserved on experimental crops of dwarf and low-growing rice samples (figure; table). In model experiments, when sowing 100, 300, 500, 700 pcs / m² of viable seeds and when making optimal doses of fertilizers, the survival rate of the seedlings was high and more rice plants remained. But when sowing 900 pieces / m² of seed, the survival rate of seedlings decreased significantly. The results of the experiments show that with

Formation of rice density in agrocenosis and grain yield depending on increasing dosages of nitrogen fertilizers and seeding rate

Rice Variety	Seeding Rate, kg/ha	Number of Plants pcs/m ²		Field Germination Capacity, %	Sprouts Survival Rate, %	Number of Productive Stalks, pcs/m ²	Tilling Capacity, pcs/plant	Grain Yield, h.kg/ha
		Sprouts	Before Harvest					
1	2	3	4	5	6	7	8	9
N0P0, Control								
Kuban 3	100	144	110	48,0	76,4	186	1,69	33,4
	200	243	189	40,5	77,8	254	1,34	37,0
	250	300	240	40,0	80,0	301	1,25	38,1
	300	370	286	38,9	77,4	334	1,17	41,8
HCP ₀₅	–	13,2	14,1	–	–	12,6	–	4,0
N120P120 kg/ha								
Kuban 3	100	151	116	50,3	76,8	480	4,22	42,2
	200	243	194	40,5	79,8	513	2,64	51,5
	250	314	247	41,9	78,7	531	2,15	58,1
	300	370	287	38,9	77,6	519	1,81	55,5
HCP ₀₅	–	15,3	13,4	–	–	16,7	–	4,3
N150P120 kg/ha								
Kuban 3	100	143	109	47,7	76,2	508	4,66	50,6
	200	237	187	39,8	78,2	518	2,72	54,1
	250	305	243	40,5	79,7	553	2,28	67,7
	300	366	291	38,5	79,5	534	1,84	60,4
HCP ₀₅	–	14,8	14,2	–	–	16,0	–	3,3
N180P120 kg/ha								
Kuban 3	100	148	112	49,3	75,7	549	4,90	60,8
	200	250	200	41,7	80,0	571	2,86	66,3
	250	319	253	42,7	79,3	591	2,34	78,0
	300	380	295	40,0	77,6	658	2,23	65,9
HCP ₀₅	–	15,5	13,7	–	–	14,2	–	4,6
N240P120 kg/ha								
Kuban 3	100	146	116	48,7	79,5	581	5,01	66,2
	200	248	196	41,3	79,0	600	3,06	73,2
	250	315	245	42,0	77,8	631	2,58	74,0
	300	376	298	39,6	79,3	672	2,26	58,8
HCP ₀₅	–	13,5	12,8	–	–	13,8	–	4,5
N0P0, control								
Mar-zhan	130	124	95	41,3	76,6	176	1,85	35,3
	230	224	175	37,3	78,1	235	1,34	38,7
	280	278	219	38,1	78,8	278	1,27	41,3
	330	336	273	35,4	82,3	273	1,16	42,4
HCP ₀₅	–	12,1	13,4	–	–	10,8	–	4,3
N120P120 kg/ha								
Mar-zhan	130	123	102	41,2	82,8	505	4,95	44,8
	230	227	175	37,8	77,1	512	2,93	53,4
	280	296	227	39,5	76,7	535	2,36	61,5
	330	345	268	36,3	77,7	518	1,93	51,2
HCP ₀₅	–	12,3	10,3	–	–	12,0	–	4,6

Continuation of table								
1	2	3	4	5	6	7	8	9
N150P120 kg/ha								
Mar-zhan	130	119	103	39,7	86,6	516	5,01	51,5
	230	228	179	38,0	78,5	528	2,95	57,4
	280	293	231	39,1	78,8	549	2,38	70,2
	330	349	276	36,7	79,1	569	2,05	57,8
HCP ₀₅	–	13,7	12,0	–	–	14,0	–	4,4
N180P120 kg/ha								
Mar-zhan	130	125	98	41,7	78,4	522	5,33	59,0
	230	233	173	38,8	74,2	541	3,13	66,8
	280	297	229	39,6	77,1	551	2,41	73,8
	330	357	282	37,6	79,0	591	2,10	61,5
HCP ₀₅	–	14,1	12,7	–	–	13,5	–	4,5
N240P120 kg/ha								
Mar-zhan	130	121	97	40,7	80,2	539	5,56	60,1
	230	229	171	38,2	74,7	557	3,26	66,7
	280	291	225	38,8	77,3	594	2,64	65,5
	330	361	289	38,0	80,1	624	2,16	53,0
HCP ₀₅	–	5,3	5,5	–	–	6,4	–	3,8
N0P0, Control								
Liman	100	121	94	40,3	77,3	163	1,73	28,8
	200	222	163	37,0	73,4	228	1,40	32,7
	250	269	210	35,9	78,1	263	1,25	35,0
	300	335	252	35,3	75,2	314	1,25	38,4
HCP ₀₅	–	12,5	12,8	–	–	11,4	–	4,6
N120P120 kg/ha								
Liman	100	119	100	39,7	84,0	490	4,90	42,4
	200	219	167	36,5	76,3	514	3,08	57,5
	250	284	217	37,9	76,4	530	2,44	64,2
	300	341	257	35,9	75,4	518	2,02	57,4
HCP	–	14,2	13,1	–	–	12,3	–	5,0
N150P120 kg/ha								
Liman	100	124	96	41,3	77,4	515	5,36	51,9
	200	224	174	37,3	77,7	558	3,21	65,0
	250	287	232	38,3	80,8	601	2,60	71,6
	300	347	265	36,5	76,4	540	2,04	61,9
HCP ₀₅	–	14,4	15,2	–	–	13,7	–	4,1
N180P120 kg/ha								
Liman	100	123	95	41,2	77,4	553	5,76	57,0
	200	228	167	38,0	73,2	571	3,42	66,5
	250	286	228	38,1	79,7	641	2,81	69,2
	300	352	273	37,1	77,6	675	2,47	57,1
HCP ₀₅	–	15,5	14,3	–	–	13,1	–	4,8
N240P120 kg/ha								
Liman	100	123	98	41,0	79,7	581	5,93	52,7
	200	227	160	37,8	70,5	600	3,75	58,5
	250	285	227	38,0	79,6	659	2,90	58,2
	300	345	275	36,4	79,5	691	2,51	53,2
HCP ₀₅	–	13,4	12,3	–	–	15,0	–	3,7

the introduction of the optimal dose of fertilizers (N180P120 kg / ha ai) and with the optimum density of germinated seedlings, the penetration of light, carbon dioxide (CO₂) and the temperature inside the agroecosystem improved and good conditions were established for the growth and development of each rice plant in agroecosystem.

Rice tillering depends on the area of nutrition [1-3], the dose, timing and methods of applying mineral fertilizers [1-3, 9, 10, 16], the depth of water within the check plots and changes in irrigation mode [9, 10, 12, 13, 15]. The results of our research showed that with an increase in the seeding rate (i.e., a decrease in the nutritional area) and an increase in plant density to the optimum level, tillering of rice stops. With the introduction of an average dose (N120P90-120 kg / ha), tillering of rice increases as compared with plants on the control (without fertilizer) and the introduction of small doses (N90P90 kg / ha AI) of fertilizers. With an increase in the dose of fertilizer to the optimum (N180P120 kg / ha) and sowing of 500, 700, 900 pcs / m², the level of tillering of rice decreased. In spite of this, with increasing doses of fertilizers, the number of productive stems increased. On crops of medium-grade rice varieties, with the introduction of optimal (N180P120 kg / ha) and high (N240P180 kg / ha AV) fertilizer dose, bushiness when sown 100 pcs / m² from 7.7-9.1 pcs / m² decreased to 1, 8-1.9 pcs / m², i.e. 4.1-4.7 times when sown 900 pieces / m² of germinating seeds. The same patterns were observed on dwarf and low-growing varieties. However, with increasing doses of fertilizers, bushiness and the number of productive rice stalks increased to a certain extent (figure). Consequently, on high agro-backgrounds, a decrease in nutritional area (i.e., an increase in plant standing density) is a factor that reduces rice bushiness.

The productivity of lateral shoots from the different rows is not the same. As the place of emergence of lateral shoots in the tillering node increases, the stem height, the length of the panicle and the number of grains on the panicle of side shoots decrease. Side shoots that appear on the lower level of the tillering node, i.e. 3-5 leaves on the bosom grows and develops synchronously, not lagging behind the main stem and is the most productive. However, depending on the density of the standing of rice plants and the area of nutrition, doses and methods of fertilizer application, the optimal number of side shoots differ [1-3, 8, 9].

In this regard, the agroecosystem of rice varieties have been systematized as follows [1-3, 10]: *thinned out plantings* (sowing of 100 of viable seeds per a m²), *moderate plantings* (sowing of 300 viable seed per a m²), *highly productive crops* (sowing 500, 700 seeds per a m²) and *thickened crops* (sowing 900 germinated seeds per a m²). When adding an optimum dosage of fertilizers (N180P120 kg/ha), the largest grain yield of medium-sized rice varieties is formed in the following agroecosystem:

a) *Thinned out crops* of medium-ripening rice varieties with appearances of 6-8 lateral shoots on each rice plant; *moderate crops* with formations of 2.5-4.0 lateral shoots; *highly productive crops* - 1.8-2.5 lateral shoots; *thickened crops* with appearances of 1.1-1.6 lateral shoots on each plant;

b) for undersized samples and rice varieties, thinned out crops form the largest grain yield when there are 9-10 lateral shoots on each plant; *moderate crops* - 3.5-5.0 lateral shoots, on highly productive agroecosystem - 2-3 side shoots; *thickened crops* - with the appearance of 1.6-2.0 side shoots on each plant;

c) As for the dwarf specimen, thinned out crops produce the largest grain yield when 9-11 side shoots appear on each plant; moderate crops - 5-6 side shoots; highly productive crops - 3-4 side shoots; thickened crops - 2.1-2.5 side shoots on each rice plants.

Improving the rice varieties agroecosystem structure is important and relevant for the intensive development of rice farming [1-3]. However, the density of plant standing, formation of optimal stalk stand and its location in space, formation of plant habitus in agroecosystem and its interaction in the physiological aspect have not been sufficiently studied.

The formation of the optimal number of productive stalks in agroecosystem depends on the number of seedlings germinated and their field germination, seedling survival rate and their standing density, dose and methods of mineral fertilizers application and varietal characteristics of rice (figure; table). Thus, in medium-sized varieties and samples, the largest grain yield is formed on highly productive crops (when sowing is 500,700 viable seeds) and application N180P120 kg / ha ae. fertilizer. With an increase in the dose of fertilizer up to N240P180 kg / ha ae. grain yield has not increased, but rather decreased.

In low-growing varieties and samples of rice, the level of yield varies: in a broad-leaved variety (Lyman), the highest grain yield is formed when the optimum dosage (N180P120 kg/ha) of fertilizers is applied. On highly productive agroecosystem in varieties and samples of rice, photosynthetic activity and the

possibility of the formation of high grain yields differ. The formation of a high grain yield in varieties and samples of rice, differing in height and architectonics, is significantly affected by plant density in agrocenosis and the number of productive stems. Thus, with the introduction of the optimal dose (N180P120 kg / ha ai) of fertilizers, a high grain yield is formed under the following conditions [1-3, 11, 14, 17]:

1) A heavy yield of grain of medium-growth varieties with narrow vertically arranged leaves (Kuban 3, Krasnodar 424, Dubovsky 129) is formed in highly productive crops, with a density of rice standing on shoots of 320-400 pcs/m², before harvesting - 250-350 pcs/m², with a food area of one plant 22-30 cm², in the period of sweeping out - 25-38 cm². In such agrocenosis, the number of productive stems is 550-650 pcs / m², or 5.5-6.5 million panicles per hectare.

2) A high grain yield in medium-sized, large-leaved varieties (Marzhan, Aral 202, Togusken 1) is formed on highly productive crops, with a density of standing of 280-350 pcs / m², before harvesting 220-250 pcs/m², with 460-580 pcs./m² of productive stalks, or 4.6-5.8 million panicles per hectare.

3) Heavy yield of low varieties with large and wide leaves (Estuary) and rice samples (ECM) is ensured at a standing density of 280-380 pcs/m², before harvesting 220-310 pcs/m², with formations 550-650 pcs/m² of productive stems, or 5.5-6.5 million panicles. We called the above-mentioned crops of rice varieties, differing in height and architecture, as **high-yielding agrocenosis** [1-3, 11]. Those crops of low- and medium-growth varieties and rice samples are **representative** of specific agrocenosis. Indicators of these agrocenosis can be preliminary morphophysiological criteria (indicators) when creating models of future productive rice varieties and this should be taken into account when developing varietal technologies for their cultivation [1-3, 11].

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ТЫҢАЙТҚЫШТАР ДОЗАСЫНА БАЙЛАНЫСТЫ КҮРІШ СОРТТАРЫ АГРОЦЕНОЗЫНЫҢ ЖӘНЕ ДӘН ӨНІМІНІҢ ҚАЛЫПТАСУЫ

Аннотация. Биіктігі және архитектурасы бойынша айырмашылығы бар күріш үлгілері мен сорттарының жоғары дән өнімінің қалыптасуына агроценоздағы өсімдіктер тығыздылығы мен егістіктегі масақты сабақтар санының елеулі әсері бар. Атап айтқанда, оптимальды агрофон (N180P120 кг/га) жағдайында ең жоғары дән өнімі төмендегі жағдайларда қалыптасады: 1) Орта бойлы, жіңішке, тік жапырақты күріш сорттарының (Кубань 3, Краснодарский 424, Дубовский 129) ең жоғары дән өнімі себілген тұқымнан өніп шыққан өсімдіктер саны 320-400 дана/м², ору алдында 250-350 дана/м² болып, тұқымнан әдепкі өніп шыққан өскіндердің қоректену алаңы 22-30 см², масақтану кезінде 25-38 см² болғанда қалыптасады. Мұндай агроценоздағы өнімді (масақты) сабақтардың саны 550-650 дана/м², немесе гектарына 5,5-6,5 млн. масақ. 2) Орта бойлы, ірі жапырақты күріш үлгілері (4-15, КзРОС 356, Кызылординский 5) мен сорттарының (Маржан, Арал 202, Түгіскен 1) ең жоғары дән өнімі егістіктегі өсімдіктер тығыздылығы өніп шыққан кезде 280- 350 дана/м², ору алдында- 220-250 дана/м², өнімді сабақтар саны 460-580 дана/м², немесе гектарына 4,6-5,8 млн. масақты сабақтар болғанда қалыптасады. 3) Аласа бойлы, ірі жапырақты сортының (Лиман) жоғары дән өнімі егістіктегі өсімдіктер тығыздылығы өніп шыққан кезде 280-380 дана/м², ору алдында 220-310 дана/м², өнімді сабақтар саны 550-650 дана/м², немесе гектарына 5,5-6,5 млн. масақты сабақтар болғанда қалыптасады.

Түйін сөздер; күріш, сорт, агроценоз құрылымына тыңайтқыштар әсері, Тыңайт-қыштар дозасына байланысты күріш сорттары дән өнімінің құралуы.

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ФОРМИРОВАНИЕ АГРОЦЕНОЗОВ СОРТОВ РИСА И УРОЖАЙНОСТЬ ЗЕРНА В ЗАВИСИМОСТИ ОТ ДОЗЫ УДОБРЕНИЯ

Аннотация. На формирование высокого урожая зерна у сортов и образцов риса, различающиеся по высоте и архитектонике, оказывают существенное влияние густота стояния растений в агроценозах, количество продуктивных стеблей. Так, при внесении оптимальной дозы (N180P120 кг/га д.в.) удобрений высокий урожай зерна формируется в следующих условиях: 1) Высокий урожай зерна среднерослых, с узким, вертикальным расположением листьев (Кубань 3, Краснодарский 424, Дубовский 129) образуется на высокопродук-

тивных посевах, при густоте стояния риса по всходам 320-400 шт/м², перед уборкой -250-350 шт/м², при площади питания одного растения 22-30 см², в период выметывания – 25-38 см². В таких агроценозах количество продуктивных стеблей равен 550-650 шт/м², или на гектаре 5,5-6,5 млн. метелок. 2) Высокий урожай зерна у среднерослых, крупнолистных сортов (Маржан, Арал 202, Тогускен 1) формируется на высокопродуктивных посевах, при густоте стояния 280-350 шт/м², перед уборкой – 220-250 шт/м², при количестве 460-580 шт/м² продуктивных стеблей, или 4,6-5,8 млн. метелок на гектаре. 3) У низкорослых, с крупными и широкими листьями сортов (Лиман) и образцов риса (ЕСМ) высокий урожай зерна формируется при густоте стояния 280-380 шт/м², перед уборкой – 220-310 шт/м², при образований 550-650 шт/м² продуктивных стеблей, или 5,5-6,5 млн. метелок.

Ключевые слова: рис, сорта, влияние удобрений на структуру агроценоза, формирование урожая сортов риса в зависимости от доз удобрений.

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NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 56 – 63

<https://doi.org/10.32014/2019.2519-1629.31>

UDC 615.017; 616.079; 615.2

MRNTI 34.45.05

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THE STUDY OF NEUROTROPIC ACTION OF ALKALOIDS AND THEIR DERIVATIVES

Abstract. The article presents the results of a study of the neurotropic action of alkaloids and their derivatives. It was established that the studied compounds 8-acetylharminine, ((E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indol-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one, lappaconitine and cytosine at a dose of 5 mg/kg have a neurotropic effect, increasing the level of the orienting reaction of animals in the «Open field» test; they also normalize the emotional state, reducing the level of anxiety and fear of animals in the test "Elevated plus maze".

Keywords: alkaloids, neurotropic action, emotional stress, alkaloid derivatives.

Introduction. Currently in the world there is an increase in the number of neurological patients, an increase in the morbidity of the nervous system. Among the main causes of the spread of diseases of the central nervous system can be called stress, psycho-emotional stress, which results in anxiety, depression, develop of addictions [2]. In this regard, there is a significant interest of researchers to neurotropic drugs [1]. Among the promising in the study of the neurotropic action of natural compounds alkaloid compounds and their derivatives should be noted.

Alkaloids are a group of natural organic compounds that are synthesized by plants [3]. Alkaloids can affect the central nervous system, including the nerve cells of the brain and spinal cord, which control many of the functions of the human body and its behavior [4,5]. Experimental evidence has been obtained that alkaloids have a broad spectrum of pharmacological properties, including neurotropic effects and can selectively bind to receptors of nerve cells [4-11].

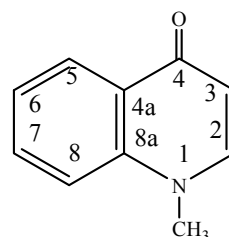
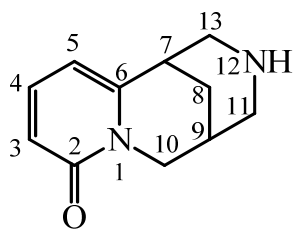
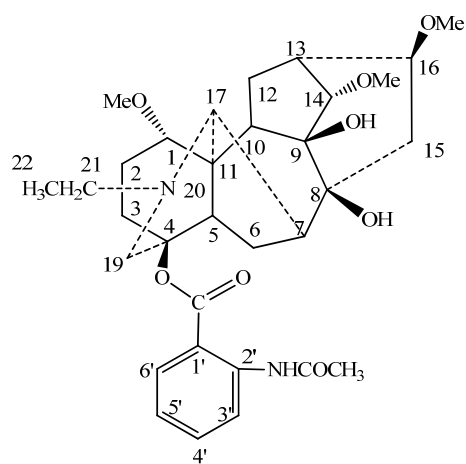
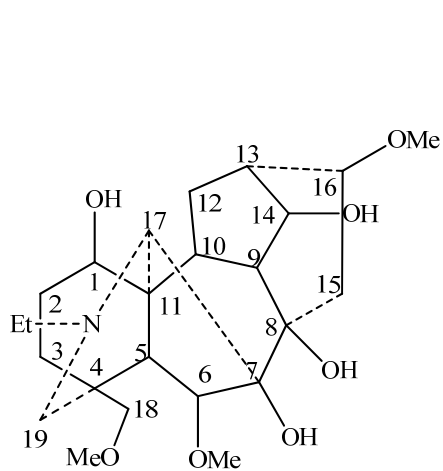
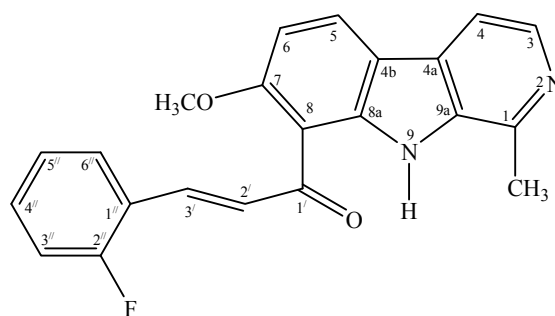
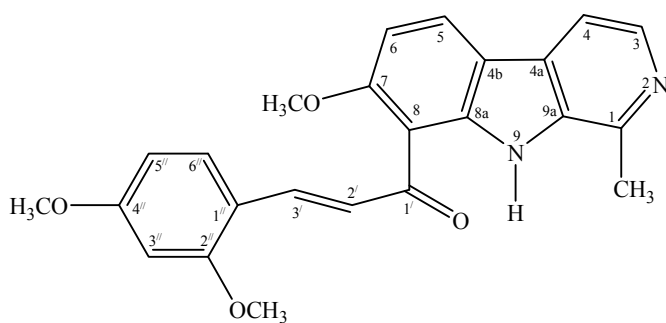
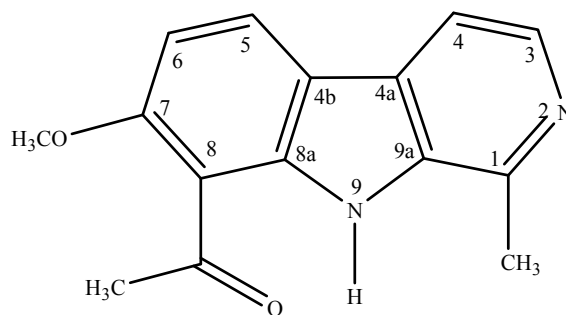
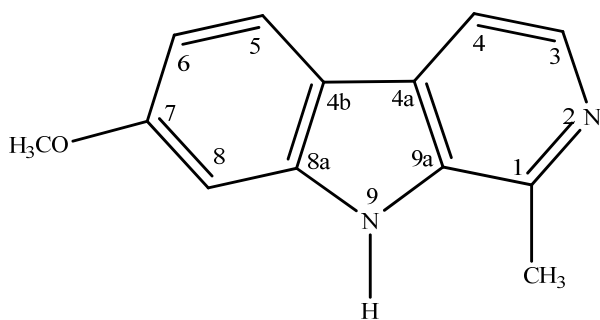
The most interesting in their chemical structure are the indole, isoquinoline, diterpene and pyrrolidine alkaloids, among which there are substances with various combinations of methoxy, hydroxy, amino, carboxy and heterocycles, as well as conformational and optical isomers, which can serve as a source for obtaining various drugs, including neurotropic drugs.

Thus, the indole alkaloid, harmine, has an effect on the central nervous system (CNS), showing its effect in neurological diseases [12, 13]. Diterpene alkaloids have a broad spectrum of biological activity, which allows them to be considered as a source of promising pharmacological compounds [14, 15].

Objective: to study the neurotropic action of alkaloid compounds and their derivatives on experimental stress models.

Material and Methods: The following compounds were presented for the study: harmine (1), 8-acetylharminine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4), delkozine (5), lappaconitine (6), cytosine (7), echinopsine (8).

Previously a computer simulation of the molecules of the substances and virtual docking with the proposed biological target dopamine receptor D2 were carried out. The ligand-target interaction strength was evaluated by the binding energy index.



The experimental part was carried out in accordance with the “Rules of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes” and according to the requirements for the study of new pharmacological substances in adult rats (60 animals) equally males and females, the initial body weight is 240 - 370g. Rats are from own vivarium of International research and production holding "Phytochemistry" (Karaganda). The animals were in standard vivarium conditions on the usual diet and free access to water and food. In addition, observations of the general state of the animals were made: changes in the body weight of animals, motor activity, appetite and response to external stimuli.

Emotional stress was modeled by placing the rats in tight plastic cylinders with their subsequent immersion in water up to the neck level (20-22⁰C) for 2 hours daily for four days [16]. The test substances at a dose of 5 mg/kg were injected to animals for seven days before emotional stress modeling and then daily 1 hour before placing the animals in plastic cylinders. As the comparison drug, the drug “Piracetam” (OJSC “Borisov Medical Preparations Plant” Republic of Belarus) [17] was used, which was administered to animals in a similar pattern. All drugs were injected daily by mouth as an aqueous solution in a volume of 1 ml/kg. The animals of the control and intact groups received purified water in an appropriate volume.

On the fourth day after emotional stress modeling, the behavioral effect of the studied compounds was assessed using standard methods in the following tests: “Open field” [18] and “Elevated plus-maze” [19].

The “Open Field” test represents a field with a diameter of 100 cm, bounded by 40 cm high sides. The pad is laid out on 16 squares. The animal was placed in the center of the field and within two minutes the number of stances (vertical locomotor activity) and locomotion (horizontal locomotor activity), as well as grooming and the number of defecation (bolus) and urination were visually recorded. The measurements were carried out in silence and under the light of a lamp.

As it is well known, emotional stress is characterized by a manifestation of fear and anxiety, therefore, the assessment of neurotropic activity was performed using the “Elevated plus-maze” test (anxiolytic activity). The test method "Elevated plus maze" allows to identify the anxiolytic activity of drugs. It is based on the ability of animals under the action of drugs to overcome the natural fear of falling from a height and open areas [2]. The rat was placed in the center of the installation, which consisted of 4 arms, crosswise diverging from the central platform at a right angle, 45 cm long and 10 cm wide (wall height of closed arms is 10 cm): two opposite open, without walls, and two closed, dark. In the center of the labyrinth's criss-cross arms there is an open area measuring 10 by 10 cm. Experiments were carried out under normal lighting for 3 minutes. The test allows to assess the level of anxiety of animals under the influence of pharmacological agents. During the experiment, the time spent by animals in open and closed arms, the number of entries in open and closed arms, the number of hanging and peeping from an open arm, the number of stances, grooming, time spent on the central site, the latent period of the first entry into an open arm, urination and defecation number were obtained.

Statistical processing of the results was carried out using the “Statistica 8.0” software package. The results are presented as “mean ± standard error of the mean”. Intergroup differences were assessed by the non-parametric Mann-Whitney U-test. For pairwise related groups, the nonparametric Wilcoxon test was used.

The results of the study. During the experiment, it was noted that the body weight of the rats in all groups remained within the limits of the initial data; no significant changes in the weight gain of the animals of all groups were observed (table 1).

Investigation of the effects of the studied compounds on the orienting-exploratory behavior of animals using the “Elevated plus maze” method. According to a study it was found that emotional stress increases a sense of fear and anxiety in animals. Thus, when checking the behavioral reactions in the “Elevated plus maze” test, it was revealed that the rats of the control group had lower number of entries into open arms and the time spent in them than those of animals of the intact group by 54.5% and 89.7%, respectively. An increase in the number of entries into the labyrinth's closed arms in the control group of animals by 25% also indicated a low emotional level. A decrease in the number of peekings and the number of hanging of the control group rats compared with the indices of animals in the intact group was recorded. The number of stances of the control group rats was absent.

Table 1 – Data on weight gain of rats

Group	Weight, g	
	Before	After
Intact rats n=6	296.3 ± 20.3*	297.0 ± 20.8
Control (without treatment) n=6	367.8 ± 8.5	373.3 ± 10.2
The comparison group (Piracetam) n=6	328.0 ± 12.0	324.5 ± 22.7
Harmine (Gar) (1),n=6	303,3 ± 53,0*	307,3 ± 49,6*
8-acetylharminine (2) n=6	287.5 ± 18.6	291.3 ± 24.3
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) n=6	243.0± 10.2	241.8 ± 6.0*
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4- b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) n=6	287.5 ± 18.6	258.0 ± 32.3
Delkozine (5) n=6	295.3 ± 45.5	298.0± 47.6
Lappaconitine (6) n=6	298.0± 6.5	301.0 ± 7.7
Cytisine (7) n=6	245.0 ± 8.4*	243.3± 6.7*
Echinopsine (8) n=6	264.3± 26.2	262.3 ± 27.9
*p <0.05 compared with the values of the control group, n is the number of animals in the group.		

In the group of animals treated with 8-acetylharminine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), lappaconitine (6) and cytisine (7) at a dose of 5 mg/kg compared with the rats of the control group under conditions of experimental emotional stress showed an anxiolytic (anti-anxiety) effect.

In particular, the time spent in a closed arm in groups of animals using lappaconitine (6) decreased by 23.9%, (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) by 12.5%, cytisine (7) by 5.6% compared with the control group. The time spent by animals in open arms in groups using (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) increased by 78%, lappaconitine (6) by 76.4%, 8-acetylharminine (2) by 76.1%, cytisine (7) by 64.1% compared to control. Time of staying on the central platform in the group of animals that used lappaconitine (6) increased by 37.8% compared with the control. The administration of the harmine (1), 8-acetylharminine (2), delkozine (5), lappaconitine (6) to rats reduced the number of closed arms, as well as with the introduction of 8-acetylharminine (2) and lappaconitine (6), increased the number of peekings. The number of hanging in groups of animals with the use of 8-acetylharminine (2) and delkozine (5) increased. The number of defecation and urinations decreased in groups of animals using 8-acetylharminine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4- b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) and echinopsine (8) (table 2).

Investigation of the effects of the studied compounds on the orientational-exploratory behavior of animals using «The open field» method. As a result of «The open field» test, it was found that animals from groups using 8-acetylharminine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), lappaconitine (6), cytisine (7) and echinopsine (8) at a dose of 5 mg/kg demonstrated a higher level of orientation reaction in «the open field» test, since the number of horizontal and vertical movements is greater than the result of control group and is close to the value of the reference drug group. In animal groups using 8-acetylharminine (2), lappaconitine (6), cytisine (7) and echinopsine (8) at a dose of 5 mg/kg, the number of urination and defecation is lower than in the control group, the latency of exit from the center of the “open field” is higher (table 4).

Table 2 – The effect of the studied compounds on the behavior of rats in the test "Elevated plus maze"

Group	Time spent in a closed arm, (s)	Time spent in an open arm, (s)	Number of entries in open arms, (times)	Number of entries in closed arms, (times)	Number of peekings, (times)
Intact rats n=6	59.5±11.8*	77.3±19.3	3.3±1.9	1.5±1.3	3.0±2.4
Control (without treatment) n=6	161.0±15.6	8.0±1.2	1.5±0.6	2.0±1.4	2.0±2.3
The comparison group (Piracetam) n=6	152.0±32.0	20.5±9.8	0.8±1.0	1.5±0.6	5.0±2.2
Harmine (Gar) (1),n=6	167.0±8.7*	13.0±8.7	1.5±0.6	1.5±0.6	0.3±0.5
8-acetylharmine (2) n=6	141.3±40.1	33.5±15.4	1.0±0.8	1.3±0.5	3.0±3.2
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) n=6	140.8±32.3*	36.3±17.9	1.5±0.6	2.0±1.2	1.8±1.0
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) n=6	167.5±5.6*	9.5±3.9	1.0±0.0	1.3±0.5	0.8±1.0
Delkozine (5) n=6	164.5±11.5	9.8±4.2	1.3±0.5	1.3±1.0	1.8±2.4
Lappaconitine (6) n=6	125.5±80.4	35.4±10.8	1.3±0.5	1.5±1.0	2.5±1.3
Cytisine (7) n=6	152.0±23.6*	22.3±6.3	1.3±0.5	2.0±0.8	1.3±0.5
Echinopsine (8) n=6	167.3±12.2*	12.0±2.0	0.8±0.5	1.3±0.5	0.5±0.6

*p <0.05 compared with values of the control group animals, n is the number of animals in the group.

Table 3 – The effect of the studied compounds on the behavior of rats in the test "Elevated plus maze"

Group	Number of hangings, (times)	Number of stances, (times)	Time spent in the central platform, (s)	Number of defecation	Number of urination
Intact rats n=6	9.0±2.1	2.5±1.3	34.5±12.1	1.3±0.5*	0.5±0.6
Control (without treatment) n=6	2.5±2.1	0	11.5±8.3	3.3±1.2	0.3±0.6
The comparison group (Piracetam) n=6	2.5±1.0	0.3±0.5	6.3±2.3	0	0.3±0.5
Harmine (Gar) (1),n=6	1.8±1.7	8.0±3.2	0.5±1.0	0.3±0.5	0.3±0.5
8-acetylharmine (2) n=6	4.3±1.5	0	3.5±1.9	0	0.3±0.5
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) n=6	1.0±0.2	0	5.0±3.1	0	0.3±0.5
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) n=6	0.8±0.5	0	3.0±1.6	0	0
Delkozine (5) n=6	3.0±2.2	0	5.3±2.2	0.8±0.5	0.5±0.6
Lappaconitine (6) n=6	2.8±1.5	0	18.5±9.7	0.3±0.5	0.3±0.5
Cytisine (7) n=6	2.5±1.7	0	1.3±0.10	0.3±0.5	0.3±0.5
Echinopsine (8) n=6	3.3±1.8	0	0.8±0.10	0	0.3±0.5

*p <0.05 compared with values of the control group animals, n is the number of animals in the group.

Table 4 – The effect of the studied compounds on the behavior of rats in the test "Open field"

Group	Spectrum of indicative research activity		Spectrum of anxiety		
	Number of horizontal movements	Vertical movement activity	Grooming	Number of defecation	Number of urination
Intact rats n=6	21.0±2.7	6.8±1.3	1.5±1.3	1.3±2.5	0.5±0.6
Control (without treatment) n=6	5.3±5.3	4.8±1.0	2.0±0.8	2.8±2.1	1.0±0.8
The comparison group (Piracetam) n=6	13.0±4.5*	6.8±2.9	1.0±0.8	2.5±1.9	0.5±0.6
Harmine (Gar) (1),n=6	8,0±3,2	5,8±2,1	3,8±1,7	2,7±1,4	0,2±0,5
8-acetylharminine (2) n=6	17.0±5.9	4.5±2.5	1.0±0.8	0.3±0.5	0.3±0.5
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) n=6	13.8±6.3	9.0±2.9	1.5±1.7	2.2±0.9	0.0±0.0
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) n=6	9.5±2.6*	5.3±1.0	0.75±0.9	3.0±1.4	0.3±0.5
Delkozine (5) n=6	8.9±4.9*	4.8±2.8	4.0±0.8*	4.0±3.2	0.5±0.6
Lappaconitine (6) n=6	13.3±3.5*	4.0±2.2	2.3±1.3	0.3±0.5	0.3±0.5
Cytisine (7) n=6	24.8±7.0	7.8±2.9	1.25±0.50	0.0±0.0*	0.3±0.5
Echinopsine (8) n=6	31.8±2.5	11.0±2.6	2.5±1.3	0.0±0.0*	0.3±0.5

*p <0.05 compared with values of the control group animals, n is the number of animals in the group.

Findings. As a result of the experiments, it was found that the alkaloids of the indole series 8-acetylharminine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), diterpenic alkaloid lappaconitine (6), and also cytisine (7) at a dose of 5 mg/kg show a neurotropic effect, increasing the level of the orienting reaction, normalize the emotional state, lowering the level of anxiety and fear in animals.

According to the results of molecular docking, it was established that the studied molecules of the alkaloid compounds of the indole series interact with the dopamine receptor D2. According to the results of docking, the maximum indicators of binding are: (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) (G-score = -10.2), 8-acetylharminine (2) (G-score = -7.5), which indicates a good ability of these compounds to bind to the dopamine receptor D2.

Thus, it was established that alkaloid compounds 8-acetylharminine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) have a comparatively strong bond with the dopamine receptor D2. The prospects for the development of new neurotropic drugs based on alkaloid compounds have been identified.

Source of research funding. The work was performed under the grant project №AP05134907 "Molecular docking and bio-screening of new natural compounds" with the financial support of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan.

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АЛКАЛОИДТАР МЕН ОЛАРДЫҢ ТУЫНДЫЛАРЫНЫҢ НЕЙРОТРОПТЫҚ ӘСЕРІН ЗЕРТТЕУ

Аннотация. Мақалада алкалоидтар мен олардың туындыларының нейротроптық әсерін зерттеу нәтижелері ұсынылады. 5 мг/кг дозадағы 8-ацетилгармин, ((E)-1-(7-Метокси-1-метил-9H-пиридо[3,4-b]индол-8-ил)-3-(2,4-диметоксифенил) проп-2-ен-1-он, лапаконитин және цитизин қосылыстары «Ашық алаң» тестінде жануарлардың бағдарлау реакциясының деңгейін көтеретін нейротроптық әсерге ие екендігі және «Көтеріңкі крест тәрізді лабиринт» тестінде олардың мазасыздық деңгейі мен қорқыныш сезімін төмендетіп, эмоциялық жағдайын ретке келтіретіні анықталды.

Түйін сөздер: алкалоидтар, нейротроптық әсер, эмоциялық күйзеліс, алкалоидтардың туындылары.

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ИЗУЧЕНИЕ НЕЙРОТРОПНОГО ДЕЙСТВИЯ АЛКАЛОИДОВ И ИХ ПРОИЗВОДНЫХ

Аннотация. В статье представлены результаты исследования нейротропного действия алкалоидов и их производных. Установлено, что изучаемые соединения 8-ацетилгармин, ((E)-1-(7-Метокси-1-метил-9H-пиридо[3,4-b]индол-8-ил)-3-(2,4-диметоксифенил)проп-2-ен-1-он, лапаконитин и цитизин в дозе 5 мг/кг обладают нейротропным действием, повышая уровень ориентировочной реакции животных в тесте «Открытое поле», также нормализуют эмоциональное состояние, понижая уровень тревожности и чувства страха у животных в тесте «Приподнятый крестообразный лабиринт».

Ключевые слова: алкалоиды, нейротропное действие, эмоциональный стресс, производные алкалоидов.

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NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 3, Number 333 (2019), 64 – 72

<https://doi.org/10.32014/2019.2519-1629.32>

UDC 592/599

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**SOME MORPHOLOGICAL PECULIARITIES OF
A GREAT GERBIL (*Rhombomys opimus* Licht 1823)
FROM THE MIDDLE ASIA DESERT PLAGUE FOCUS**

Abstract. (*Rhombomys opimus* Lichtenstein, 1823) - the main host of the plague microbe (*Yersinia pestis*) in the Central Asian desert focus of the plague. Despite the large number of scientific papers on various aspects of the biology of this species, its population differences remain poorly studied. The material for the study was the collection of skulls of the great gerbil of the Kazakh Scientific Center for Quarantine and Zoonotic Infections named after M. Aykimbaev. More than 600 great gerbil skulls were investigated in total. The purpose of the study was to clarify the differences in the main signs of the structure of the head bones of a great gerbil from different parts of its range. The article provides information on the main craniometric properties of gerbils from different parts of the range.

Key words: population, area, craniometry, host.

Introduction. The great gerbil (*Rhombomys opimus* Lichtenstein, 1823) belongs to the order *Rodentia*, the family *Cricetidae*, the subfamily *Gerbillinae*. Thirteen subspecies of this rodent are described in the literature, while according to some data it is believed that only a typical great gerbil is found in Kazakhstan - *Rhombomys opimus opimus* (Figure 1), according to other sources there are three [1, 2]. A significant part of the range of this species runs through the territory of Kazakhstan [3]. Family lifestyle and complex underground burrows, determine the important role of this species in desert ecosystems, as well as close ecological ties with other members of biocenoses [4]. However, without in-depth study of hosts, as well as their population differences, an understanding of the general patterns occurring in natural plague foci seems impossible. Despite the fact that a large number of works were devoted to various aspects of the biology of a great gerbil, there are still many issues to be studied. One of which is the population variability of gerbils. This issue is of great academic and practical importance, since it is believed that different populations may have different susceptibility to the plague microbe [5, 6].

The study of the characteristics of the structure of the bones of the skull, can provide a key to the question of how great the differences between representatives of the same species in different parts of the range [7]. Craniometry is one of the main methods in systematics and population ecology for establishing the taxonomic identity of a species, subspecies, or population. Despite the emergence of new molecular genetic methods, morphological methods, in particular, craniometry, have been successfully used to this day to determine the systematic affiliation of various species [8-12]. The study of differences in the linear dimensions of the bodies of animals, as well as craniometric indicators, makes it possible to identify the discontinuity between populations, as well as regional groups [13-17].

In this article, the authors provide information about the collection material of the skulls of the great gerbil of the zoological museum of the Kazakh Scientific center for quarantine and zoonotic diseases named after M. Aykimbaev.

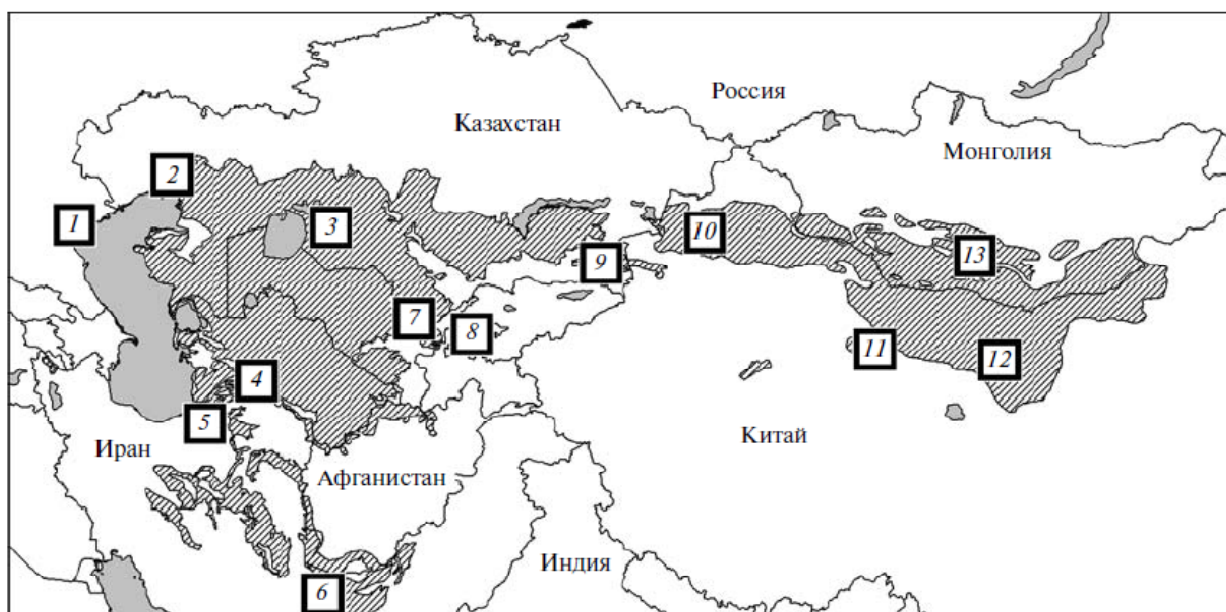


Figure 1 – The location description scheme of 13 great gerbil (*Rhombomys opimus*) subspecies within the range:
 1 - *R. o. obolenskii*, 2 - *R. o. pallidus*, 3 - *R. o. opimus*, 4 - *R. o. minor*, 5 - *R. o. sodalis*, 6 - *R. o. sargadensis*,
 7 - *R. o. dalversinicus*, 8 - *R. o. fumicolor*, 9 - *R. o. major*, 10 - *R. o. giganteus*, 11 - *R. o. pezvovi*,
 12 - *R. o. alaschanicus*, 13 - *R. o. nigrescens* [1]

Materials and methods. The authors investigated skulls of great gerbil from the museum collection of the Kazakh Scientific center for quarantine and zoonotic diseases named after M. Aykimbaev.

The studied gerbil skulls were mined from the following places: Taukum desert, Zhalanashkol, Northern Karakum (Turkmenistan), Moynkum desert, Fergana depression, Panfilov district (now Almaty region), Mangyshlak, Kalmykovo, Bakanas ancient delta plain, Northern Pre-Aral. It should be noted that the collection materials were the 60-70-ies of the last century, moreover, the exact coordinates of the location of the gerbil were not indicated. In this regard, we have used only available data.

623 skulls were measured, according to 5 characteristics, and only mature individuals were examined. Such parameters were measured as the total length of the skull, the condylobasal length of the skull, the length of the cerebral part of the skull, the maximum width of the skull, the maximum height of the skull. Males and females were measured and recorded separately, due to the presence of sexual dimorphism in great gerbils. Skulls were measured with caliper (SHC-1 GOST 166-89). All parameters of the measured skulls were entered into the MC Excel electronic database.

Below are tables with craniometric data for representatives of various populations of great gerbil (tables 1 and 2).

Results. In general, the most significant indicators in the *total and condylobasal length of the skull* are found in gerbils from Taukum, Zhalanashkol, Bakanas ancient delta plain (BAP). Then were gerbils from the Panfilov region, the Northern Karakum (Turkmenistan) and the Northern Pre-Aral. Gerbils from the Fergana depression, Kalmykovo region of West Kazakhstan oblast, are even less long, but they are larger than the gerbil from the Moynkum desert and Mangyshlak (figure 2).

The maximum width of the skull was greatest by males from the Northern Karakum, Zhalanashkol, Taukum, Panfilov region, and Bakanas ancient delta plain. Then, followed gerbils from Kalmykovo and Northern Pre-Aral, Fergana depression and Mangyshlak. Gerbils from the Moynkum desert had the smallest width of the cerebral part.

The length of the cerebral part. Males from Bakanas ancient delta plain, Taukum desert, Zhalanashkol, Northern Karakum, Panfilov district, Northern Pre-Aral, Fergana depression and Kalmykovo had the

Table 1 – Craniometric parameters (mm) of males of great gerbil from different parts of the range, above limits, below average

Parameter	Taukum desert	Zhalanashkol	Northern Karakum (Turkmenistan)	Moyynkum desert	Fergana depression	Panfilov district	Mangyshlak	Kalmykovo (West Kazakhstan region)	Bakanas ancient plain	Northern Pre-Aral
Total length of the skull	42.8-47.6 44.8	42.1-46.5 44.7	41.5-46.5 43.9	35.9-44.2 41.4	41.9-45.1 43.3	43-46.3 44.3	32.3-42.1 38.3	40.9-45.5 43	42.1-47.5 44.5	42.8-44.5 43.6
Condylobasal length of the skull	40-44.8 42.3	39.4-44.2 42.3	39-43.8 41.5	32.2-42.1 39	38.8-42.1 40.6	40.8-44.1 41.8	29.9-40 36.1	38.9-43.6 40.8	40.6-44.2 42.2	40.5-42.1 41.3
Length of the cerebral part	17.2-20.8 18.9	17.1-20.1 18.8	17.2-20 18.6	14.5-18.9 17.5	17.2-19.2 18.3	17.5-19.6 18.5	13.3-18 16.1	17-19.5 18.3	17.9-20.8 19.2	17.8-19.2 18.4
Maximum skull width	22.5-26.8 24.4	22.5-26.2 24.8	23.9-25.7 24.8	20.8-24.8 23	21.6-24.2 23.1	22.2-25.6 24.2	17.5-23.5 21.3	22.1-25.2 23.7	22.6-26.3 24.1	22.8-24.2 23.7
Maximum skull height	14.5-16.7 15.5	14.6-16.2 15.4	14.2-15.5 15.1	13.8-15.6 14.7	14.6-15.6 15.2	14.1-16.2 15.4	12.9-15.6 14.3	14.2-16 15	14.8-16.2 15.4	14.9-15.8 15.3

Table 2 – Craniometric parameters (mm) of great gerbil females from different parts of the range, above the limits, below the average

Parameter	Taukum desert	Zhalanashkol	Northern Karakum (Turkmenistan)	Moyynkum desert	Fergana depression	Panfilov district	Mangyshlak	Kalmykovo (West Kazakhstan region)	Bakanas ancient plain	Northern Pre-Aral
Total length of the skull	40.1-43.5 42.2	39.9-46.9 43	40-45.4 42.7	36.9-43 39.6	40.8-41.5 41.2	38.5-42.9 41.4	31.5-41.5 37.9	40-44.5 41.9	38-43.5 40.9	40.1-42.5 41.6
Condylobasal length of the skull	37.9-41.2 39.9	38.2-43.9 40.4	38.2-42.8 40.6	34.1-40.9 37.3	38.7-39.5 39.1	36.2-41.8 39	29.5-38.9 35.5	37.5-41.2 39.7	35.9-42.1 38.8	37.1-39.9 38.8
Length of the cerebral part	17-18.8 17.8	16.5-19.1 17.6	17-18.9 17.9	15.5-18.4 16.6	16.8-17.8 17.4	16.2-18.3 17.1	12.8-17 15.4	16.7-18.6 17.7	16-18.8 17.5	16.1-17.9 17.4
Maximum Skull width	22.5-24.4 23.4	22.2-26.5 24	23-25.4 24.1	20.6-24.1 22.2	22.1-23 22.6	21.1-25.2 23.2	17.8-23.1 21.2	14.5-25.1 22.7	21.2-25.1 22.9	22.1-23.8 23.1
Maximum skull height	14.1-15.5 14.9	14.1-16.8 15.1	14-15.5 14.7	13.6-15.2 14.3	14.6-15.2 14.9	14-15.5 14.7	12.3-15.5 13.9	12.2-15.7 14.6	13.8-15.8 14.6	14.5-15.1 14.8

most long-cerebral part, while gerbils from Moyynkum shorter, but longer than gerbils from Mangyshlak. A similar trend was found in relation to the maximum height of the skull (figure 3).

Females from the Zhalanashkol, Northern Karakum, Taukum, Kalmykovo, Northern Pre-Aral regions possessed the greatest total length of the skull. Then followed samples from the Panfilov district, the Fergana basin and the Bakanas ancient plain. While the gerbils from Moyynkum and Mangyshlak were significantly smaller.

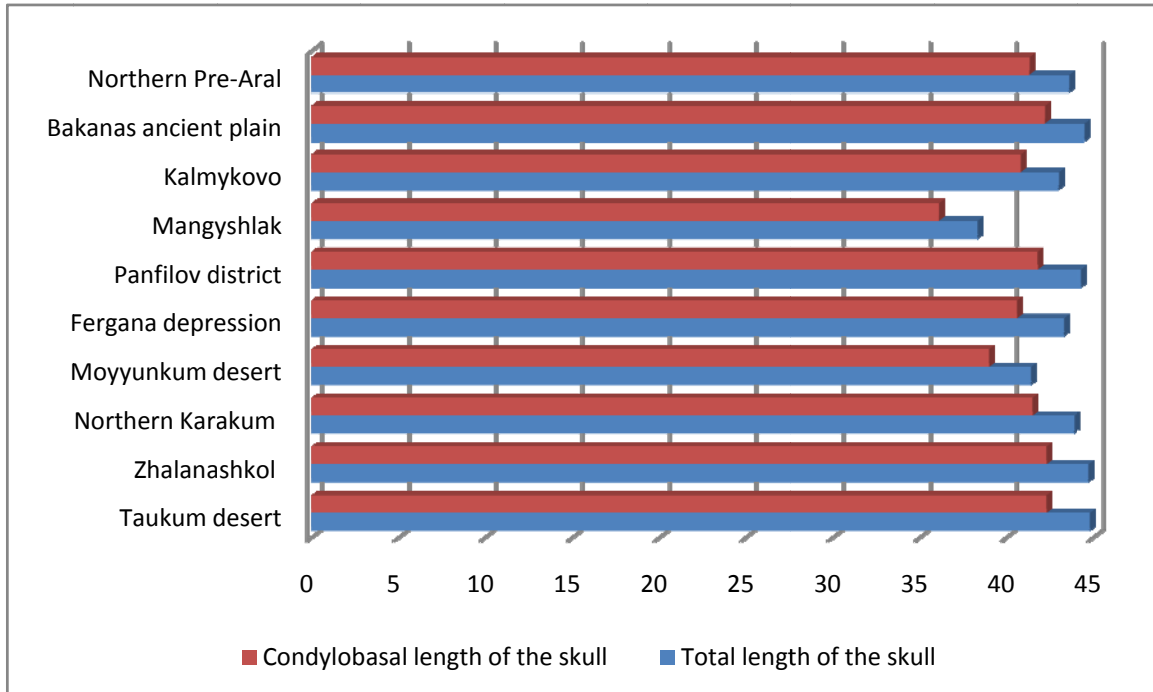


Figure 2 – Total and condylobasal length of the skull in males of great gerbils from different habitats

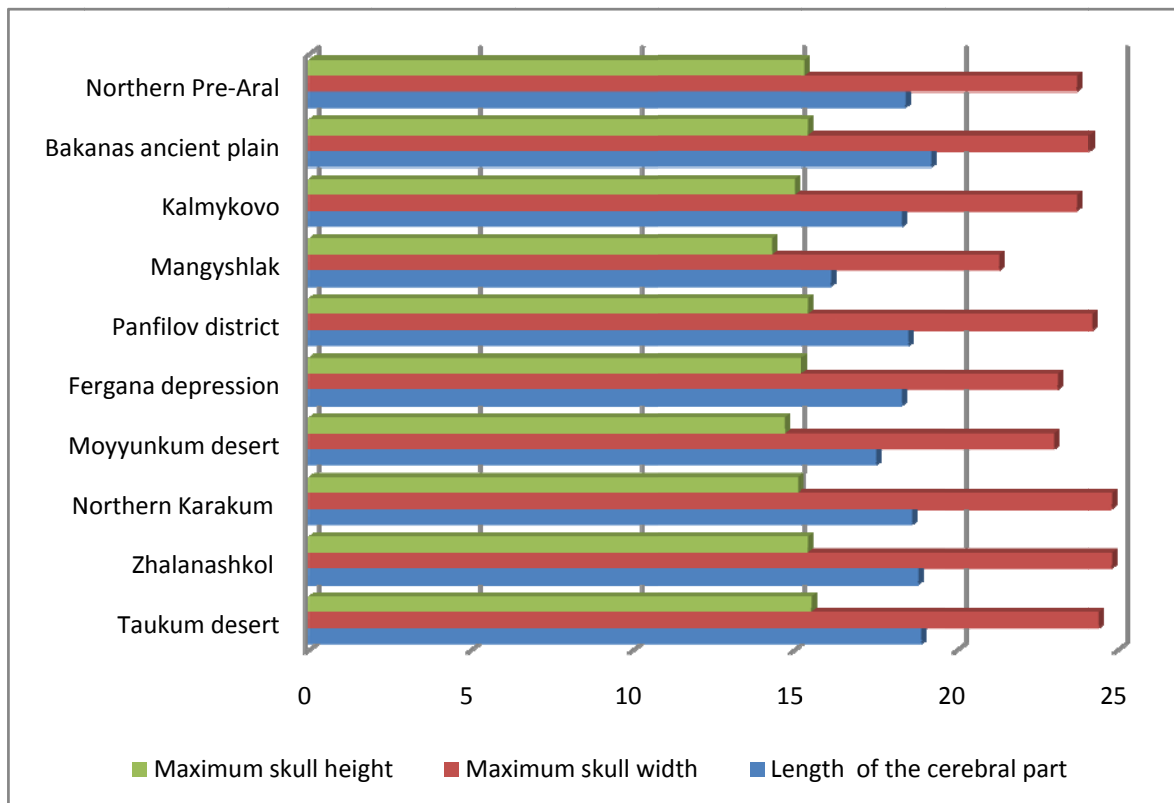


Figure 3 – The length of the cerebral part, the maximum width and maximum height of the skull in males of great gerbils from different habitats

As for the **condylobasal length**, the Northern Karakum and Zhalanashkol prevailed here. While females from the Taukum desert and Kalmykovo were slightly inferior to the above-mentioned places, while the Panfilov district, the North Pre-Aral region, the Bakanas ancient plain, and the Fergana depression were similar. Skulls from Moyynkum and Mangyshlak were characterized by the smallest length (figure 4).

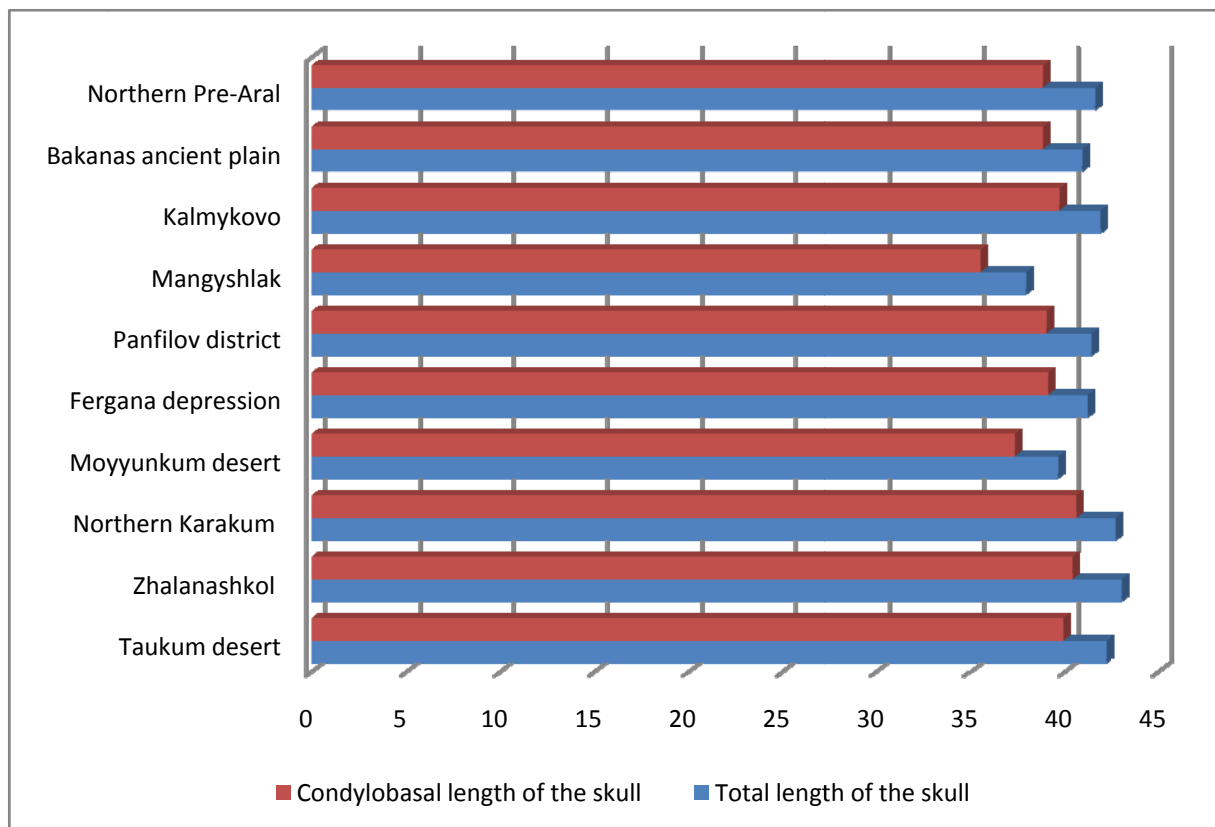


Figure 4 – General and condylobasal length of the skull in females of great gerbils from different habitats.

The **maximum width of the skull** was greatest for skulls from the Northern Karakum and Zhalanashkol, then from Taukum, Panfilov region and Northern Pre-Aral region. The Bakanas ancient plain, Kalmykovo and Fergana depression followed after, and the skulls from Moyynkum and especially Mangyshlak had the smallest width.

Significant differences in the **maximum height of the skull** were not found, we can only select a few large parameter in gerbils from Zhalanashkol, Fergana depression, Taukum, Northern Pre-Aral, Panfilov, Kalmykovo, Bakanas ancient plain and Northern Karakum. Skulls from Moynkum and Mangyshlak also had the lowest height.

The **length of the cerebral part** was the largest by gerbils from the Northern Karakum, Taukum desert, Kalmykovo, Zhalanashkol, Bakanas ancient plain, Northern Pre-Aral and the Fergana depression. Skulls from Panfilov region had a slightly smaller length, the most modest indicators were those of the Moyynkum desert and Mangyshlak (figure 5).

Findings. Considering the results of the study, it can be said that there are differences in some parameters of the skull between gerbils from different populations of its range. The distinction between the gerbils from Moynkum and Mangyshlak in particular is striking. Perhaps this is due to habitat conditions and food resources. Despite the fact that all studied gerbils from its Kazakhstan part of the range live at the same latitude and belong to the so-called subzones of the northern deserts [18], it is still likely that the Bergman's rule comes into force here [19]. What is indirectly confirmed by other researchers [20-22].

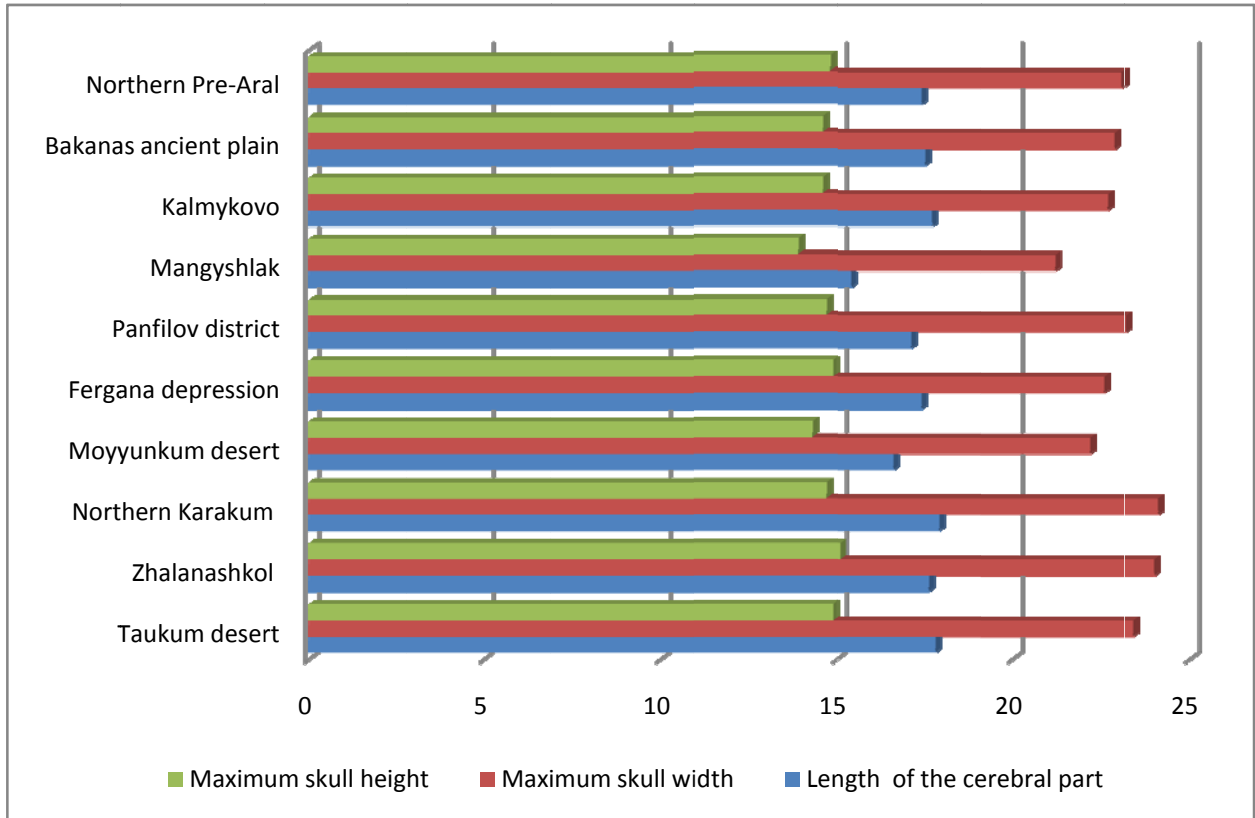


Figure 5 – The length of the cerebral part, the maximum width and maximum height of the skull in females of great gerbils from different habitats

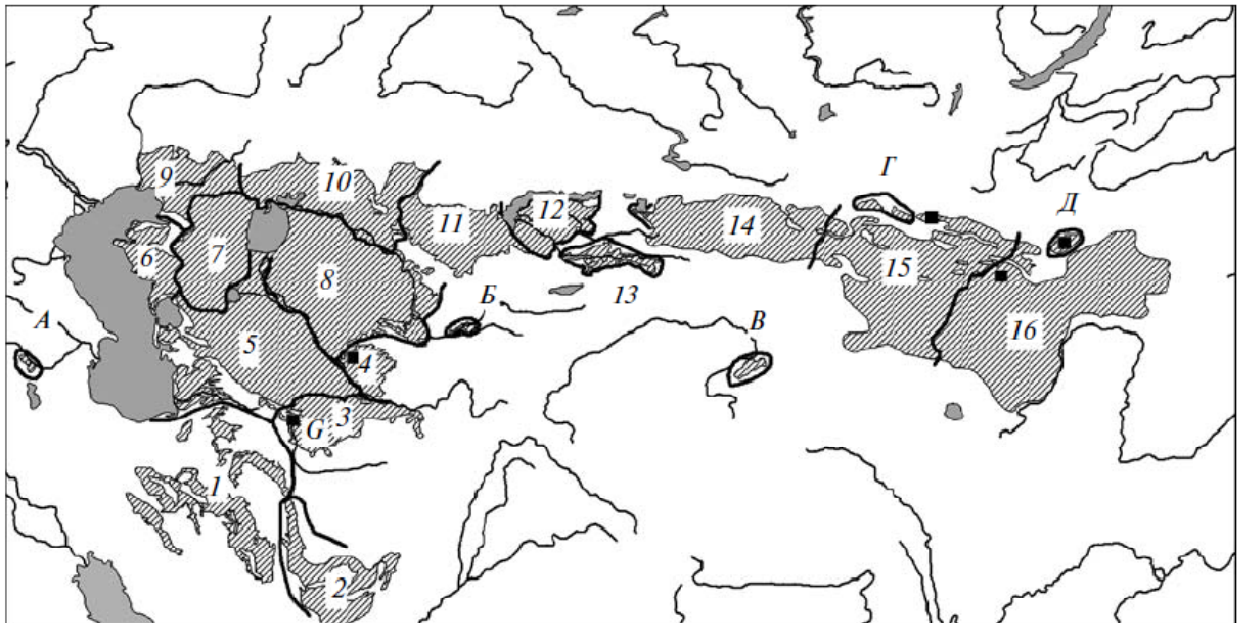


Figure 6 – The location description scheme of regional complexes and autonomous groups of populations within the range of a great gerbil (*Rhombomys opimus*). Regional complexes:
 1 - Central Iranian, 2 - Sistan-Balochistan, 3 - Southeast Karakum, 4 - Karshi, 5 - Turkmen, 6 - Mangyshlak, 7 - Ustyurt, 8 - Kyzylkum, 9 - Northeast Pre-Caspian, 10 – Pre-Aral, 11 - Betpakdala-Muyunkum, 12 – Pre-Balkhash, 13 - Ilian, 14 - Dzhungarian, 15 - Gobi-Beyshan, 16 – Gobi-Alashan,
 Autonomous population groups: A - Prearaksinsk, B - Ferganian, B - South Tarim, G - Oroknur, D - Bayandov [18]

The total and condylobasal length of the skull in both females and males had differences between populations. Parameters such as the maximum width of the skull and the length of its cerebral part varied greatly between representatives of different habitats, in both sexes. What is probably associated with different body weight in representatives of different populations. At the same time, the maximum height of the skull varied slightly, which is probably not related to the body weight of the animals.

Perhaps the explanation for the fact that the skulls of the gerbils from Mangyshlak differed most strongly from others lies in the fact that they belong to another regional complex [23], namely, the Ustyurt (figure 6). In this case, how to explain the similarity of representatives of other regional complexes among themselves? This question remains open. It is obvious that without complex studies involving morphological and molecular genetic methods, it is not possible to find an explanation for this phenomenon.

Source of research funding. *The work was prepared within the framework of the grant financing project: "Population ecological options of a host, vector, and causative agent of plague in the Central Asian natural desert plague focus". (Code of the program AP05133153).*

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ОРТААЗИЯЛЫҚ ШӨЛДІ ОБА ОШАҒЫНДАҒЫ ҮЛКЕН ҚҰМТЫШҚАНЫНЫҢ (*Rhombomys opimus* Licht 1823) КЕЙБІР МОРФОЛОГИЯЛЫҚ ЕРЕКШЕЛІКТЕРІ

Аннотация (*Rhombomys opimus* Lichtenstein, 1823) – Ортаазиялық шөлді оба ошағындағы негізгі оба микробын (*Yersinia pestis*) тасмалдаушысы. Осы түрдің биологиялық аспектілеріне арналған ғылыми еңбектердің көп болғанына қарамастан, оларың популяциялық айырмашылықтары аз зерттелген. Зерттеу материалдары М. Айқымбаев атындағы Қазақ карантиндік және зооноздық инфекциялар ғылыми орталығының коллекциялық материалынан алынды. Барлығы 600-ден астам үлкен құмтышқаны зерттелді. Зерттеудің мақсаты әртүрлі аймақтық бөлімдерде таралған үлкен құмтышқандарының бас сүйектері құрылысының негізгі белгілерін анықтау болды. Мақалада әртүрлі аймақтық таралу бөлімдеріндегі үлкен құмтышқандарының негізгі краниометриялық ерекшеліктеріне анықтама берілді.

Түйін сөздер: популяция, аймақ, краниометрия, тасымалдаушы.

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НЕКОТОРЫЕ МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ БОЛЬШОЙ ПЕСЧАНКИ (*Rhombomys opimus* Licht 1823) ИЗ СРЕДНЕАЗИАТСКОГО ПУСТЫННОГО ОЧАГА ЧУМЫ

Аннотация. (*Rhombomys opimus* Lichtenstein, 1823) – основной носитель чумного микроба (*Yersinia pestis*) в Среднеазиатском пустынном очаге чумы. Несмотря на большое количество исследований, посвященных различным аспектам биологии данного вида, его дифференциация на отдельные природные популяции, ввиду недостаточной изученности, остается не до конца ясной. В последние годы появились единичные работы по изучению генома различных внутривидовых группировок большой песчанки, однако, методы, основанные на сравнительном исследовании краниометрических показателей у представителей данного вида из различных изолированных популяций, остаются актуальными. Материалом для исследования послужила коллекция черепов большой песчанки Казахского научного центра карантинных и зоонозных

инфекций им. М. Айкимбаева. Всего было исследовано более шестисот черепов большой песчанки из различных регионов Среднеазиатского пустынного очага чумы. Целью исследования было выяснение различий в основных признаках строения головных костей большой песчанки из различных частей ее ареала. В статье дается информация об основных краниометрических показателях песчанок из различных частей ареала.

Ключевые слова: популяция, ареал, краниометрия, носитель.

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МАЗМҰНЫ

<i>Туруспекова С.Т., Цой Р.Т.</i> Табиғи радиациялық фонның адам денсаулығына әсері.....	5
<i>Рахимов Қ.Д.</i> Табиғи препараттардың біріншілікті және дәріге тұрақты қатерлі ісіктерге антибластомдық әсерін зерттеу.....	11
<i>Жумашов С.Н., Туқтаев Қ.Р., Жумашов Б.С.</i> Сары фосформен жедел улантырғанда тимустың морфологиялық өзгерістері.....	16
<i>Айсина Д.Е., Ниязова Р.Е., Атамбаева Ш.А., Имянитов Е.Н., Иващенко А.Т.</i> Сүт безі қатерлі ісігінің mRNA кандидатты гендерінің 3'UTR-де miRNA кластерлерінің байланысу сайттары.....	20
<i>Сапаров Қ.Ә., Әкен С.Е., Әйтенова А.М., Олжабаева Ж.Б., Тұрлыбекова Д.Д.</i> Таулы және дала аймағында тіршілік ететін омыртқалылардың өкпелерінің ультрақұрылымы.....	27
<i>Заядан Б.К., Акмуханова Н.Р., Маторин Д.Н., Садуақасова А.К., Тореханова М.М., Болатхан К., Балоуч Х., Бауенова М.О.</i> Микробалдырлар негізіндегі биологиялық белсенді қоспалардың құбылмалы бахтақтың өсуіне және микрофлорасына әсерін зерттеу.....	39
<i>Медеуова Ф.Ж.</i> Тыңайтқыштар дозасына байланысты күріш сорттары агроценозының және дән өнімінің қалыптасуы.....	48
<i>Романова М.А., Сейдахметова Р.Б., Тоқтархан Н.А., Жанымханова П.Ж., Әдекенов С.М.</i> Алкалоидтар мен олардың туындыларының нейротроптық әсерін зерттеу.....	56
<i>Есжанов А.Б., Саякова З.З., Садовская В.П., Нуртазин С.Т., Кабышева Н.П., Жунусова А.С., Абдирасилова А.А., Рысбекова А.К., Атиабар Б.Б.</i> Ортаазиялық шөлді оба ошағындағы үлкен құмтышқанының (<i>Rhombotus opimus</i> Licht 1823) кейбір морфологиялық ерекшеліктері.....	64

СОДЕРЖАНИЕ

<i>Туруспекова С.Т., Цой Р.Т.</i> Влияние природного радиационного фона на здоровье человека.....	5
<i>Рахимов К.Д.</i> Исследования антибластомных природных препаратов на исходных и лекарственно резистентных вариантах опухолей.....	11
<i>Жумашиов С.Н., Тухтаев К.Р., Жумашиов Б.С.</i> Морфологические изменения тимуса при острой интоксикации желтым фосфором.....	16
<i>Айсина Д.Е., Ниязова Р.Е., Атамбаева Ш.А., Имянитов Е.Н., Иващенко А.Т.</i> Кластеры сайтов связывания miRNA в 3'UTR mRNA кандидатных генов рака молочной железы.....	20
<i>Сапаров Қ.Ә., Әкен С.Е., Әйтенова А.М., Олжабаева Ж.Б., Тұрлыбекова Д.Д.</i> Ультраструктуры легких позвоночных, обитающих в горных и степных биотопах.....	27
<i>Заядан Б.К., Акмуханова Н.Р., Маторин Д.Н., Садуакасова А.К., Тореханова М.М., Болатхан К., Балоуч Х., Бауенова М.О.</i> Исследование влияния биологически активной добавки на основе микроводорослей на рост и микрофлору радужной форели.....	39
<i>Медеуова Г.Ж.</i> Формирование агроценозов сортов риса и урожайность зерна в зависимости от дозы удобрения.....	48
<i>Романова М.А., Сейдахметова Р.Б., Токтархан Н.А., Жанымханова П.Ж., Адекенов С.М.</i> Изучение нейротропного действия алкалоидов и их производных.....	56
<i>Есжанов А.Б., Саякова З.З., Садовская В.П., Нуртазин С.Т., Кабышева Н.П., Жунусова А.С., Абдирасилова А.А., Рысбекова А.К., Атиабар Б.Б.</i> Некоторые морфологические особенности большой песчанки (<i>Rhombotus opimus</i> Licht 1823) из среднеазиатского пустынного очага чумы.....	64

CONTENTS

<i>Turuspekova S.T., Tsoy R.T.</i> The impact of the Background Radiation on the health.....	5
<i>Rakhimov K.D.</i> Studies of antitumor natural products on the original and drug-resistant variants of tumors.....	11
<i>Zhumashov S.N., Tukhtaev K.R., Жумауов Б.С.</i> Morphological changes of the thymus during acute intoxication with yellow phosphorus.....	16
<i>Aisina D.E., Niyazova R.E., Atambayeva Sh.A., Imyanitov E.N., Ivashchenko A.T.</i> Clusters of miRNAs binding sites in 3'UTR mRNA of breast cancer candidate genes.....	20
<i>Saparov K., Aken S., Aitenova A., Olzhabayeva Zh., Turlybekova D.</i> Ultrastructure of the lungs of vertebrates in habiting mountain and steppe zones.....	27
<i>Zayadan B.K., Akmukhanova N.R., Matorin D.N., Sadvakasova A.K., Torekhanova M.M., Bolatkhan K., Balouch H., Bauyenova M.O.</i> Study of the influence of biologically active additive using microalgae on the growth and microflora of rainbow trout.....	39
<i>Medeuova G.Zh.</i> Rice varieties' agrocoenosis formation and grain cropping capacity depending on fertilizer quantity.....	48
<i>Romanova M.A., Seidakhmetova R.B., Toktarkhan N.A., Zhanymkhanova P.Zh., Adekenov S.M.</i> The study of neurotropic action of alkaloids and their derivatives.....	56
<i>Yeszhanov A.B., Sayakova Z.Z., Sadovskaya V.P., Nurtazin S.T., Kabysheva N.P., Zhunusova A.S., Abdirasilova A.A., Rysbekova A.K., Atshabar B.B.</i> Some morphological peculiarities of a great gerbil (<i>Rhombomys opimus</i> Licht 1823) from the middle asia desert plague focus.....	64

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www.nauka-nanrk.kz

ISSN 2518-1629 (Online), ISSN 2224-5308 (Print)

<http://biological-medical.kz/index.php/en/>

Редактор *М. С. Ахметова, Т. М. Апендиев, Д. С. Аленов*
Верстка на компьютере *Д. Н. Калкабековой*

Подписано в печать 07.06.2019.
Формат 60x881/8. Бумага офсетная. Печать – ризограф.
4,75 п.л. Тираж 300. Заказ 3.