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The materials of the journal can be used by professors, teachers, independent researchers, doctoral students, undergraduates, students, teachers of lyceums and schools, scientists and everyone who is interested in science.

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THE ARAL SEA DEGRADATION AND BIOLOGY DESCRIPTION OF ACTIONS ON THEIR ELIMINATION

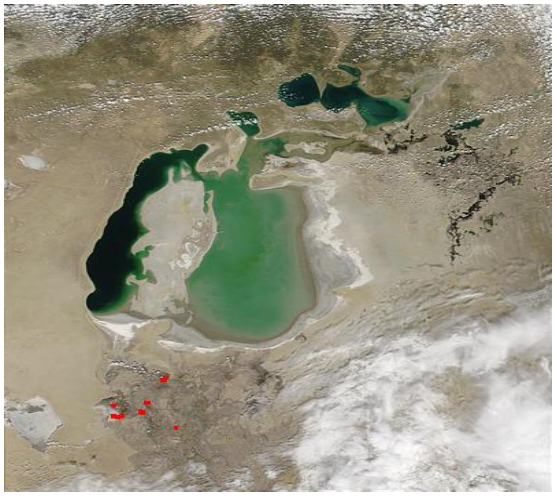
Z.Sh. Muxidova[1], B.A. Mukhamedgaliev[2]
Associate professor of a branch Astraxan STU in Tashkent regions[1]
Doctor of a chemical science, professor of a Tashkent university building and sivil engineering[2]
https://doi.org/10.5281/zenodo.18950314

Abstract*. This article represents the updated version of the texted version on the state of environment of the Republic of Uzbekistan, prepared in 2024. Its purpose is providing of the broad sections of the public and decision-makers with easy for understanding, modern and reliable environmental information about region.*

Keywords*: ecology, Environmental Protection, Pollution, water resources, the population, Aral Sea, desert "Aralkum", The regional flora.*

Introduction

The basic attention in the report is given to the description of the some priority national environmental problems, identified at the development of the National Environmental Action Plan for Sustainable Development of the Republic of Uzbekistan: Deficit of water resources; Degradation of pasture and arable lands; air pollution of urban territories; Environmental pollution in oil fields area; Environmental pollution with industrial and municipal solid waste; Shortage of forests and especially protected territories; Pollution of the water bodies with wastewater. Most of the sands and soils in the Pre-Aral area are light and easily transported by wind [1].

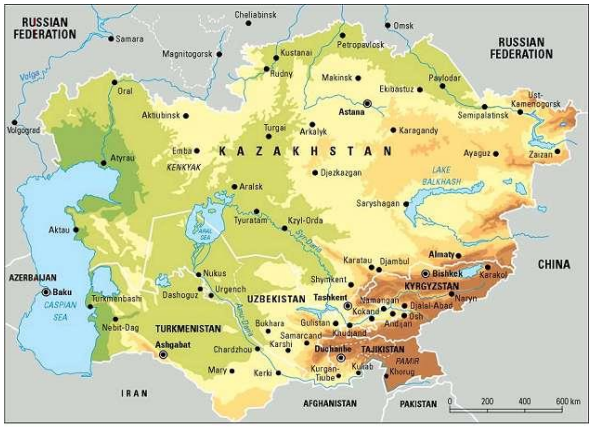


From picture is seen that Aral SEA divided on two parts, on Big Aral and Small Aral

The brief characteristic of the causes of occurrence of problems and description of actions on their elimination is given in this report. The article is based on the official statistical information, materials of the Ministry of Natural Resources and Environmental Protection of the Republic of Uzbekistan [2]. Central Asia (territory is 1.7 mln. sq.km) is situated in the mid-part of Eurasia at the crossroad of ancient caravan routes between Europe and Asia, Middle and Far East and mainly coincides with the geographical borders of the Aral Sea, completely including territories of Tajikistan, Uzbekistan, a large part of Turkmenistan, Kyrgyzstan and the south of Kazakhstan.

As one of the most ancient centers of world civilization, this region has vast territories of arid and semiarid zones with only 5% of densely populated oases. The basin is inner water body of the discharge less Aral Sea which was the fourth largest inland lake in the world before 1960. The dependence of the Central Asian civilization's development of water resources dates back to ancient times. Water and irrigation have always been the basis of life, the development of every living thing, and the main component of nature in the region.

By the beginning of the 20th century, 7-8 million people lived in the region. Irrigated lands made up about 3.5 million hectares and had irrigation networks of different levels. It was the foundation of society's economic base. At present the population of the region has increased 7 times, exceeding more 50 million people (57.4 million people in 2010). Irrigated lands had doubled (7.5-7.9 milllion hectares).



The Map of a Central Asia. Red line is specified zones Priaraliya

Based on geographical and archeological research it was established that the Aral Sea has had periodical changes of its water area, i.e. expansions are followed by with drawals. This was brought about by climate change and changes in the state of the environment in the region. With the development of land use, anthropogenic factors affected the natural periods of sea fluctuations changing flows of the Syrdarya and Amudarya. This is especially explicit in the present. The beginning of irrigated agriculture in the region dates back to the 6th-7th centuries B.C. and coincides with flourishing the most ancient civilization where irrigation was a major decisive factor of historical and socio-economic development. Today the Aral and surrounding territories are world-known for ecological disasters attributed mainly to anthropogenous factors. The growth in water consumption connected to cultivation of new irrigated territories, where mainly cotton and rice are grown, together with the increase in the population working in agriculture, the flow of water to the sea from the two major river systems -the Amudarya and Syrdarya - completely stopped.

- Main reasons of the Aral crisis
- ☐ before 1960 amount entering on Aral Sea and vaporizing water from Aral Sea a were equal, t.e.57-60 kub.km water entered and as much as were vaporized
- ☐ In 1960 Soviet union planned to create monopoly a cotton growing in Central Asia and developed agricultural irrigation network
- ☐ The Result: Aral sea is sentenced to ruins Soviet union main by exporter of the cotton in the world.

☐ Area irrigations lands increased nearly in two with 5 mln.gektars in 1960 on 9,2 mln.gektars in 1980

☞ To this effect fence of water increased from Aral Sea with 40 cubes kilometers on 136 cubes kilometers

In spite of intensive glacier melting which should have led to increase of territory of the Aral Sea, during last 25 years disastrous reduction of the largest inland water body takes place. The Aral Sea is the largest inland body of salty reservoirs in the world. Situated in the centre of the Central Asian deserts at an altitude of 53 metres above the sea level, the Aral Sea functions as a gigantic evaporator. About 60 km^2 of water evaporates per year.

🗐 Concrete reasons of the crisis Aral Sea

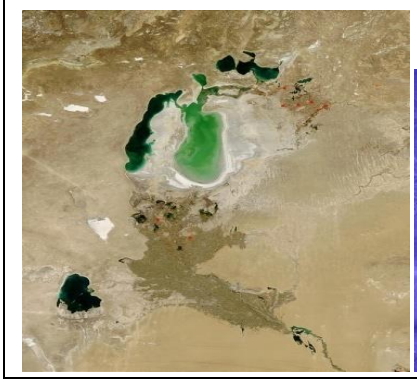
☐ Sowing technical type plants requiring much water (cotton-requires much water)

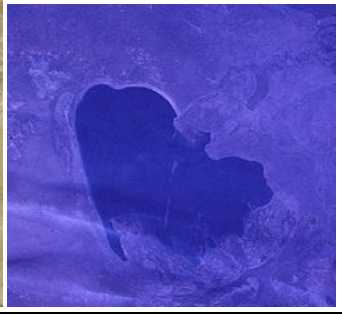
☐ Use the barrel lands, were in some cases used sands and desert zones for these integer

➢ inefficient irrigation systems Creation the most large in world canal of a Karakum

☐ Irrigacioning systems were not saved good-conditioned, more than 50% whole water going for irrigation were lost.

The sea contributed to hydrothermal regime improvement, influenced water regimes of arid plants, pastures productivity, and provided normal functioning of artesian wells etc. Ecological balance in the basin was formed in the first half of the 20th century and was stable up to the beginning of the 1960's, with a volume of 1,064 kmi, and a water territory of 66.4 thousand kmI. Because of irrevocable removal of river water on irrigated territories, ecological balance began to decline. Only half of the previous river runoff reached the Aral Sea. But even this quantity of water was not sufficient to support sea level at 53 m. However, as a result of a tendency of economy development in agrarian areas, leading to growth of irrigated territories and volumes of irrevocable water consumption during years of water shortages, water flow into deltas of the Amudarya and Syrdarya rivers was reduced sharply. In 1982 and 1983 this made up only 2.28 and 3.25 km^3, respectively. Since 1961 the sea level has declined with increasing speed from 20 to 80-90 cm per year.





☐

☐

The lake "Sarikamish" was formed to account of the ascent of underground water and collectoring water of Aral Sea

During the last 50 years, from 1960 to 2010, the sea received less than 2,000 km^3 of river water, which led to the lowering of the sea level by 22 m, accompanied by a reduction of the volume of the water area by 87%.

As a result of the complete stop of the Amudarya and Syrdarya runoff and expansion of irrigated territories without any control of the Aral Sea and environmental needs, a serious complex of ecological, social and economic problems was formed in the Pre-Aral area. These problems by origin and level of consequences have an international character. The sea has lost its fishery and

transport importance. It was divided into two parts, the Bolshoi and the Maly (Northern) Aral, and moved 140-190 km away from the original shore. From exposed salty bed (35 thousand kmI) up to 100 million tons of salty dust flew out annually. Suspended solids in the form of aerosols with agricultural pesticides, fertilizers and other harmful components of industrial and municipal wastes prevail in the composition of the winds.

- Overweening use pesticide
- The Barrel floor forced to enter the enormous amount a pesticide (the pesticides, herbicide). In 1987 in Uzbekistan at the average on 1 gectar land was incorporated more than 350 kg pesticide.
- Pesticides: the largest factor on whole world, in 35 times greater than on average factor in USSR

Due to the reduction in the sea dimensions, and the increase in evaporation and drainage-collecting water, water salinity considerably increased from 9.94 g/litre in 1965, to about 22 g/litre in 2010.

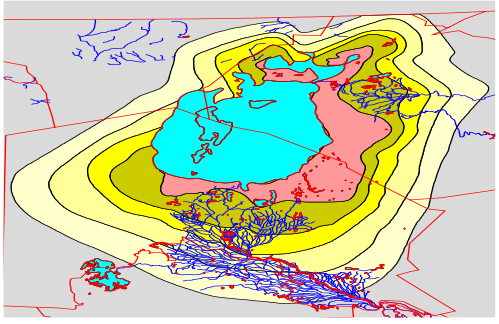
Sharp continental climate is a feature of the Pre-Aral area climate.

During the last 10-15 years the drying off of the Aral Sea, brought about noticeable changes in climate conditions. In the past the Aral was considered a regulator mitigating cold winds from Siberia and reducing the summer heat. Climate changes have led to a dryer and shorter summer in the region, and longer and colder winters. The vegetative season has been reduced to 170 days. The pasture productivity has decreased by a half, and meadow vegetation destruction has decreased meadow productivity 10 times. On the shores of the Aral Sea precipitation was reduced several times. Average precipitation magnitude is 150-200 mm with considerable seasonal ununiformity.

High evaporation (up to 1700 mm per year) is marked while air moisture is reduced by 10%. Air temperature during winters has fallen, and summer temperatures have increased by 4-6 degrees C, including observations of 54 degrees C. Frequent occurrence of long dust storms and ground winds is characteristic feature of the Pre-Aral area climate. Strong winds often blow in the region. They are the most intensive on the western coast - with perhaps more than 50 days of storms per year. Maximum wind velocity reaches 23-28 m/s. These climatic conditions defined that agriculture without irrigation is impossible. The result is intensive accumulation of salt in the soil leading to water use for watering plants and washing off lands.

Most of the sands and soils in the Pre-Aral area are light and easily transported by wind.

The drying off of the Aral Sea resulted in two different kinds of desertification. The newly dried sea bed, and the artificial water logging of irrigated lands. As a result, a new desert "Aralkum" appeared in the centre of the great deserts. It is solid salt-marsh consisting of finely-dispersed sea depositions and remnants of mineral deposits, washed away from irrigated fields.



Centre of broadcast sand and salts

Place of to settle sand and salts > 80 т/км^2

A new qualitative phase of desertification affecting the Pre-Aral ecosystem degradation, regional and global climate, mountainous flow-forming systems and water-salty regime of agricultural zone takes place.



Picture on the left: ground covering salt to broadcast with wind. Drawing on the right: bottom, coated by salts

The sea bed, formerly referred to as a so-called "fresh water maker" of vast water collecting basin at the expense of rich sea hydrobiocenose activity, is an artificial anthropogenous volcano, throwing tremendous masses of salt and finely-dispersed dust into the atmosphere. Pollution is increased because the Aral Sea is located along a powerful air stream running from west to east. It contributes to aerosol transference into upper layers and fast spread in the atmosphere of the Earth. That is why traces of pesticides from the Aral region were found in the blood of penguins in the Antarctic, and typical Aral dust has been found on Greenland's glaciers, in Norway's forests, and Byelorussia's fields, all situated thousands of kilometers away from Central Asia. One of the dangerous consequences of the drying off of the Aral Sea, is the increasing degradation of mountainous glaciers of the Himalaias, Pamir, Tiyan-Shan, and Altay, feeding the Syrdarya and Amudarya.



From picture made from artificial satellite is seen greater fields covered by salt (specified by red ellipse).Call attention red arrow is specified new forming field to salts beside seashore The

increase of dust on glacier surfaces and mineralization of precipitation on them lead to intensive melting of glaciers. At present, 1081 glaciers have disappeared in the Pamir-Altay area , 71 glaciers in the Zaili Alatau area, and the volume of glaciers in Akshirak has been sharply reduced.



From picture made from artificial satellite possible to notice what speed away wind in distant distances mixture dust of sand and salts

On average, valley glaciers in the Tiyan-Shan area retreat 7.5-13.1 m per year and grow thicker at the same time. This is a dangerous process for a dry region, because in Central Asia, mountainous glaciers are the only ancient remaining storage of fresh water supply and are the main atmospheric moisture condensators of the region. If the cover of moraine depositions increases, they no longer will be moisture condensators and sharp reduction of the river flow will start. The Aral disaster has deteriorated the sphere of inhabitation of the region sharply, due to polluting of the atmosphere, the drinking water and the soil.

An evaluation of the field with drawl from the dry parts of the Aral Sea bed shows that this magnitude varies from several hundred thousand tons to 20-30 million tons per year. In the composition of dust cloud suspended solids in the form of aerosols with agricultural pesticides, fertilizers and other harmful components of industrial and municipal sewage prevail. Salt content makes up 0.5-1.5%. Sand-and-salt aerosol effects on oasis soils and pastures are predominantly negative. Replacing multilayer herbage by single-layer, reduces the quantity of useful feeding plants, and often plants that have no feeding value are cultivated. Two million hectares of fertile lands disappeared as a result of overwatering and as a result of fast rise of ground water they got polluted for the second time.



Influence upon health of the population

Today these lands are either water logged or salinized. Former arid soils of the Pre-Aral area with automorphic feed and moisture regime became meadow-swamp soils with hydromorphic

regime. To support this regime artificially it is necessary to raise standards by 2-3 times, in order not to activate the secondary salinization process. A vicious circle of agriculture was formed in this region, where heavy swamped lands are left. The land-improvement condition of irrigated soils in Central Asia is worsened by collective-drainage water saturated with pesticides and discharged as return runoff into numerous local landscape depressions. As a result, artificial reservoirs-accumulators appear. These reservoirs are a real disaster for surrounding lands. Some of them cause secondary pollution when poisonous bed depositions become dry and are brought on irrigated lands, ruin them and pollute the atmosphere in the surrounding regions.

The most spread pollutants in the Aral Sea are: oil hydrocarbons, phenols, synthetic surface-active substances (SSAS), chlororganic pesticides (COP), heavy metals and minerals. The abundant use of pesticides with high physiological reaction (B-58, metaphos, corotan, butiphos, hexachloran, lindan, DDT etc.) poses a tremendous threat to living organisms. Reservoirs carrying water with undecided compounds of heavy metals and chlororganic pesticides, led to the destruction of fishery, the appearance of cancerogenic diseases, and changes in citogenetic indices. The maximum pollution level by oil hydrocarbons in 1970 was 54 MPC (maximum permissible concentration) in the Maly Aral (MPC=0.05 mg/dmi), and 80 MPC in the Bolshoi Aral. Since 1978 the tendency to oil hydrocarbons pollution stabilization at the level of MPC is marked. Phenols made up 28 MPC (MPC=0.001 mg/dmi)in the Maly Aral, and 63 MPC in the Bolshoi Aral. At present there is no information about phenol pollution because observations have been stopped. Concentrations of SSAS and heavy metals do not exceed MPC.

Salinization increased from 10 g/l to 40-50 g/l because of lack of fresh water inflow.

In the past the uniqueness of the Aral Sea contributed to richness and diversity of the biota which could be compared with Africa. The Pre-Aral area possessed half of the biological species of the former USSR, many of these, however, have disappeared or are threatened. There were 500 kinds of birds, 200 species of mammals and 100 species of fishes, thousands of insects and invertebrates.

Before 1960 the river deltas were home to over 70 kinds of mammals and 319 types of birds. At present only 32 kinds of mammals and 160 types of birds remain. In low streams of the Syrdarya River, more than 100 thousand hectares of alluvial soils became salt-marsh, and more than 500 thousand hectares of swamp and medow-swamp soil became dry. This resulted in the transformation and destruction 5-7 kinds of herbs needed for fodder for sheep, horses, camels and goats. Diseases and death of cattle began, musk-rats cultivation stopped, and sheep live-stock decreased sharply.

The regional flora is impressive and includes 1,200 flowers, 560 types of tugai forests of which 29 are endemic to Central Asia. The flora of the Aral-Sea coast includes 423 kinds of plants of 44 families and 180 genera. The highest diversity of sand vegetation is concentrated on the former islands of the western coast. The dry strip of the Aral is characterized by lower diversity in comparison with the coast. Among them are 30 species which are valuable fodder plants, 31 kinds of weeds, and more than 60 kinds of local flora are potential phytomeliorants for dried coasts. The change in water balance caused mineralization of the water in the Aral Sea basin, which led to the loss of unique biocenosis and a number of endemic species of animals. Inflow reduction into the Aral caused irreversible changes of hydrological and hydrochemical sea regimes and hydro systems. Salt balance changes increased the sea salinity 3 times, transforming it into a desert.

The formerly flourishing sea ecosystem supported 24 species of fishes that are disappearing. These include carp, perch, sturgeon, salmon, sheat-fish and spike. There were 20

kinds of fish in it, but fishery was based mainly on bream, sazan, aral roach (vobla). Barbel and white-eye fish were caught in the Aral Sea. The first signs of the negative impacts of salinization on ichtyofauna of the Aral Sea, appeared in the mid 1960's when salinity reached 12-14%. On shallow water the salinity of water increased faster than in the open parts of the sea, negatively affecting spawning places. By 1971 the average salinity exceeded 15% and resulted in the destruction of fish spawn. Since 1971 the average salinity has reached 12% in the open part of sea, and the first signs of negative impact on fish have appeared. Some kinds of fish have slowed their growth, and the number of fish has been sharply reduced. By the mid 1970's average salinity of the sea exceeded 14%, and the natural reproduction of the Aral fish was completely destructed. In the late 1970s several species of fish did not reproduce at all. By 1980 salinity exceeded 18%.

The ecosystems of delta valleys have been transformed greatly by agricultural land use for many centuries. Irrigated or cultivated fields, rice fields and non-cultivated agricultural lands which are characterized by different stages of soil and vegetation cover rehabilitation, are singled out. The following anthropogenic factors that brought about changes in the ecosystems should be considered according to their significance: pastures, land-use, agriculture, transport, city, rural, military objects, hydrotechnical (artificial reservoirs, dams, canals, sewage accumulators), and cattle-breeding. The process of degradation in the Aral region caused progressive crises in the social and economic spheres. The primary victims of the crises were the most vulnerable layers of population, namely children, women, ill-paid inhabitants of cities and rural areas. The region has the highest child mortality rate in the former USSR (10-12 children per 100 newly born), high level of maternity death: about 110 women per 1000 births. Diseases such as TB, infections and parasites, typhus, hepatite, paratyphoid always accompany poverty. The disease rate has a tendency to increase. In the epicenter of ecological disaster, anemia, dysfunction of thyroid the gland, kidney and liver diseases are wide spread. Blood, oncological diseases, asthma and heart diseases are progressing. Medical research proves that the incidence and growth of these diseases are directly dependent on ecological disaster.

In agriculture, there is a steady tendency to transition to ecological management of production. One of the main principles of the above-mentioned tendency is maintenance of positive humus balance in soil at the expense of introduction of alternation of crops and application of organic fertilisers. For the decision of the set forth above problems of economy of our republic on department «Ecology and ground science» Tashkent university building and sivil engineering, the center of science on maintenance of ecological and industrial safety of the Central Asian global environmental problems and industrial enterprises of all branches of our republic is created. The center of science renders the necessary competent and practical help at the decision of various problems both natural, and ethnogeny character, and also develops necessary recommendations under their decision.

Conclusion. We believe that researchers not only be connected with researchers of Uzbekistan, but our academic collaboration will form the foundation of one of the most important scientific projects to solve the environmental problems that threaten a lot of population in whole Central Asia and even the whole globe.

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KOKMARAZ (TUYAKORIN) - *HELIOTROPIUM LASIOCARPUM* F.E. M – POISONOUS HERBS

A.E. Egamberdiev[1], A.M. Nigmatullaev[1], H.N. Olimova[1], U.Kh. Kurbanov[1], N.I. Mukarramov[2]
Institute of Chemistry of Plant Substances named after Acad. S.Y. Yunusov of the Academy of Sciences of the Republic of Uzbekistan, Tashkent, Uzbekistan[1]
Research Institute of Plant Quarantine and Protection, Tashkent, Uzbekistan[2]
https://doi.org/10.5281/zenodo.19365191

Abstract. *Heliotropium lasiocarpum is an annual plant. It grows erect and, under favorable conditions, reaches a height of 120-130 cm on wastelands. In densely planted fields, its height does not exceed 3-5-10 cm, often reaching 30-60 cm. The length of the root reaches 10-20 cm. The stem is short, densely covered with hairs.*

The widespread distribution, development and chemical composition of the Heliotropium lasiocarpum plant in the arid regions of Uzbekistan are described in detail.

Keywords: *heliotropium lasiocarpum, heliotrope toxicosis, mumps (turtle), toxic hepatitis of the istiqol.*

Introduction

Many types of weeds are weeds in our fields, some of which are poisonous. These plants, along with the grains of grain crops, enter the human and animal bodies, causing them serious diseases, sometimes even death. In 1945-1946, a serious disease called heliotrope toxicosis (or heliotrope toxicosis) broke out in some regions of the Republics of Uzbekistan, Tajikistan and Kazakhstan. Doctors previously called this disease "exogenous toxic hepatitis".

This disease was mainly caused by people who ate sour bread and sour porridge cooked from wheat or barley groats. A person with this disease has pain in the armpit and under the right ribs, that is, in the upper half of the right side of the abdomen, and sometimes this pain spreads to the entire abdomen. Some patients become weak, feel nauseous, lose weight. Nausea and vomiting are more common in children. Some patients feel well at the beginning of the disease and continue to work without consulting a doctor, but as the disease progresses, they become incapacitated and are forced to stay in bed.

The liver of a person with cholera is first damaged, the liver enlarges and hurts when palpated. There is also severe pain in the stomach, intestines, and organs located in the abdominal cavity. Blood circulation and the work of the central nervous system are abnormal. In general, the affected organs do not function normally, water metabolism in the body is disrupted, water accumulates in the abdomen and swells, that is, cholera occurs. The patient becomes very thin; the skin color turns pale.

After some time after starting to eat sour bread and sour porridge, water begins to accumulate in the patient's abdomen. The accumulation of water sometimes occurs very quickly, 3-6 days, and sometimes gradually, 5-6-7 weeks. Sometimes a lot of fluid accumulates in the patient's abdomen, which hinders movement, prevents the body and internal organs from holding in a normal position. During this period, the patient is forced to lie still. The abdomen of some patients becomes very swollen, its circumference reaches 100-110 cm, and during the illness the

water accumulated in the abdomen reaches 50-90 liters. As a result of such a large accumulation of water in the abdomen, the work of internal organs is disrupted, especially blood circulation is disturbed, and the patient has difficulty breathing, sometimes shortness of breath, increased heart rate, and a feeling of anxiety appears. Some patients feel well even when they have fluid in their abdomen. Such patients refuse to go to the hospital and even do light work. However, most patients become incontinent and quickly get tired as soon as fluid begins to accumulate in their abdomen.

Materials

Some patients do not have fluid in their abdomen and the disease is generally mild. In the above years, 18-20% of people with cholera die, about a third recover completely and regain normal functioning, but in most cases, the liver does not recover normally. Such patients often feel weak and complain of pain under the right rib cage when walking or doing physical work. Although industrial toxic hepatitis had also appeared in parts of Central Asia in 1914, 1917, and 1930, the cause of its appearance was unknown until 1945-1946.

All those who contracted this disease said that they had contracted it after eating sour bread or sour porridge made from wheat or barley. After that, botanists began to pay attention to weeds that grew intermingled with wheat, barley, tarik, and other crops. It was known that in all regions where the disease of the legume appeared, the fields where grain crops were sown were heavily contaminated with the grass of the legume (the seeds of which are hairy heliotrope). It was found that the seeds of this grass were mixed with the grain harvested from these fields. At present, it is clearly known that a person or animal who eats the seeds of the legume, which are rich in heliotrine and lasiocarpine alkaloids, together with grain or flour, will contract the disease of the legume (toxic heliotrope).

The poisoning properties of the seeds of H. lasiocarpum in animals have been studied. The amount of *H. lasiocarpum* seeds that are toxic to animals varies from animal to animal. For example, a rooster eats 0.6 grams per kilogram of its live weight, while mice, guinea pigs, and rabbits do not become poisoned even when they eat 10 grams of seeds per kilogram of their live weight. A rat will die from poisoning if it eats more than 20 grams of seeds per kilogram of its live weight. Pigs and sheep will be poisoned if they eat 3 grams of fenugreek seeds per kilogram of their live weight. Cats and dogs will die from poisoning if they eat 2-3 grams of fenugreek seeds per day within a month. When baking bread and other foods containing *H. lasiocarpum* seeds, even high temperatures do not affect the alkaloids. These alkaloids have the ability to accumulate in certain parts of the human body and are excreted very slowly from this place. Therefore, if food containing alkaloids from camel's horn is consumed for a certain period of time, even if these alkaloids are present in very small quantities, the body cannot escape poisoning.

H. lasiocarpum seeds - hairy heliotrope plant is an annual poisonous herb belonging to the camphor family. The species of plants belonging to this family reach 220. Most of them grow in countries with a warm and temperate climate. About 10 species of *Heliotropium* species grow in Uzbekistan. They are found on the plains and in the foothills. After the widespread occurrence of toxic heliotrope disease in various parts of Uzbekistan in 1945, the population began to call this disease by its name, that is, "heliotrope".

Botanical description of *Heliotropium lasiocarpum*. *Heliotropium lasiocarpum* is an annual plant. It grows upright and, when conditions are favorable, on wastelands, reaches a height of 120-130 cm. In densely planted crops, its height does not exceed 3-5-10 cm, often 30-60 cm. The length of the root reaches 10-20 cm. The stem is short, densely covered with hairs.

The leaves are alternate (in a row) and thickly located on the stem and lateral branches, connected to them by a stipule. The leaf blade is oval, or ovate, or rounded in shape. Both surfaces of the leaves are covered with short, but stiff white hairs. The veins on the upper surface of the leaves are in a row, and the veins below are convex. The flowers are small, white, and the tube is covered with short white hairs. The flowers are curled up until they open, and the flower at the end of the stem and lateral branches is on one side of the branch. The calyx is covered with hairs and contains five oblongs, arrow-shaped, sharp-tipped sepals.

The seed consists of four nuts (grains). After ripening, they are easily separated from each other. These seeds are egg-shaped, 1-1.5-2 mm long. The surface is slightly rough, greenish-gray in color, covered with short white hairs. When crushed on paper, an oily stain forms. The seed contains up to 20% oil. Due to the fact that the seeds of *H. lasiocarpum* are covered with white hairs, it is very easy to distinguish it from the seeds of the Eichwald heliotrope, which grows in northern and central Kazakhstan and is one of the plants of this type, as well as from the seeds of annual plants called Bukhara, Olga and Khorasan heliotropes. Because their seeds do not have hairs. The H. lasiocarpum plant produces a lot of seeds. A medium-sized plant can produce up to 4,000 seeds. In plants growing in wastelands, the number of seeds can reach 15,000.

Distribution of *Heliotropium lasiocarpum*. *Heliotropium lasiocarpum* is widespread in arid areas of Uzbekistan. This plant is found in the Buka, Bekabad, Parkent, Khavos, Mirzachul, Syrdarya, Yukarichirchik districts of Tashkent region, Bulungur, Kattakurgan, Urgut, Pastdargam, Zomin, Gallaorol, Jizzakh districts of Samarkand and Jizzakh regions, and Beshkent, Koson, Kamashi, Yakkabag, Chirakchi districts of Kashkadar region. However, this poisonous weed is still absent from agricultural crops in Khorezm region and Karakalpakstan.

H. lasiocarpum is rare in the Fergana Valley. In Namangan region, this plant is found in small quantities in Chust, Pop, Kosonsoy, Yangikurgan, Uchkurgan, and Uychi districts. On the slopes of shallow ravines between Chust and Pop, another species of *Heliotropium* plant, *Heliotropium olga,* can be found in nature. *H. lasiocarpum* is also rare in Andijan region. In addition to Uzbekistan, *H. lasiocarpum* can be found in Tajikistan, Kyrgyzstan, Turkmenistan, and the southern regions of Kazakhstan. In Russia and Central Asia, this plant also grows in Azerbaijan, Armenia, the Krasnodar Territory, and the southeastern regions of Russia. In addition, this plant is widespread in Afghanistan, Iran, Arabia, and the northwestern part of India.

Methodology

H. lasiocarpum usually has a different distribution in different fields. If the crops are densely planted, *H. lasiocarpum* almost does not grow at all or grows very little, and in fields where the crops are sparsely planted, this weed overwhelms everything. This weed is especially common on black plowed and waste lands. *H. lasiocarpum* grows abundantly along roadsides, along ditches and borders, around walls and buildings. This plant grows naturally on the slopes of ravines, in gravelly riverbeds and on sandy deposits on river banks. In the plains and foothills, this plant is widespread in fertile lands planted with wheat and barley. Horsetail is always abundant in millet stalks.

In irrigated areas, *H. lasiocarpum* is rarely found in areas planted with wheat, barley, sorghum, sesame, flax, cotton, alfalfa, and mung beans. It is occasionally found in irrigated and dryland melons. In general, this plant grows less in irrigated areas because it prefers soft soil, and therefore does not grow well in soils that are compacted after irrigation.

Development of *H. lasiocarpum*. The shoots of *H. lasiocarpum* germinate in the first and second half of April. Sometimes, in areas with soft soil, its seeds germinate even in August, but

this is rare. In May, the plant's crown develops and grows and buds. In late May and early June, the first flowers of the inflorescences located at the bottom of the stem begin to open (the lower flowers open first, the upper ones later). The plant blooms profusely in late June and throughout July. In the foothills, its flowering continues until late August.

The seeds of the lowest flowers, which open first, ripen and begin to fall in late June and early July. The seeds are mostly fully ripe in August, but the last flowers, located at the top of the stem, continue to open into August. By September, the seeds are fully ripe and the plant partially dies. The plant stops growing in October, after the first frosts. Thus, its growing season is about six months long. The growing season of *H. lasiocarpum* in the foothills is one month shorter. For example, in August, it is already in full bloom in the foothills, while in the plains it is just beginning to bear fruit.

On the plains, the first ripe seeds of *H. lasiocarpum* begin to fall in late June, and in the foothills - in late July, that is, after the grain harvest is complete. In the post-war period, grain crops were heavily contaminated with *H. lasiocarpum* seeds. This year, in the Buka, Chust and other regions, the contamination of seed samples taken from various places with *H. lasiocarpum* seeds sometimes reached 10%, and in the waste generated during grain cleaning, it reached 50%.

Sometimes winters are cold, but there is little snow. Therefore, in many places, winter grain crops are frost-bitten, as a result of which they rarely sprout in spring. Therefore, the arrival of heavy spring rains delays the growth of winter crops. All of these conditions create favorable conditions for the spread of *H. lasiocarpum*. This leads to the widespread contamination of grain crops with *H. lasiocarpum* seeds.

Our observations revealed that *H. lasiocarpum* contaminated grain crops in rainfed areas, but was rarely found in irrigated areas. When conditions are favorable, this poisonous plant can spread widely, and its seeds can mix with grain crops and contaminate them. In this case, it can cause severe diseases in humans, domestic animals, and birds.

To prevent this, it is necessary to completely clean the crops from *H. lasiocarpum* grass. To do this, first of all, it is necessary to clean the seed grain from *H. lasiocarpum* seeds. If the seed grain is contaminated with *H. lasiocarpum* seeds, this seed should be cleaned with a sieve with a mesh of 1.5-2 mm. When barley and wheat are sieved with such a sieve, the *H. lasiocarpum* seeds mixed with it are easily separated. It is quite difficult to clean millet from *H. lasiocarpum* seeds, and it is absolutely impossible to clean barley and wheat chaff from *H. lasiocarpum* seeds. To completely clean the chaff contaminated with *H. lasiocarpum* seeds, the chaff should be passed through a mill separator No. 5. In this case, it is first passed through a round-mesh sieve, then through a 1.5 x 2 mm long-mesh sieve.

H. lasiocarpum plants that have grown on plowed land or among grain crops are weeded. They should be weeded before the seeds begin to ripen, that is, in May and June. In addition, it is necessary to implement appropriate agricultural techniques on each of the plowed lands on the plains, hills and hills to ensure that the crops grow at a normal thickness. Because *H. lasiocarpum* cannot grow among densely planted crops, and even if it grows, its height does not exceed 10-15 cm. The grain harvest can also be protected from contamination with *H. lasiocarpum* seeds by timely harvesting of grain crops. Because the majority of *H. lasiocarpum* seeds ripen in the second half of the year, while grain crops, under normal conditions, ripen in the first half of the year.

By the time the seeds of *H. lasiocarpum* ripen, the main part of the alkaloids is 0.4-0.5% in the leaves, and some in the stem. Therefore, during grain harvesting, it is necessary to carefully monitor that the stems and leaves of this poisonous plant are not harvested together.

If the stems and leaves of *H. lasiocarpum* are harvested together with grain crops, the grain will be crushed into dust during threshing and can enter the mouths and noses of people who are threshing grain, poisoning them. Such an incident occurred in the Buka district. A bakery worker who baked bread from wheat flour contaminated with *H. lasiocarpum* seeds contracted scurvy before eating it because the mucous membranes of his nose and mouth were contaminated with toxic dust while preparing the dough. Therefore, grain crops in areas contaminated with *H. lasiocarpum* should be threshed and cleaned of dust before being ground into flour, and the grain should be threshed first and then ground.

In areas where scurvy occurs, all residents should be aware of *H. lasiocarpum* and its harmful effects, and necessary measures should be taken to eradicate this plant and protect the grain from its seeds. Agronomists, employees of the production and supply agencies, health workers, and all residents in areas where *H. lasiocarpum* grows should be well informed about this poisonous weed, its characteristics, and measures to combat it.

Chemical analysis of *H. lasiocarpum*. In this research work, two different extraction methods of *H. lasiocarpum* plant - percolation and ultrasonic extraction methods - were compared. The plant sample was collected from Syrdarya region, dried and ground and analyzed. The alkaloid concentration was isolated from the extracts obtained by both methods and compared in terms of composition.

Results and discussion. During the study, 1000 grams of dried and ground *H. lasiocarpum* plant sample was extracted in 80% ethyl alcohol by two different methods - traditional percolation and ultrasonic extraction. In the percolation method, the plant was extracted 13 times, and the release of alkaloids was monitored at each stage using a solution of KVA (silicic-tungstic acid). The extraction process was continued until no alkaloids remained in the sample. The obtained extracts were combined and the solvent was evaporated using a rotary evaporator, yielding a total of 11.6 grams of extract.

Then, 5 grams of this extract was taken and the alkaloid concentration was isolated in the following steps. First, 5 grams of the extract was dissolved in 100 ml of 5% sulfuric acid solution and filtered. The filtrate was washed with chloroform and made alkaline to pH 9–10 using 5% ammonia solution. Alkaloids were isolated from the solution by 3-fold extraction with chloroform. After the solvent was evaporated, 2.6 grams of the alkaloid concentration was isolated.

Using the extraction method using ultrasonic equipment, the same amount (150 g) of the plant was extracted 3 times, each for 30 minutes. At each step, the release of alkaloids was monitored with a KVC solution. After the alkaloid was gone, the extracts were combined, the solvent was evaporated in a rotary evaporator, and a total of 15.3 grams of extract was obtained. 5 grams of this extract was also taken, and the alkaloid concentration was separated based on the same general method as above, resulting in a total of 2.8 grams of alkaloid concentration.

The ultrasonic extraction method significantly reduced the time - it was completed in 1 day, while the percolation method required 13 days. In terms of solvent consumption, 4 times less consumption was also noted in the ultrasonic method. The total amount of extract was also greater in the ultrasonic method (15.3 grams), which indicates high efficiency.

Conclusion

According to the results of the analysis, the extraction method using ultrasonic equipment is recommended as a more effective, time-saving and solvent-saving method compared to the traditional percolation method. This method can be widely used in practice for the extraction of

alkaloid-containing plants [1]. In addition, alkaloids such as heliotrine, heliotrine N-oxide, lasiocarpine, lasiocarpine N-oxide, trachelantamine [2], and echinatine have been isolated [3].

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THE GENUS *LAPPULA* MOENCH IN THE FLORA OF THE TAMDY RELICT MOUNTAINS

Sh.S. Fayzullayev[1], H.Q. Esanov[2]
Bukhara State University[1,2]
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Abstract. *This article provides data on new growth localities of species belonging to the genus Lappula Moench distributed in the Tamdy relict mountains. The studies were conducted in the Tamdy of the Navoi region between 2022 and 2025. Based on existing literature data and the results of field research, 9 species of the genus Lappula were recorded in the study area, of which five species (Lappula patula, L. spinocarpos subsp. ceratophora, L. microcarpa, L. consanguinea, and L. spinocarpos) are reported for the first time for this region.*

Keywords: *Kyzylkum, Tamdy, Lappula, relict mountain, flora, glochidiate spines corolla tube.*

Introduction

Globally, the genus *Lappula* comprises 50–60 species and is the second-largest genus within the tribe Eritrichieae, following the genus *Eritrichium*. Members of the genus are distributed across Eurasia, western North America, North Africa, and Australia. Despite its broad geographical range, the center of diversity for the genus is considered to be Central Asia [2].

Lappula species are annual, occasionally biennial, or perennial herbs, covered with stiff or soft hairs, and possess blue or white funnel-shaped or bell-shaped corollas. Five distinct appendages are present at the apex of each corolla tube. Flowers are (almost) sessile or pedicellate; the pedicel sometimes elongates and curves downward during fruiting; sepals accresce with the fruit. Nutlets are arranged obliquely or vertically relative to the gynobase, often heterocarpic; nutlets are triangular-ovate to ovate in dorsal view, with a concave or, rarely, convex back. The margins of the fruit are surrounded by one or several rows of marginal prickles (spines), which are either free or fused to varying degrees. The fruit often features a membranous marginal wing formed by the united bases of transparent or glochidiate spines, which may be spread out or curved inward; in rare cases, nutlets are glabrous and firmly attached to the gynobase [8].

Species of *Lappula* were initially included within the genus *Myosotis* L., based on the similarity of generative and vegetative characters between the members of these two genera. In the late 18th century, J.E. Gilibert (1782) and Moench (1794) independently described the genus *Lappula*. Following the 20th century, the volume of research conducted on the genus increased significantly. Specifically, M.G. Popov (1953) reported in the "Flora of the USSR" that 44 species of *Lappula* existed, 21 of which were new to science at that time. He classified these species into two sections and 14 series. C.J. Wang (1981) categorized the *Lappula* species in China into two sections and seven subsections. In the recent past, S.V. Ovchinnikova (2005) recorded 70 species within the genus *Lappula*, organizing them into eight sections and 14 series. Despite the continuous taxonomic changes in the tribes of the Boraginaceae family over the last 100 years, the genus *Lappula* has been consistently included in the tribe Eritrichieae Benth. et Hook. since it was first described in 1876 [1].

Recently, S. Ovchinnikova (2006) utilized nutlet surface characteristics and pericarp ultrastructure to determine evolutionary patterns and phylogenetic relationships within the tribe Eritrichieae [5]. Subsequently, based on this data, she divided the genera within Eritrichieae into six subtribes (Ovchinnikova 2009). Based on the specific characteristics of the nutlets and pollen grains, she included the genera *Lappula* and *Lepechiniella* Popov as the sole members of the subtribe Echinosperminae [6].

Modern research within the genus continues to this day [3, 4]. In recent years, intensive scientific work has been carried out on the modern re-inventory of the flora of Uzbekistan. According to the obtained data, 118 species belonging to 31 genera and 10 tribes of the Boraginaceae family have been identified in the flora of Uzbekistan. Of these, 28 species belong to the genus *Lappula* [7]. This information further underscores the significant position of the genus *Lappula* in the flora of Uzbekistan.

Materials and Methods

The object of the research is the members of the genus *Lappula* Moench distributed in the flora of the Tamdy relict mountains. Scientific names of the species were verified using online databases such as POWO (www.plantsoftheworldonline.org), GBIF (https://www.gbif.org), and Plantarium (https://www.plantarium.ru). Morphological characters were determined using specialized scientific literature, including the "Key to the Plants of Central Asia" and the "Flora of Uzbekistan." Herbarium specimens were analyzed based on the collections belonging to the Tamdy Mountains stored in the National Herbarium of Uzbekistan (TASH), Moscow State University (MW), and the Komarov Botanical Institute of the Russian Academy of Sciences (LE).

Results and Discussion

The Kyzylkum Desert, one of the largest arid regions in Uzbekistan, consists of sandy plains and relict mountain ranges rising between them. These relict mountains differ sharply from other desert landscapes of the region due to their distinct geological structure, edaphic factors, and strictly isolated ecological conditions. In modern scientific literature, the Kyzylkum relict mountains are recognized as unique natural areas where a number of rare and endemic plant species are preserved, as well as distinct centers of speciation. Therefore, analyzing the evolution of the vegetation cover of these areas, especially the deep study of their floristic composition using modern methods, is considered one of the urgent issues in botanical science. The Tamdy relict mountain range, chosen as the research object, also falls into the category of such unique areas with high floristic value.

The Tamdy relict mountains are considered a territory belonging to the Kyzylkum relict mountains botanical-geographical region within the Kyzylkum district (Tojibaev et al., 2016). The research area is located in the Tamdy district. The Tamdy district covers an area of 42.4 thousand km², making it the third-largest district in Uzbekistan and the second-largest in the Navoi region. Due to its territorial vastness, location in the Kyzylkum desert, and the surrounding relict mountains, the Tamdy district is rich in plant diversity. The flora of the region consists of desert and mountain elements. This serves as one of the primary reasons for conducting floristic research across the territory [9].

The Tamdy relict mountains possess a unique floristic composition, where rare and endemic species are widely distributed. This area is considered one of the regions with high floristic diversity in the Kyzylkum desert [12, 13, 14]. Furthermore, several species not previously recorded in the region were identified as a result of the scientific research conducted [10, 11, 15]. Field studies conducted between 2022 and 2025 recorded more than 310 species of vascular plants

in the region. Preliminary studies indicate that members of the Boraginaceae family occupy a significant position (27 species) in the research area. Within the family, the genus *Lappula* stands out due to its species richness.

Analysis of field studies and herbarium databases (TASH, MW, LE) revealed that 9 species of the genus occur in the flora of the Tamdy relict mountains. Among them, 5 species were recorded for the first time for the research area. Information regarding these species is provided below:

***Lappula patula* (Lehm.) Menyh.** «Tamdy district, Karatau relict mountain, 572 m a.s.l., 41.616911° 64.300600°. Small stony soils, 16.IV.2024. Sh.S. Fayzullayev». Ancient Mediterranean. Widely distributed on plains and in the lower mountain zone; occurs in fine-earth, stony, gravelly, and sandy soils. Weed.

Distribution: Europe, Asia, North Africa.

***Lappula microcarpa* (Ledeb.) Gürke** «Tamdy district, Karatau relict mountain, 18 km north-east of Zarafshan city, 505 m a.s.l., 41.642448° 64.399465°. Stony-gravelly soils, 07.V.2025. Sh.S. Fayzullayev»; «Tamdy district, 11 km north-east of Zarafshan city, 620 m a.s.l., 41.599649° 64.342903°. Gravelly soils, 07.V.2025. Sh.S. Fayzullayev»; «Tamdy district, 8 km east of Aktau relict mountain, 545 m a.s.l., 41.644179° 64.576841°. Small stony, gravelly slopes, 09.V.2025. Sh.S. Fayzullayev». Pontic–Ancient Mediterranean. Occurs on stony, gravelly, fine-earth, and loess soils, as well as on abandoned lands. Distributed in foothills and the lower mountain zone. Weed.

Distribution: Asia, Himalaya, Tibet, Siberia, Eastern European Russia.

***Lappula spinocarpos* (Forssk.) Asch. ex Kuntze** «Tamdy district, eastern side of Shushaktau relict mountain, 298 m a.s.l., 41.742437° 64.768530°. Stony slopes, 15.IV.2025. Sh.S. Fayzullayev»; "Tamdy district, Charikty, 12 km north-east of Zarafshan city, 420 m a.s.l., 41.666027° 64.287746°. Saline soils, 16.IV.2025. Sh.S. Fayzullayev». Mediterranean-Irano-Turanian. Grows in sandy, gravelly, and stony soils. Weed.

Distribution: Irano–Turanian, Saharo–Arabian, Mediterranean, South Asia.

***Lappula consanguinea* (Fisch. & C.A. Mey.) Gürke** «Tamdy district, northern slopes of Zimbiltau relict mountain, 718 m a.s.l., 41.524103° 64.437489°. Saline soils, 15.IV.2025. Sh.S. Fayzullayev». Euro-Siberian-Central Asian. Occurs in fields, abandoned lands, pastures, weed-infested areas, and around residential areas. Distributed on plains, in foothills, and in the lower and middle mountain zones. Weed.

Distribution: Europe, Asia, Siberia.

***Lappula spinocarpos* subsp. *ceratophora* (Popov) Y.J. Nasir (= *Lappula ceratophora* (Popov) Popov)** «Tamdy district, Kurgantau relict mountain, 586 m a.s.l., 41.511558° 64.296857°. Gypsaceous slopes, 16.IV.2024. Sh.S. Fayzullayev»; «Tamdy district, Yamantau relict mountain, 18 km south-west of Zarafshan city, 437 m a.s.l., 41.457356° 64.046536°. Gravelly slopes, 18.IV.2024. Sh.S. Fayzullayev»; «Tamdy district, western part of Aktau relict mountain, 380 m a.s.l., 41.668503° 64.423569°. Stony, gravelly soil, 22.IV.2024. Sh.S. Fayzullayev». Irano-Turanian. Grows in gravelly deserts, stony outcrops, variegated beds, and on gypsaceous and stony slopes. Used as fodder.

Distribution: Central Asia, Iran, Iraq, Pakistan, Saudi Arabia.

According to scientific research conducted in the Kyzylkum relict mountains in recent years, 8 species were recorded in the flora of the Sultanuvays relict mountain (R.Kh.

Yesemuratova, 2022), 5 species in the flora of the South-Eastern Kyzylkum relict mountains (A.R. Batoshov, 2016), and 3 species in the flora of Bukantau (G.A. Serekeyeva, 2011).

Conclusion

Based on the analysis of field research and data from the National Herbarium of Uzbekistan (TASH) as well as foreign collections (MW, LE), it was determined that 9 species belonging to the genus *Lappula* of the Boraginaceae family are distributed in the flora of the Tamdy relict mountains in the Navoi region. As a significant scientific novelty of the study, 5 species of the genus — *Lappula patula, L. spinocarpos* subsp. *ceratophora, L. microcarpa, L. consanguinea*, and *L. spinocarpos* — were recorded for the first time for this territory. The indicators of species diversity in the Tamdy relict mountains were found to be significantly higher compared to other regions of the Kyzylkum, specifically the flora of Sultanuvays (8 species), South-Eastern Kyzylkum (5 species), and Bukantau (3 species). The accumulation of new floristic data confirms that the flora of the Tamdy relict mountains is not yet fully studied and scientifically justifies the necessity of continuing systematic inventory work in the region.

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ENTOMOPATHOGENIC FUNGI (*METARHIZIUM*): CURRENT CHALLENGES, STRATEGIC OPPORTUNITIES, AND FUTURE PROSPECTS FOR SUSTAINABLE PEST MANAGEMENT

M.F. Razikova[1], D.Kh. Kuchkarova[2], N.A. Khujamshukurov[3]
Tashkent State Technical University named after Islam Karimov[1]
Department of Biotechnology, Department of Engineering Communications of the Tashkent University of Architecture and Civil Engineering[2]
Tashkent Institute of Chemical Technology, Department of Biotechnology, Joint China-Uzbekistan Laboratory "Soil Ecobiotechnology", Tashkent, Uzbekistan[3]
https://doi.org/10.5281/zenodo.19397649

Abstract. *This article discusses the current state, existing challenges, and future development trends of utilizing entomopathogenic fungi (using fungi of the genus Metarhizium as an example) as insecticidal, antifungal, and antibacterial biopreparations, as well as biological fertilizers that stimulate plant growth and development. In particular, the prospects for using entomopathogenic fungi in agriculture are evaluated based on several factors, including the primary functional sources of fungal-based microbiological fertilizers (nitrogen fixation, phosphorus mobilization, decomposers of N, P, K, and trace elements), the advantages of producing biological protection agents, the mechanisms of action of entomopathogenic fungi (antagonism, mycoparasitism, hyperparasitism, microbial competition for nutrients among themselves and with insects and nematodes, anabiosis, and endophytism), the impact of entomopathogenic fungi of the genus Metarhizium on insect pests, the significance of entomopathogenic fungi as biofertilizers, and the safety aspects of their use. Furthermore, the secondary metabolites of Metarhizium fungi, their insecticidal, antibacterial, and antifungal effects, as well as the current market share and prospects of biopesticides in the global pesticide market, are highlighted. Additionally, one of the reliable safety aspects of using entomopathogenic fungi is explained by the fact that the toxin production rate of these fungi under natural conditions is synthesized in very small quantities, rendering them insignificant in terms of toxicity. Nevertheless, from a standpoint of comprehensive safety, it is noted that promoting and widely implementing the use of secondary products of entomopathogenic fungi, rather than their direct primary products, is a safer and more effective approach.*

Keywords: *entomopathogenic fungi, biopesticides, virulence mechanisms, abiotic stress tolerance, sustainable agriculture, integrated pest management.*

Introduction

Global agriculture faces significant threats under the conditions of climate change, including rising average temperatures, soil degradation, water scarcity and increasing salinization, as well as the growing number and impact of pest insects and diseases. Notably, microbial pathogens are exhibiting adaptability to existing treatments, which leads to a sharp decline in the production rates of food and feed products.

The taxonomy of entomopathogenic fungi includes over 100 orders and more than 700 species, such as Oomycetes, Chytridiomycota, Microsporidia, Entomophthoromycota, Basidiomycota, and Ascomycota [Sharma et al., 2017; Wang et al., 2017; Xie et al., 2019]. Among

them, the most widely used fungi in biopesticide production are *Beauveria bassiana*, *Metarhizium anisopliae*, *Isaria fumosorosea* (Paecilomyces fumosoroseus), *Lecanicillium lecanii* (Verticillium lecanii), and *Purpureocillium lilacinum* (Paecilomyces lilacinus) [Xie et al., 2019; Park et al., 2012; Sasan et al., 2012].

An important feature of entomopathogenic fungi is their ability to colonize the plant rhizosphere, stimulating plant growth and development [Venkatesh et al., 2022; Yinmei et al., 2022]. Furthermore, scientific sources highlight the increasing role of fungi in sustainable agriculture and global food security, as well as updated descriptions of fungal and fungus-like taxa as of 2024, indicating new prospects for fungal applications in agriculture [Manawasinghe et al., 2025; Hyde et al., 2024].

The prospects of using fungi in agriculture are evaluated based on several factors. These include their ability to promote plant growth [Hossain et al., 2017; 2020; Thambugala et al., 2020], enhance tolerance to various stress factors, and provide protection against phytopathogenic microbes and pest insects [Thambugala et al., 2020, 2022; Adedayo et al., 2023]. In addition, fungi are highly valued for their bioremediation properties, such as mitigating stress factors in soil environments—including reducing mineral depletion, decomposing heavy metals, and converting salts into plant-available forms [Kim et al., 2013; Baron et al., 2018, 2021].

Literature Review

Microbial fertilizers based on fungi. Microbial fertilizers derived from fungi serve as a primary source of essential elements (nitrogen fixation, phosphorus mobilization, and destructors of N, P, K, and microelements) [Sánchez-Esteva et al., 2016; Itelima et al., 2018; Gulshan et al., 2024; Ortiz et al., 2022; Panda, 2022; Kumar et al., 2023]. They exist in various forms, including liquid, dry, and paste-like (e.g., Agright™; BioFert; Green Awamori; JumpStart; Shayona; Rootnet; MnSol B; JumpStart) [Sheoran et al., 2013; Leggett et al., 2015; Sánchez-Esteva et al., 2016; Gómez-Muñoz et al., 2018; Simpson et al., 2020; Geethalakshmi et al., 2021]. Application methods differ, including seed treatment, root application, and foliar spraying, and they are environmentally friendly—minimizing chemical fertilizer use and soil degradation, harmless to warm-blooded animals, and able to decompose complex substances such as lignin, cellulose, and phosphorus [Kjøller et al., 2002; Pritsch et al., 2011; El-Gendi et al., 2021; McKelvey et al., 2011]—while remaining cost-effective alternatives to chemical agents [Itelima et al., 2018; Ortiz-Urquiza, 2021; Gulshan et al., 2022; Ortiz et al., 2022].

Despite their advantages, there are several challenges in using entomopathogenic fungi as insecticidal, antifungal, antibacterial, or plant growth-promoting biopreparations:

1. Fungal spores require specific environmental conditions (moisture, pH) and time for development and effective action, which leads some farmers to consider them less effective than chemical fertilizers, as fungal-based biopreparations generally act slower [Hernández-Fernández et al., 2021; Ferreyra-Suarez et al., 2024].
2. Industrial production of fungal biopreparations requires complex technological processes to maintain the required concentration of cells/spores. The presence of other microbial species in the soil can reduce the effectiveness of the target biopreparation due to competitive interactions [Chakraborty et al., 2021; Čaušević et al., 2024; Kong et al., 2024].
3. Ecological awareness, selective activity, and proper application of biopreparations are hindered by insufficient farmer education and slow adoption of modern agricultural information technologies, slowing market growth compared to chemical agents [Bagga et al., 2024; Fadiji et al., 2024; Mouratiadou et al., 2023].

4. Lack of state support for production and commercialization, insufficient regulatory control, and poor quality monitoring lead to biopreparation adulteration and reduced effectiveness [Khobragade et al., 2024; Acharya et al., 2020; Atieno et al., 2020; Yadav et al., 2024a,b,c].

5. Biopreparations are often formulated for only one or a few plant/pest species, and incorrect storage or application practices by end-users reduce their effectiveness. Training sales personnel and educating farmers are crucial for improving adoption and market competitiveness.

6. Manufacturers are not fully implementing advanced production technologies, including stabilizing microbial viability under field conditions. Innovative carriers such as nanocoatings and biochars, which enhance survival in adverse soil conditions, are underutilized [Minkosse et al., 2023; Neuberger et al., 2024; Brondi et al., 2022, 2025; Manawasinghe et al., 2025]. Combining endophytic fungi with nitrogen-fixing rhizosphere bacteria can improve efficacy [Singh et al., 2022; Li et al., 2023; Rodríguez et al., 2023].

7. Genetic engineering approaches such as CRISPR-Cas9 have begun to improve stress tolerance, symbiotic efficiency, and metabolic activity of target microbes [Peng et al., 2022a,b; Yang et al., 2024; Ma et al., 2025], yet large-scale industrial application of genetically modified strains remains limited due to concerns about unexpected mutations and metabolite production.

Research Methodology. Research on the production and practical application of biopesticides was conducted based on global market analyses and projections up to 2030 from leading economic research centers, including Markets and Markets (MM), Fortune Business Insights (FBI), Precedence Research (PR), Market Analysis Report (MAR), and Global Market Insights (GMI). Additionally, analyses were performed using open scientific databases such as Scopus, WoS, PubMed, Lens, PubMed Abstract, CrossRef, and Google Scholar.

Analysis and Results

The Significance of Entomopathogenic Fungi as Protective Agents. Fungi-based biocontrol agents have several advantages. In addition to their entomopathogenic effects against insect pests [Peng et al., 2021; Hyde et al., 2019; Wang et al., 2024], they are distinguished by their antifungal, antibacterial [Dara, 2019a; Pérez-Pizá et al., 2024; Liao et al., 2025], nematocidal [Berhanu et al., 2024], and bioherbicidal activities against weeds [Htet et al., 2022] [Ayaz et al., 2023; Chaudhary et al., 2024]. They are also noted as environmentally sustainable biopreparations that mitigate chemical resistance [Rauf, 2024; Wang et al., 2024; Diepenbrock et al., 2024] and prevent soil and water pollution [Chaudhary et al., 2024; Diepenbrock et al., 2023; Ranadev et al., 2025; Saminathan et al., 2025].

The mechanism of action of entomopathogenic fungi is mainly explained by antagonism (antibiotics, siderophores, pH changes, etc.) [Avis et al., 2001; Ansari et al., 2005; Vinale et al., 2008], mycoparasitism [Németh et al., 1991; Howell, 2003], hyperparasitism [Askary et al., 1998; Whipps et al., 2008; Benhamou et al., 2012], competition for nutrients with other microbes, insects, and nematodes [Alabouvette et al., 2009; Pedrini, 2018; Freimoser et al., 2019; Spescha et al., 2023; Puža et al., 2023; Barszczewska et al., 2025], anabiosis [Ortiz-Urquiza et al., 2013; Zhao et al., 2016; Quesada Moraga et al., 2022; Hong et al., 2023], and endophytism [Ahsan et al., 2024].

Scientific sources indicate that for industrial cultivation of entomopathogenic fungi, both primary and secondary products are utilized [Poveda et al., 2021; Manawasinghe et al., 2025]. While wheat bran is commonly used as a widespread substrate, rice bran and milled rice are widely applied in many countries. For instance, studies conducted by Indian researchers reported higher

conidial production (25.2 ± 0.13 g/100 ml) on milled rice compared to rice bran (1.15 ± 0.1 g/100 ml) [Anitha et al., 2017].

Entomopathogenic Fungi Belonging to the Genus *Metarhizium*. The genus *Metarhizium* has been extensively studied, with species such as *M. anisopliae*, *M. guizhouense*, *M. pingshaense*, and *M. taii* being most widely examined [Bischoff et al., 2009]. Modern molecular-genetic analyses have identified around 100 species in this genus [Bischoff et al., 2009; Fernández-Bravo et al., 2021]. Overall, more than 700 species belonging to approximately 90 genera of entomopathogenic fungi have been documented as biocontrol agents against insect pests, forming the basis of commercial biopreparations. The most studied genera include *Beauveria* (*B. bassiana* (Balsamo-Crivelli) Vuillemin), *Metarhizium* (*M. anisopliae* (Metschnikoff) Sorokin), *Isaria* (*I. fumosorosea* Wize), *Lecanicillium* (*L. lecanii* (Zimmerman) Viegas), and *Hirsutella* (*H. thompsonii* Fisher) [Chen et al., 2015; Bamisile et al., 2021].

Depending on their nutrition type, entomopathogenic fungi are recommended against various pests, including arthropods [Dara, 2019], aphids, locusts, thrips [Gulzar et al., 2021], larvae [Wakil et al., 2017; Yasin et al., 2019], moths [Ali et al., 2015; Tahir et al., 2019], bees, mosquitoes, whiteflies, and fruit flies [Dong et al., 2016; Bamisile et al., 2020; Canassa et al., 2020; Usman et al., 2020]. Some studies also indicate that these fungi improve soil structure and microbiota, enhance nutrient availability and water absorption in plants, and stimulate plant immune responses [Sasan et al., 2012; Jaber et al., 2014; Behie et al., 2015; Jaber et al., 2018]. Furthermore, the use of entomopathogenic fungi in plant protection increases plant resistance to chemical pesticides [Bamisile et al., 2021]. Commonly studied targets include arthropod pests such as *Bemisia argentifolii*, *Bombyx mori*, *Brevicoryne brassicae*, *Cetonia aurata*, *Choristoneura fumiferana*, *Coptotermes formosanus*, *Culex pipiens*, *Delia antigena*, *Drosophila melanogaster*, *Empoasca vitis*, *Epilachna sparsa*, *Galleria mellonella*, *Heliothis virescens*, *Manduca sexta*, *Musca domestica*, *Myzus persicae*, *Oryctes rhinoceros*, *Otiorhynchus sulcatus*, *Phaedon cochlearia*, *Plutella xylostella*, *Rhagoletis pomonella*, *Rhopalosiphum padi*, *Schistocerca gregaria* [Pedras et al., 2002; Pedras et al., 2003].

The Role of Entomopathogenic Fungi as Biofertilizers. As previously noted, entomopathogenic fungi also act as biofertilizers. They stimulate plant growth and resistance to stress factors by producing phytohormones. For example, they synthesize auxins [Dutta et al., 2014], gibberellic acid [Khan et al., 2014], cytokinins [Kang et al., 2012], and indole acetic acid [Gao et al., 2017], thereby enhancing metabolic processes, activating cell division, promoting root and lateral root development, accelerating seed germination, regulating pigment production, and optimizing photosynthesis [Gao et al., 2017; Bamisile et al., 2021].

Safety Aspects of Using Entomopathogenic Fungi. The increasing diversity of insect pests and saturation of soil microbiota with phytopathogens reduces crop yields by up to 50%, which in turn increases reliance on chemical pesticides. Chemical pesticides negatively affect the environment, soil composition, and human health, causing allergies, blood disorders, infectious diseases, and immune deficiencies, as well as reducing the export potential of agricultural products.

However, several issues remain regarding the use of entomopathogenic fungi in agriculture [Smagghe et al., 2023; Vivekanandhan et al., 2024a; Shahbaz et al., 2024]. Their widespread dissemination in the environment may lead to unintended consequences beyond their insecticidal and biofertilizer benefits [Kumar et al., 2024; Vivekanandhan et al., 2024b]. Direct application to crops may result in fungal spores (blastospores, conidia) being incorporated into the produce,

potentially producing metabolites that can induce allergic reactions in humans [Zimmermann, 2007].

For example, *Metarhizium* species synthesize six types of destruxins (A, B, E, A1, A2, B1) and cytochalasins (C and D) [Zimmermann, 2007; Strasser et al., 2000; Vey et al., 2000]. Additionally, the FKI-1079 strain of *M. sp.* produces novel insecticidal antibiotics, hydroxyfungerin A and B, which exhibit inhibitory activity against brine shrimp (*Artemia salina*) [Uchida et al., 2005]. Fermentation extracts of *M. anisopliae* also yield two new mutagenic metabolites, NG-391 and NG-393 [Krasnoff et al., 2006].

The production of destruxins depends on cultivation conditions, substrate composition, culture form (liquid or solid), and storage methods. Most studies report increased destruxin production in peptone- and rice-based media, while no destruxins were detected on Czapek-Dox solid medium [Wang et al., 2004]. Moreover, the amount of destruxin produced does not necessarily correlate with the insecticidal activity of *M. anisopliae*, indicating that destruxins are not the sole determinant of pathogenicity [Amiri-Besheli et al., 2000; Wang et al., 2004; Zimmermann, 2007]. Therefore, one of the most reliable safety aspects is that entomopathogenic fungi naturally synthesize toxins in very low amounts, posing negligible risk of toxicity.

Furthermore, the interactions of entomopathogenic fungi with symbiotic soil bacteria, beneficial microbiota, and antagonistic microbes remain incompletely understood. Environmental factors such as soil moisture, temperature, and nutrient availability directly affect the efficacy of biopreparations, limiting their effectiveness. Therefore, utilizing secondary rather than primary products of entomopathogenic fungi may offer a safer and more efficient approach.

Studies have shown that volatile organic compounds from *B. bassiana* and microorganisms such as *Bacillus subtilis*, *B. methylotrophicus*, *Pseudomonas stutzeri*, *Arthrobacter agilis*, *Trichoderma atroviride*, and *Cladosporium halotolerans*—including 2,3-butanediol, acetoin, dimethyldisulfide, C16-dimethylamine, 6-pentyl-2H-pyran-6-one, and 3-methylbutanol—can act as elicitors that promote plant growth and protect against phytopathogens. Moreover, combined application of *B. bassiana* and *M. anisopliae* exhibits high activity against *Spodoptera frugiperda* larvae, enhances cucumber growth and biochemical composition, and prevents root rot (*Rhizoctonia solani*) [Adame-Garnica et al., 2026]. Additionally, *B. bassiana* and *Trichoderma atroviride* synthesize 3-methylbutanol, which shows activity against insect pests and phytopathogens [Batool et al., 2020].

Conclusion

The global biopesticide market reached USD 2.6 billion in 2021, USD 2.9 billion in 2022, USD 3.2 billion in 2023, USD 3.5 billion in 2024, and USD 6.72 billion in 2025, and it is projected to reach USD 7.46 billion in 2026. According to leading global analytical centers, the size of the global biopesticide market, based on FBI statistics, was USD 3.72 billion in 2024, USD 9.31 billion in 2025, and is expected to reach USD 11.48 billion in 2026, growing to USD 40.61 billion by 2034, with an expected compound annual growth rate (CAGR) of 17.1% [FBI, 2026].

FBI statistics indicate that in 2025, the North American biopesticide market dominated with a 37.56% share, with major companies such as Syngenta AG, Bayer AG, BASF SE, and Bioceres S.A. occupying leading positions in the production and sales of biopesticides. These trends highlight the relevance for Uzbekistan to expand the use of entomopathogenic fungi, promote the production of locally sourced biopreparations for the domestic market, and actively implement them in agricultural practice.

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SCREENING OF PANCREATIC LIPASE INHIBITORS IN ENDOPHYTIC FUNGI OF MEDICINAL PLANTS OF UZBEKISTAN

M.M. Yuldosheva[1], D.M. Ruzieva[2], K.V. Kondrasheva[3], G.A. Rasulova[4], H.A. Odilova[5]
PhD, Acting Associate Professor, Department of Natural Sciences, University of Business and Science, Tashkent[1]
Senior Research Scientists, Candidate of Biological Sciences Laboratory of Biochemistry and Biotechnology of Physiologically Active Substances, Institute of Microbiology[2]
Senior Research Scientists, Candidate of Biological Sciences Laboratory of Biochemistry and Biotechnology of Physiologically Active Substances, Institute of Microbiology[3]
Junior Researcher, Laboratory of Biochemistry and Biotechnology of Physiologically Active Substances, Institute of Microbiology[4]
PhD Student, Laboratory of Biochemistry and Biotechnology of Physiologically Active Substances, Institute of Microbiology[5]
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Abstract. This study presents comprehensive data on the screening of pancreatic lipase inhibitory activity of extracts obtained from 15 endophytic fungal strains isolated from six medicinal plants native to Uzbekistan. Obesity is a major global health issue associated with metabolic disorders such as dyslipidemia, cardiovascular diseases, insulin resistance, and type 2 diabetes mellitus [1, 2]. One of the most effective therapeutic strategies for obesity management is the inhibition of pancreatic lipase, the key enzyme responsible for lipid digestion and absorption in the gastrointestinal tract [3, 4]. Currently, Orlistat remains the only clinically approved pancreatic lipase inhibitor for long-term treatment. However, its use is limited due to adverse side effects such as gastrointestinal discomfort, hepatotoxicity, and metabolic disturbances [5, 6]. Therefore, the identification of novel, safe, and effective natural inhibitors is of great scientific and medical importance. Endophytic fungi are recognized as prolific producers of bioactive secondary metabolites with diverse chemical structures and pharmacological activities [7, 8]. In this study, both qualitative (chromogenic agar plate assays using Rhodamine B and phenol red indicators) and quantitative (titrimetric in vitro enzymatic assay) approaches were applied to evaluate lipase inhibitory activity. The results demonstrated that the majority of fungal extracts exhibited inhibitory activity against pancreatic lipase. Five strains showed inhibition levels exceeding 50%, indicating strong bioactivity. Among them, the highest inhibitory activity was observed in Fusarium sp. AL142R (73.7%) and F. sambucinum AL135L (65.2%), which were comparable to the standard drug Orlistat (80.5%). These highly active strains were isolated from the endemic plant Allium longicuspis [9, 10]. The findings highlight the significant potential of endophytic fungi associated with medicinal plants of Uzbekistan as a promising source of natural pancreatic lipase inhibitors and prospective candidates for the development of novel anti-obesity therapeutics [11].

Keywords: endophytic fungi, pancreatic lipase, enzyme inhibition, hypolipidemic activity.

INTRODUCTION

Obesity is a multifactorial metabolic disorder characterized by excessive accumulation of body fat and is considered one of the leading causes of morbidity and mortality worldwide. It is closely associated with several chronic diseases, including cardiovascular disorders, hypertension, insulin resistance, and certain types of cancer [12]. According to global health statistics, the prevalence of obesity has increased dramatically over the past decades, posing a serious public health challenge. Pancreatic lipase plays a central role in lipid metabolism by catalyzing the hydrolysis of dietary triglycerides into absorbable free fatty acids and monoglycerides. Therefore, inhibition of this enzyme reduces fat absorption and caloric intake, making it an effective target for anti-obesity therapy [13].

Although Orlistat is widely used as a lipase inhibitor, its long-term use is often associated with undesirable side effects. This limitation has prompted extensive research into natural sources of enzyme inhibitors, particularly microbial metabolites [14]. Endophytic fungi, which reside asymptomatically within plant tissues, have emerged as an important source of novel bioactive compounds. These microorganisms produce a wide range of secondary metabolites, including alkaloids, terpenoids, polyketides, and peptides, many of which exhibit significant pharmacological activities such as antimicrobial, antioxidant, anticancer, and enzyme inhibitory effects [15].

Previous studies have demonstrated that endophytic fungi can produce inhibitors of key metabolic enzymes, including pancreatic lipase [16]. However, the potential of endophytic fungi associated with medicinal plants of Uzbekistan remains largely unexplored [17]. The aim of this study was to investigate the pancreatic lipase inhibitory activity of endophytic fungi isolated from selected medicinal plants of Uzbekistan and to identify the most promising strains for further pharmacological studies.

MATERIALS AND METHODS

Cultivation of Endophytes

Endophytic fungal strains were cultivated in Czapek–Dox liquid medium at 28°C for 7 days under shaking conditions (120 rpm). After incubation, the fungal biomass was separated by centrifugation at 6000 rpm and stored at −40°C until further use.

Extraction of Secondary Metabolites

Five grams of wet biomass were homogenized and extracted with 50 mL of ethyl acetate. The mixture was incubated for 24 hours at room temperature with continuous shaking. The extract was filtered, dehydrated using anhydrous sodium sulfate, evaporated under reduced pressure, and dissolved in dimethyl sulfoxide (DMSO) to obtain stock solutions.

Chromogenic Assays

Lipase inhibitory activity was evaluated using agar plates containing olive oil as a substrate and Rhodamine B or phenol red as indicators. The formation of a fluorescent or colored halo indicated lipase activity, while its reduction or absence indicated enzyme inhibition.

Tube Assay

The reaction mixture consisted of pancreatic lipase, fungal extract, and phosphate buffer. After pre-incubation, substrate and indicator were added, and the reaction was monitored by observing color changes.

In Vitro Enzymatic Assay

Lipase activity was quantified using a titrimetric method based on the hydrolysis of olive oil emulsion. Released fatty acids were titrated with NaOH solution, and inhibition percentage was

calculated using standard equations. All experiments were performed in triplicate to ensure reproducibility.

RESULTS

Screening of 15 endophytic fungal strains revealed that the majority of extracts exhibited pancreatic lipase inhibitory activity.

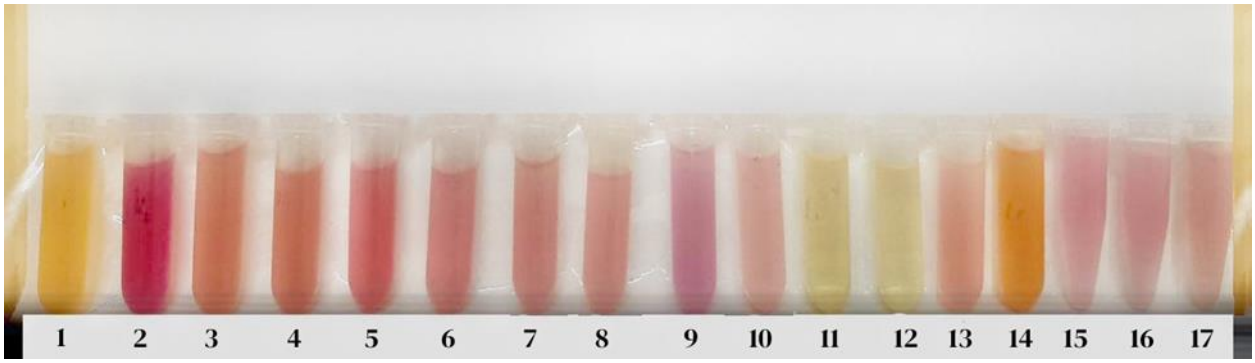


Figure 1. Screening of pancreatic lipase inhibitory activity using the tube assay with phenol red. 1 – control (without extract), 2 – standard substance Xenical. 3- S.minorum -VM83R, 4-U.consortiae - FF155L, 5- Fusarium sp. - AL142R, 6-F. sambcinum - AL135L, 7-C. tenussimum-AF183, 8- A. egypticus - HT166S, 9- M. trigonosporus – 186, 10-A. repens – 202, 11- P. brevicaule alba - CC200, 12-A. roseovolutinum – 170, 13- D. purpureofuscus - HT182, 14-M. verrucaria - HT190R, 15-N. sphaerica - HT189L, 16- A. terreus - AF104S, 17-P. brevicompactum – 171.

Qualitative chromogenic assays showed that:

- 12 strains were active in the Rhodamine B assay
- 11 strains were active in the phenol red assay

Table 1. Level of pancreatic lipase (PL) inhibition by extracts of secondary metabolites of endophytic fungi using phenol red and Rhodamine assays.

№	Endophytic fungi	**Rhodamine**		Phenol red	
		Halo diameter (mm)	% Lipase inhibition	Halo diameter (mm)	% Lipase inhibition
1	*S.minorum -VM83R*	7,4±0,07	53,4±0,23	13±0,22	55,1±0,19
2	*A.terreus - AF104S*	12±0,09	20±0,16	20±0,18	31±0,21
3	*C.tenuissimum - AF183*	8±0,06	46,6±0,17	14±0,14	51,7±0,23
4	*F.sambucinum - AL135L*	7,5±0,07	50±0,13	12±0,2	58,6±0,06
5	*Fusarium sp. - AL142R*	6,5±0,08	**56,6±0,21**	11±0,14	**62±0,14**
6	*U.consortiae - FF155L*	7±0,1	53,4±0,15	14±0,11	51,7±0,12
7	*M.trigonosporus - 186*	12±0,13	20±0,19	21±0,23	27,6±0,21
8	*A.egypticus - HT166S*	14±0,16	6,6±0,24	30±0,17	-
9	*N. sphaerica – HT189L*	14,5±0,12	3,4±0,11	28±0,13	3,2±0,27
10	*D.purpureofuscus - HT182*	16±0,09	-	30±0,26	-
11	*M. verrucaria - HT190R*	9±0,13	40±0,18	16±0,27	44,8±0,07
12	*A.roseovolutinum - 170*	13±0,11	13,4±0,19	26±0,23	10,3±0,08
13	*P.brevicompactum – 171*	14±0,16	6,6±0,18	21±0,17	27,5±0,16
14	*P.brevicaule alba - CC200*	15±0,22	-	30±0,2	-

№	Endophytic fungi	**Rhodamine**		Phenol red	
		Halo diameter (mm)	% Lipase inhibition	Halo diameter (mm)	% Lipase inhibition
15	*A.repens- 202*	15±0,18	-	32±0,09	-
16	Control	15±0,15	0	29±0,1	0
17	Xenical (standard)	6±0,24	60±0,23	10±0,15	65,5±0,21

In both tests, the highest activity, exceeding 50% and comparable to the activity of Xenical (65.5%), was observed in the extracts of the strains ***S. minorum VM83R (55.1%), C. tenuissimum AF183 (51.7%), F. sambucinum AL135L (58.6%), U. consortiae FF155L (51.7%),*** *and* ***Fusarium sp. AL142R (62%).***

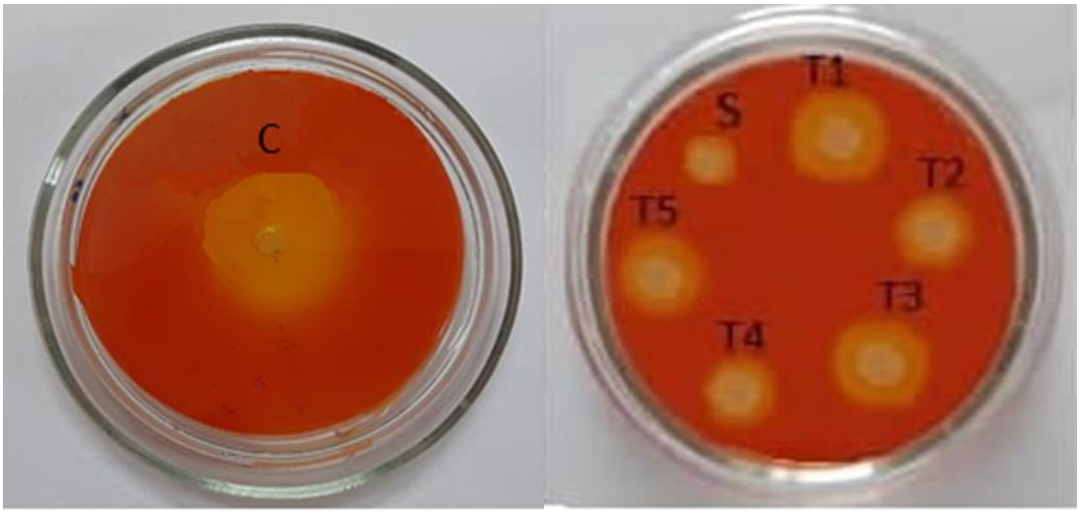


Fig. 2. Lipase inhibition by extracts of the most active endophytes (phenol red indicator). *C – control; T1- C.tenuissimum-AF183; T2–F.sambucinum-AL135L; T3– U.consortiae- FF155L; T4- Fusarium sp.-AL142R; T5-S.minorum -VM83R; S- Xenical (standard)*

The data obtained from the chromogenic plate assays were quantitatively confirmed by direct in vitro hydrolysis of olive oil by pancreatic lipase.

Table 2. Quantitative evaluation of pancreatic lipase inhibitory activity of endophytic fungal extracts using the titrimetric method.

№	Endophytic fungi	% Lipase inhibition
1	*S.minorum - VM83R*	**58,7±0,25**
2	*A.terreus - AF104S*	38,4±0,2
3	*F.sambucinum - AL135L*	**65,2±0,19**
4	*Fusarium sp. - AL142R*	**73,7±0,21**
5	*C. tenuissimum - AF183*	**52,7±0,26**
6	*U.consortiae - FF155L*	**51,7±0,13**
7	*M.trigonosporus - 186*	26,6±0,17
8	*A. egypticus - HT166S*	13,7±0,24
9	*N.sphaerica - HT189L*	3,2±0,16
10	*D.purpureofuscus - HT182*	5,3±0,19
11	*M.verrucaria - HT190R*	44,2±0,12
12	*A. roseovelutinum - 170*	10,6±0,15

13	*P.brevicompactum - 171*	18,2±0,23
14	*P. brevicaule alba - CC200*	-
15	*A. repens - 202*	23,8±0,26
16	Xenical (standard)	**80,5±0,2**

These results indicate that liquid-phase assays provide more accurate estimation of enzyme inhibition due to better interaction between enzyme and bioactive compounds.

DISCUSSION

The present study demonstrates that endophytic fungi isolated from medicinal plants of Uzbekistan possess significant pancreatic lipase inhibitory activity. The observed differences between chromogenic and titrimetric assays can be attributed to diffusion limitations and physicochemical properties of the compounds. The most active strains were isolated from *Allium longicuspis*, a plant closely related to garlic, which is well known for its lipid-lowering and medicinal properties. This suggests a possible correlation between host plant bioactivity and metabolic potential of associated endophytes.

Furthermore, the high inhibitory activity observed in *Fusarium* sp. and *F. sambucinum* indicates that these strains may produce potent bioactive metabolites with therapeutic potential. Similar findings have been reported in previous studies, confirming the role of endophytic fungi as sources of enzyme inhibitors. These results support the hypothesis that endophytic fungi can serve as a valuable resource for the discovery of novel anti-obesity agents.

CONCLUSION

Endophytic fungi associated with medicinal plants of Uzbekistan represent a promising and underexplored source of pancreatic lipase inhibitors. The most active strains demonstrated inhibitory activity comparable to Orlistat, highlighting their potential for further pharmacological and biotechnological applications. Future studies should focus on the isolation, purification, and structural characterization of active compounds, as well as in vivo evaluation of their efficacy and safety.

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AGROPHYSICAL AND AGROCHEMICAL PROPERTIES OF GRAY-MEADOW SOILS IN BOYOVUT DISTRICT, SIRDARYO REGION

O. Toshbekov[1], I.A. Abdurakhmanov[2], I.A. Rakhmonov[3], N. Malikov[4]
Gulistan State University[1,2,3,4]
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Abstract. *This article presents the results of research conducted on the study of agrophysical and agrochemical properties of gray-grassland soils with varying degrees of salinity caused by anthropogenic factors at two observation sites with a total area of 57 hectares in the Bayavud district of the Syrdarya region, Galaba (21 ha) and Navbahor (36 ha), which show that it is necessary to establish effective use of bioameliorants to improve the agrophysical and agrochemical properties of the soil in order to prevent secondary salinization occurring during the season and create favorable conditions for agricultural crops.*

Keywords: *salinity, agrophysical properties, agrochemical properties, bioameliorant, agrotechnical measures.*

Introduction

In recent years, worldwide scientific research has been conducted on priority areas for increasing the fertility of irrigated soils through modern agrotechnologies. In the Decree PF-60 dated January 28, 2022, “On the Strategy for the Development of the New Uzbekistan for 2022–2026” of the President of the Republic of Uzbekistan, necessary strategic tasks aimed at “improving and preserving soil fertility” were outlined. Therefore, modern agrotechnologies are of particular importance for determining the effect of biomeliorants on the agrophysical and agrochemical properties of irrigated soils, their fertility, and the growth, development, and productivity of agricultural crops.

It is well known that in irrigated areas, efficient and rational use of land and water resources, restoration and preservation of soil fertility, and consistent increases in crop yields are among the most pressing contemporary issues. Therefore, it is necessary to implement various agrotechnical and meliorative measures correctly and in a timely manner, to monitor soil properties and its meliorative-ecological condition in detail, and to develop scientifically grounded recommendations based on the collected data [1,3].

Rational use of land resources in agriculture is of great importance, as it is related to increasing yields from irrigated lands and improving their economic efficiency. Restoration, preservation, and enhancement of soil fertility are among the most important tasks we face. Based on the results of research conducted by O. Toshbekov, I. Abdurakhmanov, and others, it can be noted that one of the low-cost methods to reduce soil salinization or prevent secondary salinization is the use of plant resources. In this context, the drought resistance of halophytes, their ability to produce high biomass with nutritional and medicinal properties in saline soils, and their suitability for use in soils with various degrees of salinity and poor agrophysical and agrochemical indicators are particularly important [3,4].

According to E.B. Dedov, phytomelioration of saline soils requires considering the relationship of plants to their environment, their meliorative effect on soil, and their potential use

in agriculture when selecting various life forms of plants (trees, shrubs, perenial grasses) and ecologically specialized crops such as xerophytes, halophytes, halo-xerophytes, mesophytes, hygrophytes, and phreatophytes [2].

Among such plants, licorice (Glycyrrhiza glabra L.) is the most valuable pharmacological raw material. Using licorice as a phytomeliorant has shown its effectiveness in improving the agrophysical and agrochemical properties of soils and increasing the efficiency of irrigation water use. Based on the above information, the aim of this study is to determine the effects of licorice as a biomeliorant on the agrophysical and agrochemical properties of irrigated gray-desert soils with various levels of salinity, and to define agromeliorative measures necessary for enhancing the growth, development, and yield of cultivated crops.

The research was conducted during 2020–2023 in irrigated gray-desert soils with varying degrees of salinity in Boyovut District, Sirdaryo Region, at selected experimental sites (Galaba and Navbahor SIUs). In this area, the content of water-soluble salts in the arable layer and subsoil of gray-desert soils ranges from 0.3–0.9%, and the groundwater level fluctuates around 1.5–2.6 m.

One of the key parameters for increasing the biological productivity of degraded soils is the rapid growth of aboveground and underground plant biomass, which leads to the accumulation of organic residues in the soil. This also improves soil microbiological indicators [5–7]. In our experiments, by the third year of licorice growth, an increase in both aboveground and underground biomass and rapid root system development were observed. These indicators vary depending on the planting period and the level of soil salinity (Tables 1, 2, 3).

Table 1

Effect of planting periods on the formation of aboveground and underground wet biomass of licorice

Planting period	Date of sowing	Stem			Root		
		Weight of 1 stem		**Kg\ ga.**	Weight of 1 root		**Kg\ ga**
		Average	**Difference**		**Average**	**Difference**	
Autumn	25-X1 2019	167	77-215	170 67	510	200-852	193 25
Early spring	15-11-2020	135	63-197	163 20	481	165-660	175 56

Table 2

The effect of soil salinity levels on the growth and development of the above-ground organs of licorice (Glycyrrhiza glabra)

Salinity level	Stem				Lateral branches	
	Amount		Length ,sm		1st type	
					Amount, number	
	Average	Difference	Average	Difference	Average	Difference
	At the end of the first year of the growing season					
Low	1,0	1-1	69,4	51-80	24,4	17-28
	1,3	1-2	84,6	55-102	25,3	14-34
Medium	1,0	1-1	48,7	28-65	22,0	17-29
	1,2	1-2	57,6	41-74	23,1	19-30
At the end of the 3rd year of the growing season						

Low	2,6	2-4	117,4	110-140	29,2	22-39
	3,2	2-6	171,8	141-183	26,2	24-31
Medium	2,4	1-5	88,0	70-89	28,0	22-34
	2,2	2-3	91,2	67-95	27,4	24-35

Table 3

Effect of soil salinity level on the fresh root mass of licorice plants

Salinity level	Seedling density at the end of the growing season, pcs/ha	Root mass		
		One root mass,gr		**Kg\ ga**
		Average	**Difference**	
Medium	25380	397	220-540	10076
	40572	650	290-1100	26372
High	12429	257	200-370	3194
	25454	321	160-670	8171

The licorice plant (Glycyrrhiza glabra) promotes the accumulation of organic matter in soil layers due to the rapid growth of its root system. This, in turn, has a positive effect on the agrophysical and agrochemical properties of the soil.

In fields planted with licorice, it was observed that the fertility level of the top one meter of soil increased, which subsequently improved the overall physical properties of the soil. The results indicate that in fields with weakly and moderately saline soils, from the third year after planting licorice, the physical properties of the soil in areas where plant roots spread improved. Specifically, soil compaction decreased, and the total porosity was maintained in a condition favorable for plant growth (Tables 4–5).

It is known that in fields planted with cotton and cereals, soil compaction in the top layers sharply increases by autumn, and total porosity decreases. Based on these observations, it can be concluded that licorice positively influences the optimization of soil agrophysical properties.

Table 4

Dynamics of agrophysical indicators of soils planted with licorice (Glycyrrhiza glabra) (Boyovut District, "Galaba SIU")

Layer depth, cm	Soil solid fraction density, g/cm³		Soil bulk density, g/cm³		Total porosity, %	
	2020	2023	2020	2023	2020	2023
0-28	2,76	2,72	1,45	1,36	48,0	50,0
28-46	2,76	2,72	1,47	1,37	47,0	50,0
46-92	2,77	2,73	1,43	1,37	49,0	50,0
92-144	2,77	2,74	1,44	1,40	48,0	49,0
144-178	2,77	2,74	1,44	1,42	48,0	48,0
178-205	2,77	2,75	1,44	1,42	48,0	48,0

Table 5

Dynamics of agro-physical indicators of soils in fields planted with licorice (Glycyrrhiza glabra) (Boyovut District, "Navbahor SIU")

Layer depth, cm	Soil solid particle density, g/cm³		Soil bulk density, g/cm³		Total soil porosity, %	
	2020	2023	2020	2023	2020	2023

0-28	2,76	2,72	1,44	1,34	48	51
28-46	2,76	2,72	1,46	1,36	47	50
46-92	2,77	2,73	1,42	1,38	49	50
92-144	2,77	2,74	1,42	1,39	49	49
144-178	2,77	2,74	1,42	1,40	49	49

Thus, during the study, in the third year in fields planted with licorice, soil density decreased compared to the initial year by 0.10 g/cm³ in the 0–28 cm layer and by an average of 0.04 g/cm³ in the layer up to one meter. Correspondingly, the total soil porosity increased by 2–3% (Tables 4–5).

Analyzing the agrochemical indicators of the experimental field soils, by autumn 2023, in areas where the plant roots had spread, an increase in humus and nitrogen content was observed, while the mobile phosphorus and potassium content slightly decreased (Tables 6–7).

Table 6

Agrochemical indicators of soils in fields planted with licorice (Glycyrrhiza glabra) (Boyovut District, "Galaba SIU")

Layer depth, cm	Content of nutrient elements							
	Humus content, %		N, mg/kg		P_2O_5, mg/kg		K_2O, mg/kg	
	2020	2023	2020	2023	2020	2023	2020	2023
0-15	0,95	1,02	37	48	17,2	16.0	144	127
15-50	0,85	0,90	35	42	18,6	15,4	138	122
50-100	0,52	0,64	28	32	10,8	9.87	115	110

Table 7

Agrochemical indicators of soils in fields planted with licorice (Glycyrrhiza glabra) (Boyovut district, Navbahor SIU) 2020

Layer depth, cm	Content of nutrient elements							
	Humus content, %		N, mg/kg		P_2O_5, mg/kg		K_2O, mg/kg	
	2020	2023	2020	2023	2020	2023	2020	2023
0-15	0,87	1,12	28	44	18,4	15.3	128	117
15-50	0,75	0,99	32	43	16,6	14,4	118	102
50-100	0,46	0,54	21	25	11,8	10,5	120	108

Conclusion

Based on the above information, it can be concluded that the licorice plant (Glycyrrhiza glabra), by producing a large amount of aboveground and underground biomass, has a positive effect on the agro-physical and agrochemical properties of slightly and moderately saline gray-meadow soils, demonstrating its phytomeliorative significance. Therefore, we recommend the use of licorice (Glycyrrhiza glabra) as a phytomeliorant to improve the agromeliorative condition of irrigated soils with varying degrees of salinity and to increase both the yield and quality of crops.

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ROOTING ABILITY OF GOLDEN CURRANT CUTTINGS DEPENDING ON CUTTING DIAMETER AND PLANTING SCHEME

B.T. Ibragimov
Agronomist at Bukhara Scientific Experimental Station
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Abstract. *This article studies the effect of planting schemes and cutting diameter on the rooting rate of golden currant (Ribes aureum) seedlings during propagation. During the research, experiments were carried out using different planting schemes (60×10 cm, 60×15 cm, 70×10 cm, and 70×15 cm) as well as different cutting diameters (3–4 mm, 5–6 mm, 7–8 mm, and 9–10 mm). According to the results of three years of observations, the highest indicator was recorded when using a 70×10 cm planting scheme and cuttings with a diameter of 5–6 mm.*

Keywords: *golden currant, seedling cultivation, cutting diameter, planting scheme, survival rate, rooting, agricultural techniques, propagation technology.*

Introduction

It is important to suggest that golden currant is among the plants of great importance due to its high nutritional value, medicinal properties, and productivity. In particular, currant varieties stand out for their adaptability to the soil and climatic conditions of Bukhara region and their high yield potential. Therefore, improving the technologies for its propagation is considered one of the important and relevant issues today.

Materials and Methods

When propagating golden currant seedlings, the planting scheme and the diameter of cuttings are considered important factors. These two factors influence not only the rooting rate, but also the quality development of seedlings in the future. The results of the experiment clearly demonstrated the relationship between these factors. According to the results of our experiment, the rooting ability of cuttings depending on their diameter and planting scheme was studied. In the 70×10 cm control planting scheme, 100 cuttings with a diameter of 7-8 mm were planted, and the average rooting indicators were determined differently across the years.

These indicators were determined as 59.5% in 2023, 65.7% in 2024, and 69.8% in 2025, with a three-year average of 65.0%. In the 60×10 cm planting scheme, due to the dense placement of cuttings, competition among plants increased. As a result, the rooting rate of the cuttings was relatively low. According to the results for the thinnest cuttings (3–4 mm), the rooting rate reached 48.5% in 2023, 53.6% in 2024, and 56.9% in 2025, with a three-year average of 53.0%.

For the slightly thicker cuttings (5–6 mm), the rooting rate was 64.5% in 2023, 71.3% in 2024, and 75.7% in 2025, reaching an average of 70.5%. For medium-thickness cuttings (7–8 mm), the indicator was 50.4% in 2023, 59.2% in 2024, and 55.1% in 2025. However, in the thickest cuttings (9–10 mm), the rooting rate was 50.2% in 2023, 55.5% in 2024, and 59.0% in 2025, with an average level of about 54.9%. Thus, under dense planting conditions, cuttings with a larger diameter adapt to rooting with greater difficulty, and the results decrease.

Results and Discussion

According to the experiment, the 60×15 cm planting scheme provided better roo ting results because the plants had a larger nutrition area. The average rooting rate was 57.8% for cuttings with a diameter of 3–4 mm, 79.9% for 5–6 mm, and 64.9% for 7–8 mm. Even the largest cuttings (9–10 mm) showed a result of 60.6%. The 70×10 cm scheme produced the highest indicators in the experiment. Since this scheme ensured an optimal placement of cuttings, the competition between plants occurred at a normal level. As a result, the average rooting rate was 67.3% for cuttings with a diameter of 3–4 mm, 84.8% for 5–6 mm, and 54.3% for 9–10 mm. It is evident that this scheme ensured the highest level of rooting and survival of the cuttings.

In the 70×15 cm planting scheme, although the results were close to the control variant, slightly lower indicators were recorded. For example, the rooting rate was 68.3% for 3–4 mm cuttings, 77.4% for 5–6 mm, 63.6% for 7–8 mm, and 58.4% for 9–10 mm. This situation shows that excessively sparse planting can also create certain disadvantages. Overall analysis demonstrated that the most optimal results for golden currant seedlings were observed with the 70×10 cm planting scheme, especially when using cuttings with a diameter of 5–6 mm. Under very dense planting conditions, cuttings develop poorly due to strong competition, while in overly sparse planting the optimal balance of soil moisture and nutrition may be disrupted. Therefore, selecting the correct planting scheme and cutting diameter is one of the key factors for achieving high productivity in seedling cultivation (Table 1).

Effect of Cutting Thickness and Different Planting Schemes on the Rooting of Golden Currant Cuttings, % (2023–2025)

№	Planting Scheme, cm	Cutting Diameter, mm	Number of Cuttings Planted, pcs				
				2023 y	2024 y	2025 y	Average Rooting Rate of Cuttings, %
1	70x10 (назорат)	7-8	100	59,5	65,7	69,8	65,0
2	60x10	3-4	100	48,5	53,6	56,9	53,0
		5-6	100	64,5	71,3	75,7	70,5
		7-8	100	50,4	55,7	59,2	55,1
		9-10	100	50,2	55,5	59,0	54,9
3	60x15	3-4	100	52,8	58,4	62,0	57,8
		5-6	100	73,1	80,7	85,8	79,9
		7-8	100	59,4	65,6	69,7	64,9
		9-10	100	55,5	61,3	65,1	60,6
4	70x10	3-4	100	61,6	68,1	72,3	67,3
		5-6	100	77,6	85,7	91,1	84,8
		9-10	100	49,7	54,9	58,4	54,3
5	70x15	3-4	100	62,5	69,1	73,4	68,3
		5-6	100	70,9	78,3	83,2	77,4
		7-8	100	58,2	64,3	68,3	63,6

		9-10	100	53,4	59,1	62,7	58,4
RC05=				*1,59*	*1,8*	*1,01*	*0,91*
RC%=				*2,7*	*2,7*	*1,5*	*1,4*

Conclusion

As a result of the conducted research, it was determined that the planting scheme and cutting diameter are important agronomic factors in the propagation of golden currant cuttings. According to the experimental results, the highest rooting rate was recorded when using a 70×10 cm planting scheme and cuttings with a diameter of 5–6 mm. Very dense planting leads to strong competition between plants, which reduces the rooting rate. Conversely, excessively sparse planting can disrupt the balance of soil moisture and nutrient availability.

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IDENTIFICATION AND SCIENTIFIC JUSTIFICATION OF EFFECTIVE BIOTECHNOLOGICAL APPROACHES FOR ZOOPLANKTON CULTIVATION

A.T. Irisoliyev[1], A.F. Khikmatullayev[1], M.M. Egamova[2], D.R. Dekhkonova[3]
Student, Tashkent State Agrarian University[1]
Teacher of the Department of General Education Subjects, Technical School No. 4, Uzbekistan District[2] Senior Lecturer, PhD (Biological Sciences), Tashkent State Agrarian University[3]
https://doi.org/10.5281/zenodo.19363952

Abstract. *This study identifies effective biotechnological approaches for zooplankton cultivation and evaluates their biological efficiency. The research was conducted under laboratory conditions, focusing on zooplankton biomass growth dynamics, the influence of abiotic factors (temperature, pH, and dissolved oxygen), as well as feeding and cultivation technologies. The results demonstrated that zooplankton development follows a sigmoidal growth pattern, with maximum biomass observed during the exponential and peak phases. Optimal environmental conditions (22–26°C, pH 7.0–8.5, and dissolved oxygen >5 mg/L) were found to significantly enhance biomass production and survival rates. Microalgae-based feeding provided the highest biological efficiency, while mixed feeding ensured stable and consistent results. Intensive cultivation technologies showed a clear advantage in biomass productivity compared to other methods ($p < 0.01$). Based on the findings, an integrated biotechnological model was proposed, which serves as a scientific basis for improving the efficiency of zooplankton production in aquaculture systems.*

Keywords. *Zooplankton, aquaculture, biomass dynamics, microalgae, abiotic factors, intensive technology, live feed, biotechnological approaches, survival rate, growth rate*

Introduction.

Achieving high productivity in modern aquaculture systems largely depends on the availability of high-quality and nutritionally rich live feed. Zooplankton serves as a primary food source for fish larvae and juveniles, and its nutritional value is determined by the presence of biologically active compounds, including proteins, essential fatty acids (EPA, DHA), and vitamins [7,1]. Therefore, the development and optimization of zooplankton cultivation technologies remain a critical aspect of sustainable aquaculture.

In recent years, the global expansion of aquaculture production has significantly increased the demand for live feed resources. However, traditional zooplankton cultivation methods often fail to ensure stable and high productivity due to inadequate feeding strategies, fluctuations in abiotic conditions, and insufficient technological control [5]. These limitations highlight the need for more efficient and scientifically grounded cultivation approaches.

Contemporary research emphasizes the importance of biotechnological strategies in improving zooplankton production systems. In particular, microalgae-based feeding has been identified as an effective approach to enhance zooplankton growth and nutritional quality. Microalgae not only serve as a primary food source but also represent an environmentally sustainable and economically viable component in aquaculture systems [1,10,6].

Furthermore, the optimization of abiotic factors such as temperature, pH, and dissolved oxygen, along with the application of intensive and semi-intensive cultivation technologies, has

been shown to significantly improve zooplankton productivity [2,7,1]. Despite these advances, the combined effects of these approaches and their optimal integration have not been sufficiently studied in a systematic manner.

Moreover, the simultaneous assessment of biological and economic efficiency in zooplankton cultivation remains a relevant scientific and practical challenge. In modern aquaculture, it is essential not only to maximize biomass production but also to minimize production costs and ensure sustainability. Therefore, the present study aims to identify effective biotechnological approaches for zooplankton cultivation, evaluate their biological and economic efficiency, and scientifically justify their optimal integration into a comprehensive cultivation model.

Materials and Methods

The study was conducted under controlled laboratory conditions. The experimental objects included commonly used zooplankton groups in aquaculture, namely rotifers (*Brachionus* sp.), cladocerans (*Daphnia* sp.), and copepods. The experiments were carried out in artificial aquatic environments under continuous aeration and monitoring systems for a period of 15 days. Each experimental treatment was performed in triplicate (n = 3) to ensure the reliability of the results. To evaluate the efficiency of different biotechnological approaches in zooplankton cultivation, the following experimental treatments were established:

1. Microalgae-based feeding (Treatment I) Zooplankton were fed with suspensions of microalgae (*Chlorella* and *Scenedesmus*).

2. Mixed feeding (Treatment II) A combination of microalgae and artificial feed (organic-rich suspension) was applied.

3. Artificial feeding (Treatment III) Zooplankton were cultured exclusively using artificial feed.

4. Intensive cultivation system (Treatment IV) In addition to feeding, abiotic factors (temperature, pH, and dissolved oxygen) were strictly controlled.

5. Extensive cultivation system (Treatment V) Zooplankton were cultured under near-natural conditions with minimal environmental control.

2.3. Measurement and Analytical Methods

During the experiment, the following parameters were measured:

Biomass (mg/L) — determined using the gravimetric method

Growth rate (mg/L/day) — calculated based on changes in biomass over time

Survival rate (%) — estimated as the proportion of live individuals

Abiotic factors — measured using a thermometer (temperature), pH meter, and dissolved oxygen meter

Laboratory experiments were conducted over a 15-day period, during which biomass (mg/L), growth rate (mg/L/day), and survival rate (%) were measured at regular intervals. Statistical analysis was performed using Student's *t*-test, and the results were expressed as mean ± standard error (M ± m).

RESULTS AND DISCUSSION

The results of the study demonstrated that zooplankton biomass growth follows distinct biological patterns. The growth process consisted of four main phases: lag phase, exponential growth, peak (maximum) phase, and regression phase. The highest biomass values were recorded during the exponential and peak phases, which are considered optimal for zooplankton cultivation.

Dynamics of Zooplankton Biomass Growth

Table 1. Biomass Growth Dynamics

Day	Biomass (mg/L)	Standard deviation (±)	Growth phase
1	0.9	0.1	Lag phase
3	2.7	0.3	Exponential growth
5	3.5	0.4	Exponential growth
7	5.8	0.5	Maximum growth
10	7.2	0.6	Peak phase
12	5.1	0.4	Stabilization
15	4.4	0.3	Regression

As shown in the table, biomass reaches its maximum between days 7 and 10. After day 10, a regression phase begins due to nutrient depletion and changes in environmental conditions (table1, figure1)

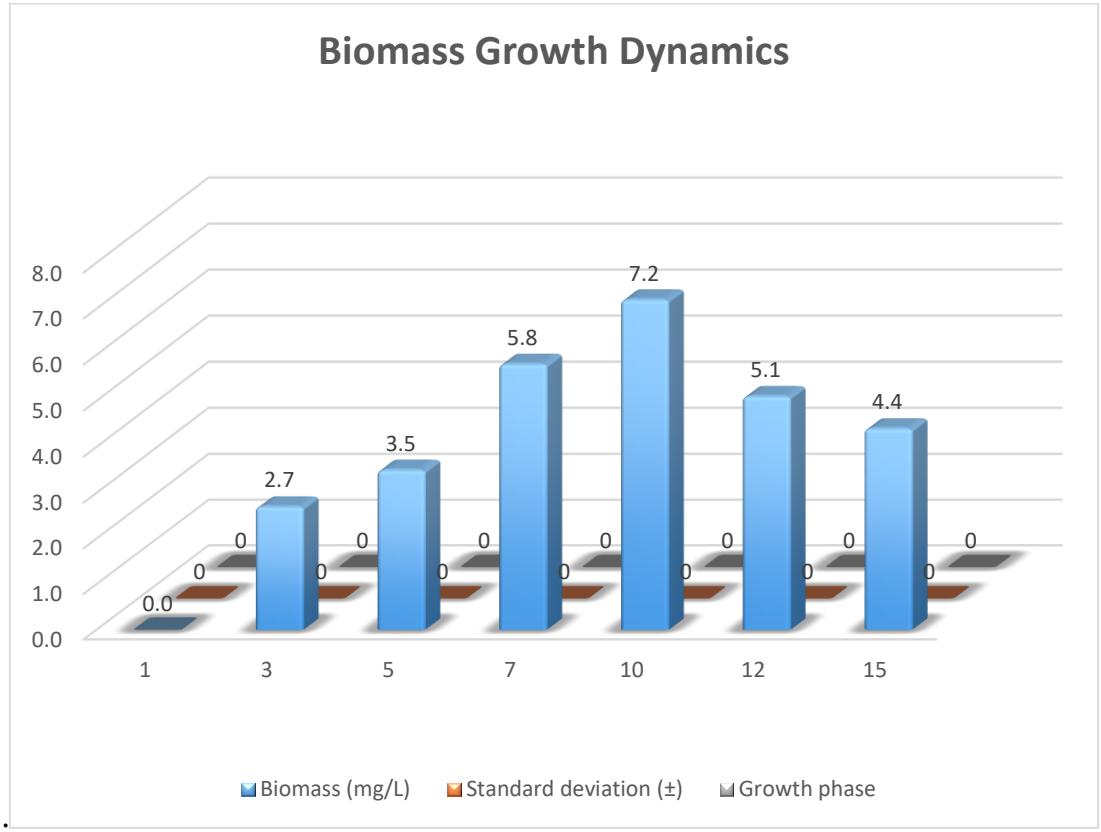


Figure 1. Dynamics of zooplankton biomass growth

This graph clearly indicates the optimal harvesting period in zooplankton cultivation.

Influence of Abiotic Factors

Table 2. Effect of Abiotic Factors

Factor	Range	Biomass (mg/L)	Effect
Temperature	22–26°C	6.8	Optimal
Temperature	18–20°C	3.2	Low
pH	7.0–8.5	6.2	Optimal
pH	<6.5	3.5	Negative
Dissolved O_2	>5 mg/L	6.5	High
Dissolved O_2	<3 mg/L	2.9	Negative

Under optimal conditions, zooplankton biomass increased up to twofold. Oxygen deficiency (hypoxia) was identified as the most critical limiting factor. (table 2, figure 2)

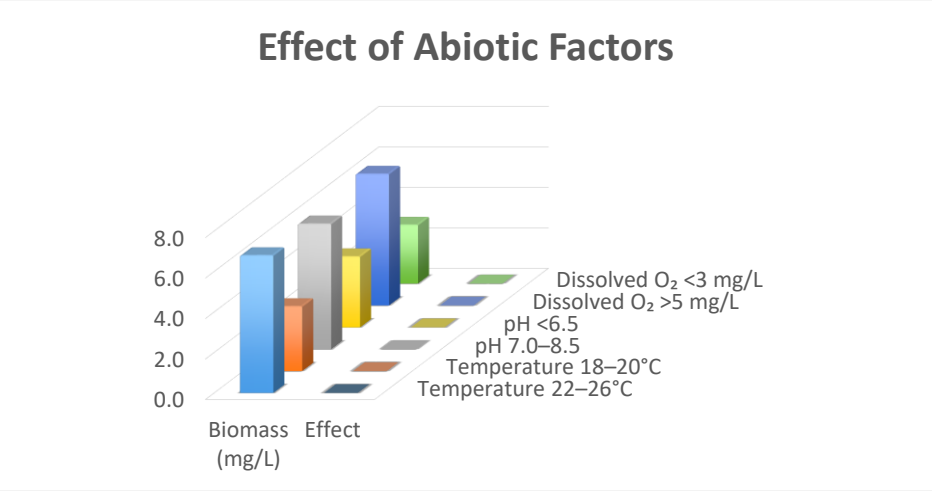


Figure 2. Effects of abiotic factors (temperature, pH, and dissolved oxygen) on zooplankton growth and biomass

Comparison of Feeding Methods

Table 3. Feeding Efficiency

Method	Biomass (mg/L)	Growth rate (mg/L/day)	Survival (%)
Microalgae	7.5	0.8	92
Mixed	6.1	0.6	85
Artificial	4.2	0.4	78

The comparative analysis of feeding methods showed that microalgae-based feeding provides the highest biological efficiency. This is due to the high nutritional value of microalgae, including proteins, essential fatty acids, and vitamins. As a result, metabolic processes are enhanced, leading to maximum biomass and survival rates. Mixed feeding (microalgae + artificial feed) produced moderate but stable results. This approach maintains nutritional balance and supports relatively stable population development under varying conditions, making it a practical and economically viable option. Artificial feeding showed the lowest biological efficiency. This is associated with the lack of bioactive components characteristic of natural food sources, resulting in reduced growth rates and survival (table 3, figure3).

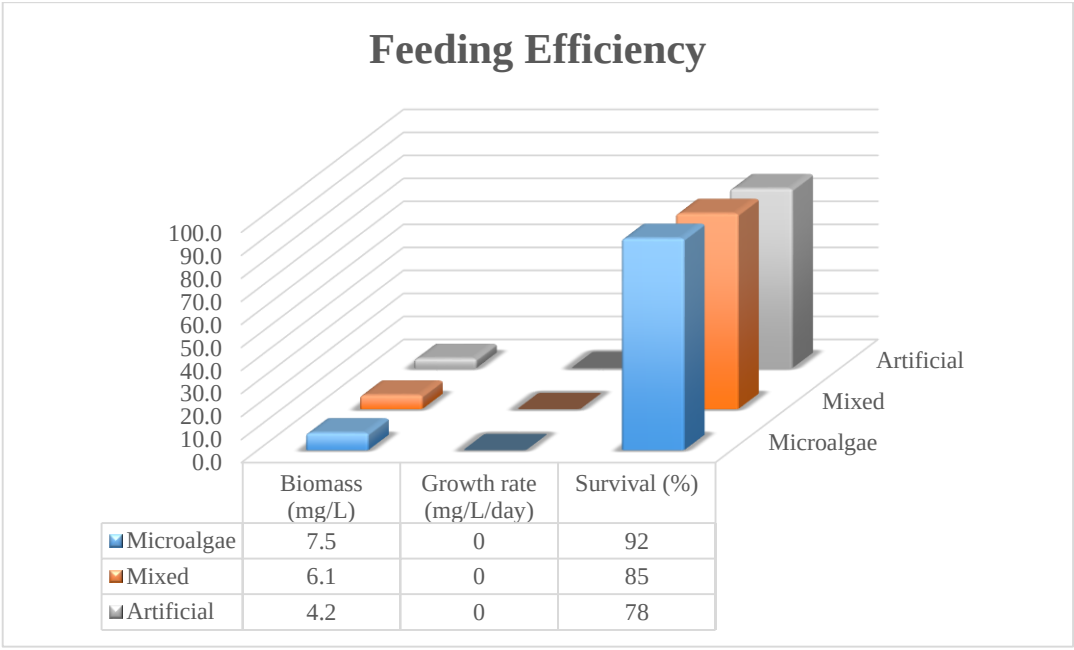


Figure 3. Feeding efficiency in zooplankton cultivation

Analysis of Intensive and Extensive Systems

Table 4. Comparison of Cultivation Systems

Indicator	Intensive	Extensive
Biomass (mg/L)	8.2	4.6
Growth rate	0.9	0.5
Survival (%)	94	80

The intensive cultivation system demonstrated superior performance compared to the extensive system across all evaluated parameters. Specifically, it produced 1.5–2 times higher biomass and exhibited significantly higher survival rates. Statistical analysis confirmed that these differences were significant ($p < 0.01$), indicating the reliability and effectiveness of the intensive approach. The results demonstrated that although individual biotechnological approaches provide certain benefits, maximum biological and economic efficiency can only be achieved through their integrated application. Microalgae-based feeding serves as the primary energy and nutrient source. Optimization of abiotic factors (temperature, pH, dissolved oxygen) stabilizes metabolic processes. Intensive technologies enable process control and maximize biomass production. Based on these findings, an optimal biotechnological model for zooplankton cultivation was developed and scientifically justified (table 4).

4. Table. Components of the Biotechnological Model

Component	Main function	Effect on outcome
Microalgae	Food source	Biomass ↑↑
Abiotic control	Environmental optimization	Survival ↑
Intensive technology	Process control	Growth rate ↑↑
Mixed feeding	Stability	Stable results

Although each component plays an important role individually, their combination ensures maximum efficiency. The information illustrates that microalgae-based feeding, abiotic optimization, and intensive cultivation technologies form a sequential and interconnected system. The integration of these components leads to increased biomass, higher survival rates, and improved overall biological efficiency. This model demonstrates the superiority of a complex biotechnological approach and provides a scientifically grounded framework for achieving high productivity in aquaculture systems. The results confirm that zooplankton biomass growth follows a sigmoidal pattern, which is consistent with previous studies [7]. The influence of abiotic factors highlights the critical role of temperature, pH, and dissolved oxygen in zooplankton development, as also reported by Boyd [1]. The superiority of microalgae-based feeding confirms its role as an optimal food source [8,9]. Furthermore, the advantages of intensive systems in increasing biomass production align with modern aquaculture practices [5,11,12].

Conclusion. The present study identified effective biotechnological approaches for zooplankton cultivation and provided their scientific justification. The results demonstrated that microalgae-based feeding and intensive cultivation technologies ensure high biological efficiency, while the optimization of abiotic factors enhances the stability of the overall cultivation process. Therefore, the application of an integrated approach to zooplankton production can significantly improve productivity and economic efficiency in aquaculture systems.

Furthermore, this study was aimed at the comprehensive evaluation of the biological efficiency of biotechnological approaches used in zooplankton cultivation and the development of an integrated model. The obtained results confirmed that zooplankton biomass growth follows a sigmoidal pattern, progressing through lag, exponential, peak, and regression phases, which is

consistent with previous studies [7,9]. The analysis of abiotic factors once again highlighted their decisive role in zooplankton development. In particular, optimal conditions—temperature (22–26°C), pH (7.0–8.5), and dissolved oxygen (>5 mg/L)—significantly increased both biomass and survival rates, indicating that environmental stability is a key factor in successful zooplankton cultivation. Comparative analysis of feeding strategies revealed that microalgae-based feeding maximizes metabolic activity and growth performance in zooplankton. These findings are consistent with recent studies, confirming that microalgae represent an optimal and natural food source [11]. At the same time, mixed feeding systems were identified as a practical and stable alternative under applied conditions. The comparison of intensive and extensive cultivation systems demonstrated that intensive technologies increase biomass productivity by 1.5–2 times through improved control and resource optimization. These differences were statistically significant ($p < 0.01$), providing strong evidence for the superiority of controlled cultivation systems. The most significant outcome of this study is the development of an integrated biotechnological model for zooplankton cultivation. This model combines microalgae-based feeding, abiotic factor optimization, and intensive cultivation technologies to achieve maximum biomass production, high survival rates, and stable yields. It can be considered a scientifically grounded conceptual framework for optimizing live feed production in modern aquaculture systems. Overall, the findings indicate that integrated biotechnological approaches are significantly more effective than individual methods. Their application contributes to increased productivity, efficient resource utilization, and improved economic performance in aquaculture.

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ENDOPHYTIC BACTERIA FROM *PLANTAGO LANCEOLATA*: PLANT GROWTH-PROMOTING TRAITS AND ANTIFUNGAL ACTIVITY AGAINST *FUSARIUM SOLANI*

Shakhlo Urmonalieva[1]
[1]National University of Uzbekistan, 100174 Tashkent, Uzbekistan;

Abstract. *The present study aimed to isolate, identify, and evaluate the plant growth-promoting and biocontrol potential of endophytic bacteria associated with the medicinal plant Plantago lanceolata L. Endophytic bacterial isolates were screened for antagonistic activity against Fusarium solani, phosphate and zinc solubilization, hydrogen cyanide (HCN) production, ACC deaminase activity, and hydrolytic enzyme production. Molecular identification of the selected isolates was performed using 16S rRNA gene sequencing followed by phylogenetic analysis. The selected strains were identified as Bacillus cereus, Bacillus paramycoides, Bacillus velezensis, Brevibacillus brevis, Brevibacillus formosus, and Pseudomonas moraviensis. Antifungal assays demonstrated strong inhibitory activity against Fusarium solani, with inhibition zones ranging from* ***20 to 36 mm,*** *and the highest activity observed for isolates* ***ZI-12 (36 mm)*** *and* ***ZI-14 (32 mm)****. Among the identified bacteria, Bacillus velezensis exhibited the highest phosphate and zinc solubilization capacity, the strongest HCN production (0.073 ± 0.003 OD), and high ACC deaminase activity (15.95 μmol α-KB mg protein^{-1} h^{-1}), while Pseudomonas moraviensis showed the highest ACC deaminase activity (16.26 μmol α-KB mg protein^{-1} h^{-1}). All selected isolates produced hydrolytic enzymes, including chitinase, protease, and amylase, although their activities differed among species. These findings indicate that endophytic bacteria associated with Plantago lanceolata possess multiple plant growth-promoting and biocontrol characteristics and represent promising candidates for the development of environmentally friendly microbial bioinoculants for sustainable agriculture.*

Keywords: *Plantago lanceolata; endophytic bacteria; plant growth-promoting bacteria (PGPB); 16S rRNA gene sequencing; Bacillus velezensis; Pseudomonas moraviensis; phosphate solubilization; zinc solubilization; ACC deaminase; hydrogen cyanide (HCN); antifungal activity; Fusarium solani; bioinoculants; sustainable agriculture.*

1. Literature Review

The increasing demand for environmentally sustainable agricultural practices has intensified interest in plant-associated beneficial microorganisms as alternatives to chemical fertilizers and pesticides. Among these microorganisms, endophytic bacteria have received considerable attention because they colonize internal plant tissues without causing disease while enhancing plant growth, nutrient acquisition, and resistance to biotic and abiotic stresses. Compared with rhizospheric microorganisms, endophytes maintain a closer association with their host plants, enabling long-term beneficial interactions and efficient delivery of plant growth-promoting compounds (Sherzad et al., 2025; Rani et al., 2022).

One of the principal mechanisms by which endophytic bacteria stimulate plant development is the production of phytohormones. Many bacterial species synthesize indole-3-acetic acid (IAA), gibberellins (GA_3), cytokinins, and other signaling molecules that regulate root

elongation, cell division, seed germination, and nutrient uptake. In addition, numerous endophytes possess ACC deaminase activity, which lowers stress-induced ethylene levels in plants and consequently improves tolerance to salinity, drought, and heavy-metal toxicity. These physiological functions make endophytic bacteria promising candidates for microbial biofertilizer development (Woo et al., 2023; Kumar et al., 2016).

Besides hormone production, beneficial endophytic bacteria contribute to plant nutrition through phosphate and zinc solubilization. Although soils often contain abundant phosphorus and zinc, these elements frequently occur in insoluble mineral forms that cannot be directly absorbed by plants. Bacteria belonging to the genera *Bacillus*, *Pseudomonas*, *Paenibacillus*, and *Brevibacillus* release organic acids and phosphatase enzymes capable of converting insoluble compounds into plant-available forms. This process increases nutrient uptake, enhances plant growth, and reduces the dependence on synthetic fertilizers (Gupta et al., 2024).

Another important characteristic of endophytic bacteria is their ability to suppress phytopathogenic microorganisms through several complementary mechanisms. Numerous isolates produce hydrolytic enzymes such as chitinase, cellulase, protease, amylase, and β-1,3-glucanase, which degrade fungal cell walls and inhibit pathogen development. In addition, the production of siderophores, hydrogen cyanide (HCN), antibiotics, and lipopeptides further enhances their antagonistic activity against economically important pathogens, including *Fusarium*, *Rhizoctonia*, and *Alternaria* species. Consequently, endophytic bacteria are increasingly recognized as environmentally friendly biological control agents (Riseh et al., 2024; Drożdżyński et al., 2024).

Medicinal plants are considered particularly valuable reservoirs of diverse endophytic microorganisms because they contain numerous secondary metabolites that influence microbial colonization and community composition. Among medicinal plants, *Plantago lanceolata* has attracted considerable scientific attention owing to its anti-inflammatory, antimicrobial, antioxidant, and wound-healing properties. The plant contains iridoid glycosides, flavonoids, phenolic acids, tannins, and polysaccharides, which contribute to both its medicinal value and the establishment of specialized endophytic microbial communities (Pol et al., 2021; Laanet et al., 2024; de Souza et al., 2024).

Several studies have investigated the diversity of endophytic bacteria associated with medicinal plants. Vendan et al. (2010) isolated 51 bacterial endophytes from *Panax ginseng* and demonstrated that many isolates produced IAA, solubilized phosphate, and promoted plant growth. Kumar et al. (2016) reported similar observations in *Curcuma longa*, where bacterial endophytes significantly enhanced seedling growth through multiple plant growth-promoting mechanisms. Krimi et al. (2016) isolated *Bacillus* and *Pseudomonas* strains from *Plantago* species and demonstrated their antagonistic activity against *Agrobacterium* and *Pectobacterium*, together with growth-promoting effects in tomato plants.

The rapid development of molecular biology has substantially improved the characterization of beneficial microorganisms. Sequencing of the 16S rRNA gene has become the standard method for bacterial identification because it enables accurate taxonomic classification, comparison with international databases, and reconstruction of phylogenetic relationships. Molecular identification provides a reliable basis for selecting elite bacterial strains with multiple beneficial characteristics suitable for agricultural and biotechnological applications (Abbas et al., 2024).

Despite the growing number of studies on endophytic bacteria associated with medicinal plants, comprehensive information regarding the diversity, molecular identity, multifunctional

plant growth-promoting traits, and biocontrol potential of endophytic bacteria inhabiting *Plantago lanceolata* under the environmental conditions of Uzbekistan remains limited. In particular, studies integrating molecular identification, phytohormone production, phosphate and zinc solubilization, ACC deaminase activity, hydrolytic enzyme production, hydrogen cyanide synthesis, and antifungal activity within a single investigation are still lacking.

Therefore, the present study aimed to isolate endophytic bacteria from different tissues of *Plantago lanceolata*, identify the most promising isolates by 16S rRNA gene sequencing, and comprehensively evaluate their plant growth-promoting and biocontrol characteristics. The results are expected to contribute to the development of effective microbial bioinoculants for sustainable agricultural production.

2.1. Determination of the antifungal activity of endophytic bacteria of the medicinal plant (*Plantago lanceolata* L.)

In vitro double-culture tests were performed for all isolated bacterial strains. This test was performed on Waxman agar (D-glucose 7 g·L−1, D-fructose 7 g·L−1, bacteriological agar 15 g·L−1, bacteriological peptone 5 g·L−1, meat extract 5 g·L−1) adapted for mold growth. After sterilization, the following substances were added: KH2PO4 3.92 μM, NaCl 4.02 μM, KCl 1.8 μM, CaCl2 100 μM, MgCl2 134 μM, H3BO3 5 μM, L-ascorbic acid 850 μM, Al2(SO4)3 0.95 μM, K2SO4 0.95 μM, and CuSO4 0.25 μM. The antifungal activity of the isolated endophytic bacteria was tested against one fungal species (Fusarium solani). To assess the antagonistic effect of different live bacteria, mycelial fragments from the edge of an actively growing fungal culture were placed in the center of a Petri dish with agar. On these plates, four bacterial isolates were inoculated in the form of stripes at equal distances from the fungal inoculum. Fungal plates without bacteria were used as controls. The plates were incubated at 28 °C for 72 h and the inhibitory activity of the bacteria against the growth of the fungus was assessed. The inhibition zones were calculated using the following formula: % growth inhibition = ((C − T)/C) × 100, where C is the radial growth of the pathogen in the control plates (mm) and T is the radial growth of the pathogen in the test plates (mm). The experiment was repeated three times (Lovecká et al., 2023, Abdusamatov et al., 2025).

2.2. DNA extraction, PCR-based fingerprinting and molecular identification

Endophytic bacteria were incubated on Tryptone Soy Agar medium at 37°C for 24 hours. A small portion of bacterial biomass from clean colonies was transferred to a sterile 1.5 ml microcentrifuge tube. DNA was isolated using the Ezup column bacterial genomic DNA isolation kit according to the manufacturer's instructions. The sample was mixed with 200 μL of digestion buffer and 20 μL of Proteinase K and incubated in a 56°C water bath for 30–60 minutes. Then, 200 μL of BD buffer and 200 μL of anhydrous ethanol were added, the solution was transferred to a DNA adsorption column and centrifuged at 10,000 rpm for 1 minute. The column was washed sequentially with PW solution and washing solution, and the DNA was eluted in 50 μL of TE buffer. The obtained DNA was stored at -20°C.

A partial fragment of the 16S rRNA gene (v3–v4 region) of the isolated DNA was amplified by polymerase chain reaction (PCR) using universal primers 27F (5′-AGAGTTTGATCCTGGCTCAG-3′) and 1492R (5′-TACGGYTACCTTGTTACGACTT-3′). The PCR reaction volume was 25 μL and the following contents were prepared: 12.5 μL OneTaq 2x Master Mix, 50 ng DNA template, each primer at 10 μM concentration and the remaining volume was filled with sterile nuclease-free water. Amplification was performed in a BioRad T100 thermocycler under the following conditions: initial denaturation at 94˚C for 5 min, followed by

35 cycles of 30 s denaturation at 94˚C, 35 s annealing at 55˚C and 1 min extension at 72˚C, and a final extension at 72˚C for 1 min. The final extension was at 72°C for 8 min. The resulting PCR products were confirmed by 1% agarose gel electrophoresis. The PCR products were purified using commercial kits. The purified PCR products were prepared for sequencing using BigDye Terminator v3.1 reagents (Dos Santos et al., 2019).

Equipment and reagents:

Equipment: ABI 3730XL DNA sequencing machine (Applied Biosystems, USA), PCR thermocycler (BBI T100), microcentrifuge (YXJ-2), UV spectrophotometer (Hitachi U-3010), buffer solutions for capillary electrophoresis and POP-7 gel, gel imaging system (Gene Genius).

Reagents: BigDye Terminator v3.1 Cycle Sequencing Kit, universal primers (e.g., M13(-21) 10 μM), DNA template (PCR product or plasmid DNA, A260/A280 = 1.6–2.0), 3 mol/L Na-acetate (pH 5.2), 70% and anhydrous ethanol, Na-acetate/ethanol mixture.

2.3. N_2 fixation capacity Determination of nitrogen fixation capacity

The evaluation of HCN production by endophytes was performed by inoculating each bacterial and fungal suspension in King's B broth medium supplemented with glycine (4.4 g/L). Each isolate tested was replicated three times. Uninoculated flasks served as controls. Sterile filter paper pieces were dipped in an alkaline picrate suspension (0.5% picric acid and 2% Na_2CO_3) and tied to the neck of the flask (one per flask). The flasks were capped and sealed with parafilm and incubated at 140 rpm for 4 days at 28 °C.

The sodium picrate lines changed color to reddish in proportion to the amount of HCN produced. A fresh piece of filter paper was added to a test tube containing 10 ml of deionized water, the color was eluted, and the color absorbance was measured at 625 nm using a spectrophotometer (SHIMADZU, model number UV1800). Before measurement, the zero absorbance at 625 nm was adjusted using distilled water **(Dadarwal et al., 1981).**

2.4. Siderophore Production

Endophytic bacterial colonies were grown in LB broth for 48 hours and used for quantitative siderophore production. 1 ml of broth from each bacterial and fungal culture (one for each) was placed in a 1.5 ml sterilized centrifuge tube, which was then sterilized before inoculation with 10 μL of freshly prepared bacterial culture (10^8 CFU/ml). Three replicates (tubes) were used for each strain. In addition, a control tube (uninoculated broth) was prepared. Cultures of endophytic isolates were incubated at 28 °C for 48 h and then centrifuged at 10,000 rpm for 10 min; the supernatant was used to measure siderophore levels. The supernatant of each culture (0.5 ml) was mixed with 0.5 ml of CAS mixture and after 20 min the optical density at 630 nm was measured using a spectrophotometer (SHIMADZU, UV1800). The amount of siderophore produced by the strains was estimated in percentage (%) siderophore units (psu), which was determined using the formula given in [38]:

$$\text{percent siderophore unit} = \frac{Ar-As}{Ar} \times 100$$

where Ar is the control absorbance at 630 nm (CAS solution and uninoculated broth), As is the sample absorbance (CAS solution and sample supernatant) (Sarvepalli et al., 2024).

2.5. Solubilization of phosphate (P) and zinc (Zn).

To determine the solubility of phosphorus (P) and zinc (Zn), Pikovskaya agar with 0.5% $Ca_3(PO_4)_2$ and mineral salt agar with 0.1% ZnO were used, respectively. Bacterial isolates were initially incubated on nitrogen-free (NF) agar. This NF agar consisted of the following composition (in g L^{-1}): glucose – 10; K_2HPO_4 – 1; $MgSO_4$ – 0.2; $CaCO_3$ – 1; NaCl – 0.2; $Na_2MoO_4 \cdot 2H_2O$ –

0.005; $FeSO_4$ – 0.1; agar – 15. After the isolates were grown on the surface of this medium for 24 hours, 6 mm diameter agar discs were prepared using a sterile cork borer. These discs were transferred to indicator media and incubated at 30 °C for 1 day for Zn solubility and 7 days for P solubility. The halozones formed around the agar during the incubation period indicated the solubilizing activity of the bacterial strain (Gupta et al., 2024).

2.6. Determination of ACC deaminase activity

Quantitative analysis of ACC deaminase activity was performed using a modified version of the method developed by Penrose and Glick (Penrose et al., 2003). This method is based on measuring the amount of α-ketobutyrate (α-KB) formed during ACC hydrolysis. Endophytic bacterial cells were grown in TSB (Tryptic Soy Broth) medium at 28 °C. After overnight growth, the bacteria were centrifuged at 10,000 × g for 10 min, the cells were washed with 0.1 M Tris–HCl (pH 7.5) and suspended in DF medium supplemented with 3 mM ACC as the sole nitrogen source. The cultures were incubated at 28 °C for 48 h, and then the biomass was harvested by centrifugation at 10,000 × g for 10 min at 4 °C.

The cells in the supernatant were removed and the cells were washed twice with another 5 mL of DF minimal salt medium. The cells were then transferred to a new tube, suspended in 7.5 mL of DF minimal salt medium supplemented with 3 mM ACC, and incubated for 24 h at 28 °C with shaking at 140 rpm/min. Induced cells were centrifuged at 6000 × g for 10 min and washed with 0.1 M Tris-HCl (pH 7.6). The tubes were then centrifuged at 12,000 × g for 5 min and the pellets were resuspended in 200 μL of 0.1 mol L−1 Tris-HCl (pH 8.5). The washed cells were labilized by adding 10 μL of toluene and vortexed at maximum speed for 30 s.

Then, 50 μL of the toluene-treated cell suspension was transferred to a new tube, 5 μL of 0.5 M ACC was added, and incubated at 30 °C for 15 min. 250 μL of the supernatant was removed, 200 μL of 0.56 N HCl and 75 μL of 2,4-DNF (0.2% 2,4-dinitrophenylhydrazine in 2 mol L−1 HCl) were added, and the mixture was incubated at 30 °C for 30 min. Then, 500 μL of NaOH (2N) was added, and the absorbance of the resulting mixture at 540 nm was measured using a Shumadzu UV-1800 spectrophotometer.

Cell suspension without ACC was used as a negative control, and medium with (NH4)2SO4 was used as a positive control. The α-ketobutyrate concentration was determined using a standard calibration curve ranging from 0.1 to 1 mM. ACC deaminase activity was calculated based on the production of μmol α-KB per 1 mg protein per hour. Total protein content was determined by the Bradford method according to the manufacturer's instructions (**Bradford et al., 1976**).

2.7. Processing and statistical analysis of the results obtained

All experiments were performed in triplicate, and the obtained data are presented as the mean ± standard deviation (SD). Statistical analyses were carried out using OriginPro 8.6 (OriginLab Corporation, Northampton, MA, USA), while Microsoft Excel and Microsoft Word were used for data organization and table preparation. Differences among treatments were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's honestly significant difference (HSD) test for multiple comparisons. Graphs were generated using OriginPro 8.6. Differences were considered statistically significant at $P < 0.05$.

The following results were obtained based on the evaluation of the antagonistic activity of the isolated isolates against the pathogenic fungus *Fusarium solani* in vitro. The bacteria were co-cultured with *Fusarium solani* in Petri dishes, and the zones of inhibition of the radial growth of the fungus were measured in mm (millimeters) (Figure 1).

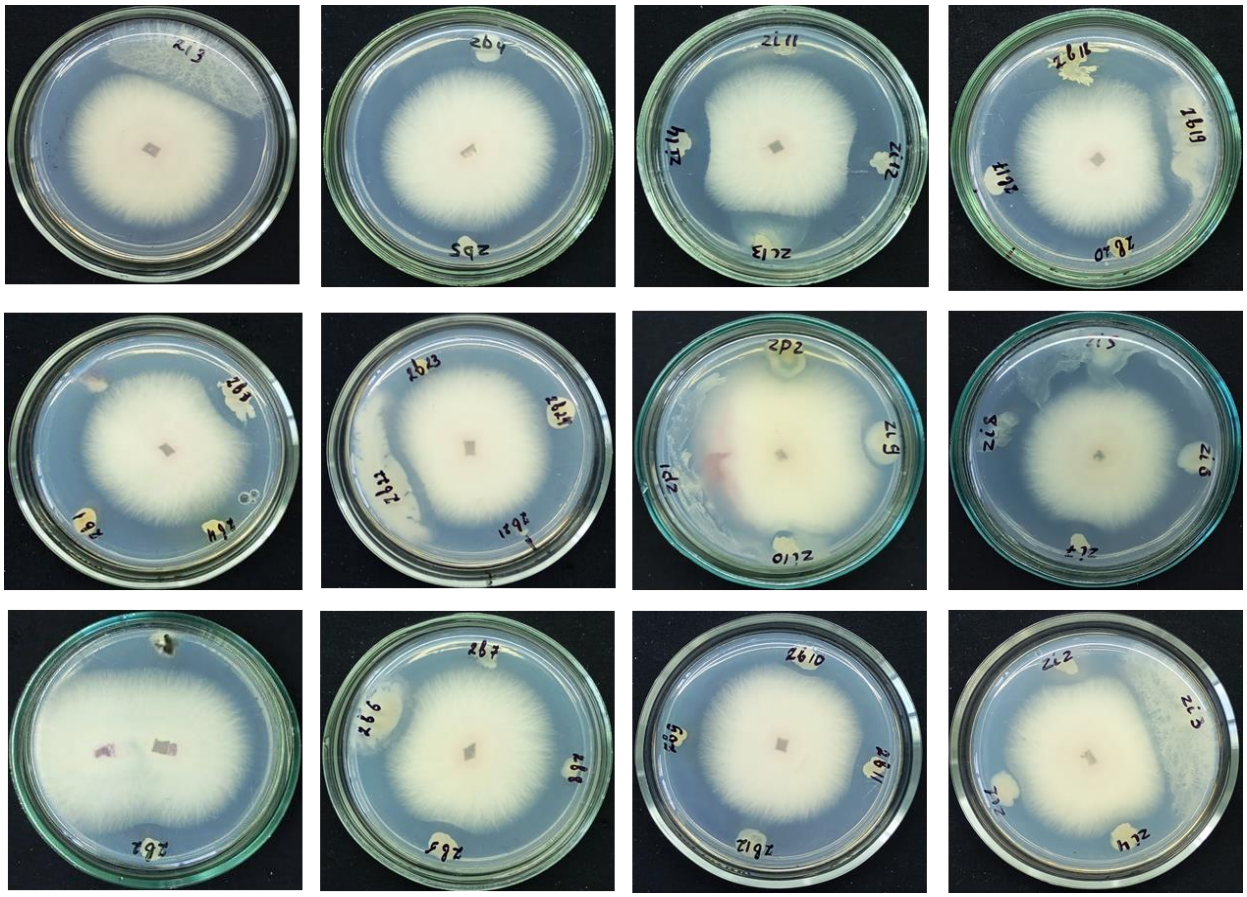


Figure 1. Antifungal activity of isolated bacteria

According to the results of the analysis, isolates such as ZB-10 (24 mm), ZB-11 (25 mm), ZB-2 (25 mm), ZB-3 (28 mm), ZB-4 (20 mm), ZB-5 (24 mm), ZI-12 (36 mm), ZI-14 (32 mm), ZI-7 (28 mm) showed significant antagonistic activity against the fungus *Fusarium solani*. In particular, isolates ZI-12 (36 mm) and ZI-14 (32 mm) had the largest inhibition zone and strongly suppressed the growth of the fungus.

Also, isolates ZI-7 and ZB-3 showed high activity with a zone of inhibition of 28 mm. ZB-2, ZB-10, ZB-5 and ZB-11 showed moderate (25, 24, 24 and 25 mm, respectively) fungistatic activity. The effect of isolate ZB-4 was relatively low (20 mm). These results indicate that endophytic bacteria can be used as an effective biological control agent against dangerous pathogens such as *Fusarium solani*, while our other isolates showed little or no activity at 20 mm.

In particular, isolates such as ZI-12 and ZI-14 stand out as promising biocontrol agents (Figure 2).

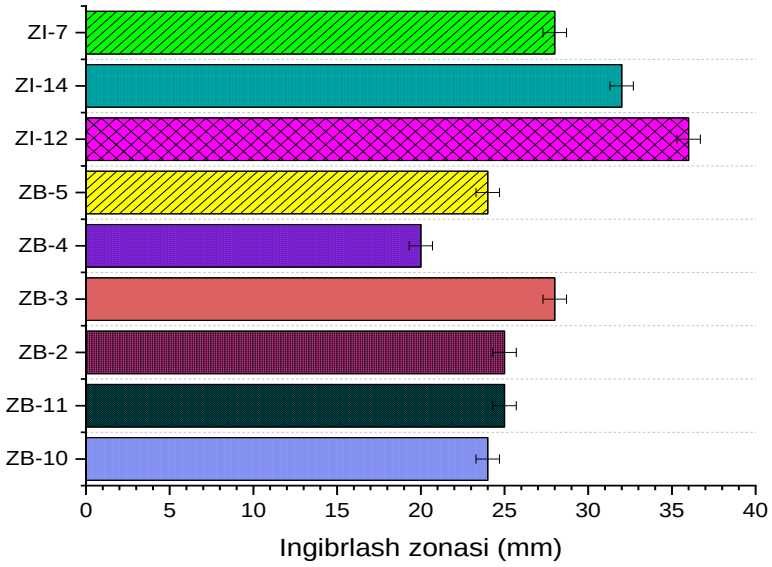


Figure 72. Antifungal activity of selected bacteria

As a result of the studies, 9 out of 49 endophyte isolates showed high levels of antagonistic activity against the pathogenic fungus Fusarium solani. These isolates effectively suppressed the growth and development of the pathogen through their antifungal metabolites, hydrolytic enzymes (e.g., cellulase, chitinase, and protease), and siderophore production ability.

The results show that among these 9 isolates, bacteria belonging to the genus Bacillus and Pseudomonas were distinguished. Their effectiveness against Fusarium solani indicates that they are promising not only in laboratory conditions, but also for future field use.

Thus, these isolates have great potential as biological control agents, and their use can partially replace chemical fungicides or help reduce their amount in reducing plant diseases caused by Fusarium solani. “A total of forty-nine bacterial isolates were collected from three samples of plant tissues of Plantago lanceolata L. After several screenings, six endophytic bacterial isolates remained. The strains were identified using 16S rRNA gene analysis and compared with their closest relatives in GenBank (NCBI). The isolated endophytic strains belong to two phyla, five of which belong to the Firmicutes and one to the Proteobacteria phylum. The strains belonging to the Firmicutes phylum are representatives of the class Bacilli, which are: Bacillus cereus (Zi14), Bacillus paramycoides (Zb5), Bacillus velezensis (Zi3), Brevibacillus brevis (Zi12), and Brevibacillus formosus (Zb11). The Proteobacteria phylum includes Pseudomonas moraviensis (Zb3), a representative of the class Gammaproteobacteria. The results are presented in Table 1.

Table 1

Identification of selected endophytic microorganisms from *Plantago lanceolata L.*

Izolyat raqami	Strain	Accession Number	Species
Zi14	IGPEB 4	PV848386.1	***Bacillus cereus***
Zb5	IGPEB 5	PV848387.1	***Bacillus paramycoides***
Zi7	IGPEB 6	PV848388.1	***Bacillus velezensis***
Zi12	IGPEB 2	PV848384.1	***Brevibacillus brevis***
Zb11	IGPEB 3	PV848385.1	***Brevibacillus formosus***
Zb3	IGPEB 1	PV848383.1	***Pseudomonas moraviensis***

Endophytic bacterial strains isolated from Uzbekistan were phylogenetically analyzed based on 16S rRNA gene sequences and their evolutionary similarity with closely related strains in international databases was determined. Bacillus cereus IGPEB 4 was placed in the same clade with strains from China (NW7) and Mongolia (MN), confirmed with high bootstrap values (99–100%). Bacillus paramycoides IGPEB 5 was observed to have a close phylogenetic relationship with a strain from Pakistan (D12). **Bacillus velezensis IGPEB 6 was found to be in the same branch as strains from India (B13) and China (Bac24), indicating high similarity between the strains. Brevibacillus brevis IGPEB 2 and Brevibacillus formosus IGPEB 3 were close to each other, forming a common clade with Brevibacillus isolates from the Philippines, Argentina, and China. Pseudomonas moraviensis IGPEB 1 was found to be phylogenetically close to strains WG410 and WG411 from China (Figure 3).**

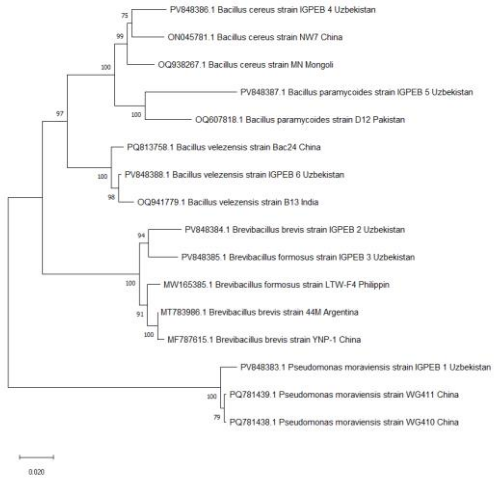


Figure 3. Phylogenetic dendrograms based on partial 16S rRNA nucleotide sequences show the relationships of bacterial isolates with closely related taxa.

Solubilization of phosphate (P) and zinc (Zn).

Organic acids secreted by bacteria (e.g. citrate, oxalate, gluconate, lactate) chemically break down insoluble phosphates into soluble orthophosphate ions ($H_2PO_4^-$, HPO_4^{2-}). In addition, phosphatase and phytase enzymes hydrolyze organic phosphorus compounds and make them available to plants. The results of the study show that Bacillus velezensis has the highest phosphate solubilization index, which indicates the potential of this bacterium to stimulate plant growth. Bacillus cereus and Bacillus paramycoides showed moderate phosphate solubilization ability. Brevibacillus brevis and Brevibacillus formosus isolates showed relatively low results in phosphate solubilization, and Pseudomonas moraviensis had the lowest index. In addition, zinc minerals (ZnO, $ZnCO_3$, $Zn_3(PO_4)_2$) are often not absorbed by plants. Organic acids produced by endophytic bacteria break down these compounds to form soluble Zn^{2+} ions. According to the results, Bacillus and Brevibacillus species recorded high zinc solubility, among which Bacillus velezensis was the most effective isolate. Pseudomonas moraviensis had the lowest activity in this process. In general, the experiments revealed that the solubility of substances varies significantly depending on the bacterial species. This indicates that the effects of endophytic bacteria on the phosphorus and zinc cycle in the soil are different, and among them, Bacillus velezensis is the most promising bioinoculant. The HCN production capacity of bacterial endophytes was assessed by qualitative and quantitative analyses. According to the results, Bacillus cereus had strong (+++)

HCN production, with a quantitative value of 0.041 ± 0.002 OD. Bacillus paramycoides showed moderate (++) production, with a quantitative value of 0.034 ± 0.002 OD.

The highest HCN production was observed in Bacillus velezensis. This isolate showed a very strong (++++) quality result, with an OD value of 0.073 ± 0.003. Brevibacillus brevis (0.024 ± 0.002 OD) and Brevibacillus formosus (0.033 ± 0.002 OD) also recorded moderate (++) production.

Pseudomonas moraviensis had the lowest HCN production, showing only a weak (+) result and a quantitative value of 0.013 ± 0.003 OD.

Overall, the results obtained indicate that the level of HCN production among bacterial endophytes varies significantly. In particular, Bacillus velezensis was characterized by its high production capacity, while Pseudomonas moraviensis recorded the lowest value (Table 2).

Table 2

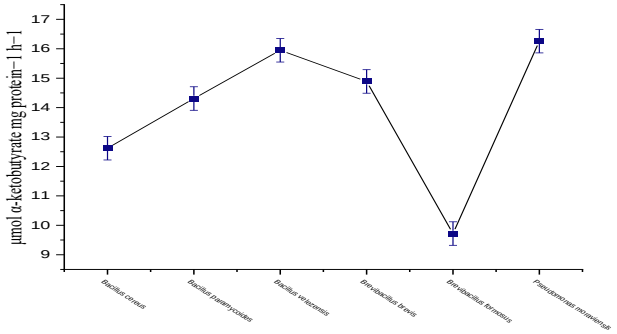
Solubilization of phosphate (P) and zinc (Zn).

	Zinc Solubilization			Phosphate Solubilization	HCN Production		Siderophore Production
Isolates	Zinc Carbonate SI (mm)[1]	Zinc Oxide SI (mm)[1]	Zinc Phosphate SI (mm)[1]	Phosphate SI (mm)[1]	HCN Qualitative	HCN Quantitative (OD)[2]	Siderophore Percent (psu)[3]
Bacillus cereus IGPEB 4	4.4 ± 0.059	3.74 ± 0.072	2.2 ± 0.035	2.9 ± 0.059	+++	0.041 ± 0.002	64.28 ± 0.72
Bacillus paramycoides IGPEB 5	3.1 ± 0.065	1.7 ± 0.040	1.2 ± 0.027	1.8 ± 0.021	++	0.034 ± 0.002	41.13 ± 0.57
Bacillus velezensis IGPEB 6	5.1 ± 0.058	6.1 ± 0.084	2.2 ± 0.034	3.4 ± 0.057	++++	0.073 ± 0.003	78.12 ± 0.68
Brevibacillus brevis IGPEB 2	2.9 ± 0.034	2.8 ± 0.095	1.7 ± 0.032	1.9 ± 0.051	++	0.024 ± 0.002	72.81 ± 0.61
Brevibacillus formosus IGPEB 3	1.7 ± 0.040	2.5 ± 0.061	1.4 ± 0.033	2.0 ± 0.042	++	0.033 ± 0.002	47.45 ± 0.66
Pseudomonas moraviensis IGPEB 1	2.5 ± 0.052	1.9 ± 0.068	1.8 ± 0.032	1.7 ± 0.035	+	0.013 ± 0.003	22.6 ± 0.53

[1] SI - Solubilization Index
[2] OD - Optical Density
[3] psu - Percent Siderophore Unit

ACC Deaminase Activity

Almost all of the 6 endophytic bacterial isolates exhibited varying levels of ACC deaminase activity when ACC was added to DF minimal salt broth medium as a nitrogen source. The activity values ranged from 9.72–16.26 μmol α-KB mg protein^{-1} h^{-1}. Of these, Bacillus velezensis and Pseudomonas moraviensis isolates exhibited the highest ACC deaminase activity (15.95 and 16.26 μmol α-KB mg protein^{-1} h^{-1}, respectively). Bacillus paramycoides (14.31 μmol α-KB mg protein^{-1} h^{-1}) and Brevibacillus brevis (14.89 μmol α-KB mg protein^{-1} h^{-1}) exhibited intermediate values. The lowest activities were observed in Bacillus cereus (12.62 μmol α-KB mg protein^{-1} h^{-1}) and Brevibacillus formosus (9.72 μmol α-KB mg protein^{-1} h^{-1}). In the absence of ACC, only 2 of these isolates (40%) retained the ability to synthesize ACC deaminase, with α-KB concentrations ranging from 0.012–0.074 μmol α-KB mg protein^{-1} h^{-1}. Experiments have shown that the addition of ACC as the sole nitrogen source dramatically activates ACC deaminase biosynthesis, which is an important factor in increasing the stress resistance of bacteria (Figure 3).



3 ACC deaminase activity of selected endophytic bacterial isolates.

The effect of temperature and pH on the synthesis of lipase and protease enzymes by endophytic bacteria was studied. For this purpose, bacteria were grown in liquid NB nutrient medium and the enzymatic activity of the three most active isolates was compared. As a result, it was found that they showed significantly higher activity. This is explained by the richness of the tomato juice nutrient composition in ascorbic acid, potassium, folic acid, phenolic substances and carotenoids such as lycopene. (Abdusamatov et al 2024.).

The selected bacterial isolates were tested for their chitinase, protease, and amylase enzyme activities. The results showed that all strains were able to produce all three enzymes to some extent, but their activity levels varied.

4. Discussion

The present study demonstrated that endophytic bacteria isolated from *Plantago lanceolata* exhibited multiple plant growth-promoting (PGP) and biocontrol traits, including phosphate and zinc solubilization, ACC deaminase activity, hydrogen cyanide (HCN) production, hydrolytic enzyme secretion, and antagonistic activity against *Fusarium solani*. These findings support previous reports indicating that medicinal plants are important reservoirs of beneficial endophytic bacteria capable of improving plant nutrition and resistance to biotic and abiotic stresses (Compant et al., 2021; Santoyo et al., 2022).

Molecular identification revealed that the selected isolates belonged to the genera *Bacillus*, *Brevibacillus*, and *Pseudomonas*. These bacterial genera are among the most extensively investigated plant-associated microorganisms because of their ability to colonize internal plant tissues and promote plant growth through multiple mechanisms. Similar findings have been reported by Compant et al. (2021), who concluded that species of *Bacillus* and *Pseudomonas* are dominant endophytes in many medicinal plants and contribute significantly to nutrient acquisition, phytohormone production, and pathogen suppression.

The antagonistic activity observed against *Fusarium solani* indicates that the selected isolates possess considerable biocontrol potential. In particular, isolates ZI-12 and ZI-14 produced the largest inhibition zones, suggesting the production of antifungal metabolites. Comparable results were reported by Mosela et al. (2022), who demonstrated that *Bacillus velezensis* effectively suppressed *Fusarium* spp. through the production of cyclic lipopeptides such as surfactin, iturin, and fengycin. Similarly, Rabbee et al. (2019) reported that *B. velezensis* inhibits fungal pathogens by combining antibiotic production with extracellular hydrolytic enzyme secretion.

The ability of the selected isolates to solubilize phosphate and zinc further highlights their agricultural importance. Phosphorus and zinc are often present in poorly soluble forms that limit plant availability. Microbial solubilization of these nutrients increases their uptake by plants and reduces the dependence on chemical fertilizers. The high phosphate-solubilizing activity of *Bacillus velezensis* observed in this study agrees with previous investigations demonstrating that this species secretes gluconic and other organic acids capable of mobilizing insoluble phosphate minerals (Sharma et al., 2023; Li et al., 2025).

ACC deaminase activity is considered one of the key mechanisms by which plant growth-promoting bacteria alleviate stress-induced ethylene accumulation. The high ACC deaminase activity detected in *Pseudomonas moraviensis* and *Bacillus velezensis* suggests that these isolates may improve plant tolerance under adverse environmental conditions. Glick (2014) emphasized that ACC deaminase-producing bacteria enhance root elongation and increase plant tolerance to salinity, drought, and pathogen infection by lowering ethylene concentrations. Similar

observations were also reported by Ali et al. (2012), who demonstrated that endophytic bacteria possessing ACC deaminase significantly improved plant growth under stress conditions.

Hydrogen cyanide production and extracellular enzyme activities provide additional evidence of the multifunctional nature of the selected isolates. HCN suppresses pathogen respiration, whereas chitinase and protease degrade fungal cell walls, thereby enhancing disease control. According to Rijavec and Lapanje (2016), HCN-producing bacteria contribute to pathogen suppression in the rhizosphere and plant tissues, while chitinase-producing *Bacillus* species have been widely recognized as efficient biological control agents against fungal diseases. The simultaneous expression of these traits observed in the present study suggests that the selected endophytes employ multiple complementary mechanisms rather than a single antagonistic strategy.

Overall, the results confirm that endophytic bacteria associated with *Plantago lanceolata* possess multifunctional plant growth-promoting and biocontrol characteristics. The combination of nutrient solubilization, ACC deaminase activity, HCN production, hydrolytic enzyme secretion, and antifungal activity indicates that these isolates have considerable potential for the development of environmentally friendly microbial bioinoculants. However, greenhouse and field experiments, together with whole-genome analysis, are required to validate their practical application and to elucidate the molecular basis of their beneficial interactions with host plants.

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THE EFFECT OF SOWING DATES AND THE LIQUID ORGANIC FERTILIZER «POTEX» ON DRY MATTER ACCUMULATION IN MUNG BEAN VARIETIES

Gulshana Bahtiyorovna Khalimova
Applicant at the Grain and Legume Research Institute, Republic of Uzbekistan.
https://orcid.org/0009-0008-1040-7767
Djurayev Mukimjon Yakubjonovich
Doctor of Philosophy (PhD) in Agricultural Sciences, Senior Researcher
https://orcid.org/0000-0002-5977-1147

Abstract. *A field experiment conducted in 2022 investigated the effects of sowing dates and the liquid organic fertilizer «Potex» on dry matter accumulation in the mung bean (Vigna radiata) varieties «Durdona» and «Hosildor». It was found that 41-45% of the final dry matter was accumulated after pod formation. The «Hosildor» variety outperformed «Durdona» by 14.6%, while sowing on July 1-5 reduced dry matter accumulation by 12.7%. The application of «Potex» increased dry matter accumulation by 0.14-0.44 t/ha at maturity. The maximum dry matter accumulation (5.16-5.17 t/ha) was achieved by «Hosildor» when sown on June 20-25 and treated with «Potex» at application rates of either 1.5 + 1.5 or 2.0 + 2.0 L/ha.*

Keywords: *mung bean, Vigna radiata, sequential cropping, sowing date, «Potex», organic fertilizer, dry matter, photosynthesis, variety, biomass.*

INTRODUCTION

Dry matter accumulation is an integrated indicator of plant photosynthetic activity, reflecting the development of the assimilatory apparatus, the duration of its functioning, and the distribution of photosynthetic products between vegetative and generative organs. In mung bean (Vigna radiata (L.) Wilczek) grown as a second crop after winter wheat harvesting, this process is particularly sensitive to sowing date. A reduction in the available growing period is accompanied by changes in temperature conditions, leaf area, and the density of surviving plants.

The patterns of biomass formation have been described by A.A. Nichiporovich et al. [1]. L. Tzudir et al. [2] established a relationship between mung bean dry matter accumulation and photosynthetically active radiation under different sowing dates. H.K. Abbas and M.N.H. Al-Yasari [3] demonstrated an increase in the biological yield of mung bean under organic fertilization. Under conditions of sequential cropping, it is important to assess the combined effects of variety, sowing date, and organic fertilizer applications.

MATERIALS AND METHODS

Field studies were conducted in 2022. Two mung bean sowing dates (June 20-25 and July 1-5), two varieties («Durdona» and «Hosildor»), and six treatment options were investigated: control (water); 1.5 L/ha at the branching stage; 1.5 L/ha at the budding stage; 1.0 + 1.0, 1.5 + 1.5, and 2.0 + 2.0 L/ha applied at the respective growth stages. In total, 24 combinations of the studied factors were evaluated. To assess dry matter accumulation dynamics, the following growth stages were distinguished: branching, budding, flowering, pod formation, and maturity.

At each growth stage, five plants were sampled from the first and third replicates of each treatment. The samples were fixed at 105 °C for 30 minutes and then dried at 70-80 °C to constant weight. The dry mass per plant was determined by weighing. Dry matter accumulation per hectare was calculated based on the actual plant stand density at the end of the growing season. Dry matter accumulation rates between growth stages were determined according to the calendar duration of the respective interstage periods.

RESULTS AND DISCUSSION

Dry matter accumulation throughout the growing season was characterized by a gradual increase from the branching stage to maturity. In the control treatment of the «Durdona» variety sown in June, dry matter per plant amounted to 0.90 g at the branching stage, 2.6 g at budding, 5.0 g at flowering, 9.6 g at pod formation, and 17.0 g at maturity. The corresponding values per hectare were 0.21, 0.62, 1.18, 2.27, and 4.02 t/ha, respectively. Thus, intensive dry matter accumulation continued after pod formation, contributing substantially to the final biomass of mature plants.

Table 1.

Dry Matter per Mung Bean Plant in the Control Treatments and under «Potex» Application (1.5 + 1.5 L/ha), 2022

Sowing Date	Variety	«Potex» Application Rate, L/ha	Flowering, g	Pod Formation, g	Maturity, g
20-25.06	Durdona	Control	5,0	9,6	17,0
20-25.06	Durdona	1,5 + 1,5	5,4	10,5	18,3
20-25.06	Hosildor	Control	5,8	11,4	20,2
20-25.06	Hosildor	1,5 + 1,5	6,2	12,4	21,5
01-05.07	Durdona	Control	4,7	8,9	16,2
01-05.07	Durdona	1,5 + 1,5	5,1	9,7	17,4
01-05.07	Hosildor	Control	5,4	10,2	18,0
01-05.07	Hosildor	1,5 + 1,5	6,0	11,2	19,3

The highest daily increase in dry matter in the control treatments was observed during the transition from flowering to pod formation (1.19-1.47 centners/ha per day). After pod formation, the daily increase declined to 0.40-0.53 centners/ha. Nevertheless, owing to the duration of grain filling after pod formation, 41-45% of the final dry matter was accumulated during this period.

On average across the studied treatment combinations, the «Hosildor» and «Durdona» varieties accumulated 4.66 and 4.07 t/ha of dry matter by maturity, respectively. The advantage of «Hosildor» was 0.59 t/ha, or 14.6%. The differences between the varieties were associated with a

more developed leaf area and a longer growing season in «Hosildor». This varietal advantage was consistently observed under both summer sowing dates.

Late sowing (July 1-5) reduced dry matter accumulation in the control treatments, from 4.02 to 3.64 t/ha in «Durdona» and from 4.73 to 4.03 t/ha in «Hosildor». The decreases amounted to 0.38 and 0.70 t/ha, respectively. On average, dry matter per plant decreased by 8.5%, while dry matter accumulation per hectare declined by 0.59 t/ha (12.7%). The more pronounced reduction in dry matter accumulation per hectare was also associated with a decrease in plant stand density.

At the branching stage, differences from the control were negligible. At the budding stage, early application increased dry matter accumulation per hectare by 4.8-13.0%, whereas application directly at the budding stage resulted in increases of 0-2.9%. At the flowering and pod formation stages, the corresponding increases were 3.8-14.2% and 1.9-13.6%, respectively.

At the maturity stage, «Potex» increased dry matter accumulation by 0.14-0.44 t/ha (3.6-10.7%). A single application at 1.5 L/ha resulted in an increase of 0.14-0.34 t/ha, while two applications at 1.0 + 1.0 L/ha increased dry matter accumulation by 0.16-0.36 t/ha. Two applications at rates of 1.5 + 1.5 and 2.0 + 2.0 L/ha provided an additional 0.25-0.44 t/ha of dry matter.

The maximum dry matter accumulation in «Hosildor» sown in June was achieved with two applications at rates of 1.5 + 1.5 and 2.0 + 2.0 L/ha, reaching 5.17 and 5.16 t/ha, respectively. In «Durdona», both application rates resulted in 4.45 t/ha under the same sowing date, while the 1.5 + 1.5 L/ha treatment yielded 4.01 t/ha under July sowing. A further increase in the total application rate from 3.0 to 4.0 L/ha did not increase maximum dry matter accumulation under early sowing.

Analysis of variance of crop dry matter at the maturity stage showed that varietal characteristics (44.3%) and sowing date (44.1%) contributed almost equally to the variation in this parameter. The contribution of the «Potex» treatment factor was 9.5%, while factor interactions accounted for 2.1%. When dry matter per plant was assessed, the contribution of variety increased to 66.4%, whereas that of sowing date was 24.5%. Thus, the effect of sowing date on dry matter accumulation per unit area is determined not only by individual plant growth but also by changes in plant stand density.

A strong positive correlation was found between dry matter accumulation and leaf area ($r = 0.967$), nodule fresh weight ($r = 0.899$), and stem height ($r = 0.883$). The relationship with leaf area was described by the equation $y = -0.19 + 1.626x$ ($R^2 = 0.936$), where y is crop dry matter (t/ha) and x is leaf area at the pod formation stage (thousand m²/ha). An increase of 1,000 m²/ha in leaf area corresponded to an increase of 0.163 t/ha in dry matter accumulation.

The combined effects of sowing date (A), variety (B), and the total «Potex» application rate (x) were expressed by the equation $y = 41.65 - 5.93A + 5.94B + 1.00x$ ($R^2 = 0.963$). For factor A, June sowing = 0 and July sowing = 1; for factor B, «Durdona» = 0 and «Hosildor» = 1. The coefficients indicate a decrease in dry matter accumulation of 5.93 centners/ha with later sowing, a varietal advantage of 5.94 centners/ha for «Hosildor», and an increase in dry matter accumulation of 1.0 centner/ha for each additional 1 L/ha of the total application rate.

CONCLUSION

1. Dry matter accumulation in mung bean increased from the branching stage to maturity, reaching its maximum daily rate during the transition from flowering to pod formation (0.119-0.147 t/ha per day). After pod formation, 41-45% of the final dry matter was accumulated.

2. By maturity, the «Hosildor» variety accumulated an average of 4.66 t/ha of dry matter, exceeding the «Durdona» variety by 0.59 t/ha (14.6%). Delaying sowing from June 20-25 to July

1-5 resulted in a decrease in crop dry matter accumulation of 0.59 t/ha (12.7%).

3. Treatment with the liquid organic fertilizer «Potex» increased dry matter accumulation at maturity by 0.14-0.44 t/ha (3.6-10.7%). The maximum values of 5.16-5.17 t/ha were achieved by «Hosildor» sown on June 20-25 and treated at application rates of 1.5 + 1.5 and 2.0 + 2.0 L/ha.

4. Dry matter accumulation was strongly correlated with leaf area (r = 0.967). Variety (44.3%) and sowing date (44.1%) contributed almost equally to the variation in crop dry matter. For sequential mung bean cultivation, the results support the advantages of June sowing and two applications of «Potex» at the tested rates.

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THE EFFECT OF MINERAL FERTILIZER APPLICATION RATES ON THE PLANT DENSITY OF LEGUMINOUS CROPS

Mukumjon Yakubjanovich Juraev
PhD in Agricultural Sciences, Associate Professor, Head of Laboratory Research Institute of Cereal and Leguminous Crops https://orcid.org/0000-0002-5977-1147
Fazliddin Khusniddin ugli Yokubjonov
independent researcher
Research Institute of Cereal and Leguminous Crops
https://orcid.org/0009-0009-3140-2401

Abstract. *This article presents the results of research on the effect of mineral fertilizer application (feeding) rates during the growing season on the plant density of leguminous crops — soybean, mung bean and common bean — under the conditions of meadow saz-alluvial soils of the Fergana region in 2022–2024. The obtained results showed that the highest survival of emerged seedlings until the end of the growing season was recorded in soybean (95.0%) with mineral fertilizer application at a rate of $N_{120}P_{90}K_{40}$ kg/ha, in mung bean (93.5%) at $N_{90}P_{90}K_{40}$ kg/ha, and in common bean (95.4%) at $N_{90}P_{90}K_{40}$ kg/ha.*

Keywords: *meadow saz-alluvial soil, leguminous crops: soybean, mung bean, common bean, mineral fertilizer rates, seed germination, plant density, seedling mortality and survival.*

INTRODUCTION. Leguminous (grain legume) crops are one of the main sources of providing humans and farm animals with high-quality plant protein in world agriculture. At present, one of the most pressing problems on a global scale is the growing demand of the population for protein and its satisfaction, and in solving this problem the importance of such grain legume crops as soybean, mung bean and common bean is invaluable. In terms of cultivation area, mung bean ranks second in the world after soybean (about 25 million hectares), which indicates the high global demand for these crops.

The soil and climatic conditions of the Republic of Uzbekistan make it possible to cultivate agricultural crops throughout the year and obtain 2–3 harvests per year. Annually, on more than one million hectares of irrigated land freed up after cereal (spike) grain crops, there is an opportunity to grow mung bean, soybean and other crops as a second (repeat) crop over the course of 120–130 days, obtaining a high-quality harvest. In recent years, in order to ensure food security and increase export potential, our country has paid special attention to cereal, grain legume and oilseed crops, and their sown areas are being consistently expanded. At present, mung bean is annually cultivated in the republic as a second crop on an area of more than 18–20 thousand hectares [7].

In the full realization of the potential yield of grain legume crops, the optimization of cultivation agrotechnics — in particular, the mineral fertilizer application rates and the plant density (plant stand density) in the field — is one of the decisive factors. On the one hand, the correct determination of the rates of nitrogen, phosphorus and potassium fertilizers ensures the growth, development and productivity of plants; on the other hand, the number of plants per unit area — the plant density — directly determines the efficiency of the use of light, moisture and

nutrient elements. The interaction of these two factors (mineral fertilizer rate ↔ plant density) plays a decisive role in the formation of the crop's final yield.

According to the data of studies conducted by A.M.Abduazimov and N.F.Mirzaev under the conditions of the Kashkadarya region, when mineral fertilizers were applied at rates of 120 kg/ha of nitrogen, 90 kg/ha of phosphorus and 60 kg/ha of potassium on soybean varieties, an additional grain yield was obtained: for the "Tumaris Man-60" variety — 9.5 c/ha, for the "Oyjamol" variety — 13.4 c/ha, for the "Selekta-201" variety — 11.2 c/ha, and for the "Amigo" variety — 7.6 c/ha; and it was established that these variants are the most economically effective [1].

In the studies of A.O.Abylkhanova, I.N.Porsev, I.A.Subbotin, V.L.Deryabin and V.V.Polovnikova, it was established that when common bean was fed during the growing season with mineral fertilizers at rates of N30P60K40 kg/ha, the growing period of the common bean plant was extended by 5–7 days, which increased photosynthesis processes by 12–15% and significantly enhanced the formation of total biomass [3].

In the studies of A.O.Abylkhanova, I.N.Porsev, V.A.Isaenko and V.V.Polovnikova, the productivity of common bean varieties and the influence of external factors on them were studied under the conditions of the Volgograd region. According to the results of the study, when mineral fertilizers were applied at rates of N30–60P60–90K40 kg/ha, the yield increased by 18–25%. Along with this, the net productivity of photosynthesis was higher by 9–13%, and the accumulation of biological dry matter increased by 12–16% [2].

In the studies conducted by R.Chikowo, the response of the common bean crop to nitrogen and phosphorus fertilizers under various soil conditions was studied. According to the results, in fields with a low level of mineral fertilizer supply, the yield was about 0.6 t/ha; however, when applied at the optimal rates of N-45 and P-60 kg/ha, an increase in grain yield of over 1.5 t/ha was achieved. This shows that phosphorus is of especially great importance for common bean [6].

As can be seen from the reviews presented above, the development of scientifically substantiated rates of mineral fertilizer application in accordance with soil and climatic conditions in growing a high and high-quality grain yield of leguminous crops is one of the pressing tasks of today.

Methodology and methods of conducting the research

The research work was carried out in 2022–2024 under the conditions of meadow saz-alluvial soils on the fields of the "Melikuzi ota" farm, operating in the Uzbekistan district of the Fergana region.

The experiment consisted of 18 variants, arranged in a single tier in 3-fold replication. On the experimental field, the furrow width was 60 cm and the length was 50 m. The area of each plot was 240 m², and the recorded (accounting) area was 120 m². The total area of the experiments was 1.3 ha. The experiment was conducted over 3 years in a short-rotation crop rotation system of 1:1 (cotton – cereals). Varieties of grain legume crops included in the State Register were sown in the experiment: soybean — "Selekta-302", mung bean — "Navruz", and common bean — "Kizil don".

Table 1.

Experimental design (scheme)

№	Type and variety of the second (repeat) crop	Annual rates of mineral fertilizers, kg/ha
1	Soybean (Selekta-302)	$N_{30}P_{90}K_{40}$
2	Mung bean (Navruz)	
3	Common bean (Kizil don)	
4	Soybean (Selekta-302)	$N_{45}P_{90}K_{40}$
5	Mung bean (Navruz)	
6	Common bean (Kizil don)	
7	Soybean (Selekta-302)	$N_{60}P_{90}K_{40}$
8	Mung bean (Navruz)	
9	Common bean (Kizil don)	
10	Soybean (Selekta-302)	$N_{75}P_{90}K_{40}$
11	Mung bean (Navruz)	
12	Common bean (Kizil don)	
13	Soybean (Selekta-302)	$N_{90}P_{90}K_{40}$
14	Mung bean (Navruz)	
15	Common bean (Kizil don)	
16	Soybean (Selekta-302)	$N_{120}P_{90}K_{40}$
17	Mung bean (Navruz)	
18	Common bean (Kizil don)	

In the experiment, the effect of feeding grain legume crops with mineral fertilizers at six different rates ($N_{30}P_{90}K_{40}$, $N_{45}P_{90}K_{40}$, $N_{60}P_{90}K_{40}$, $N_{75}P_{90}K_{40}$, $N_{90}P_{90}K_{40}$, $N_{120}P_{90}K_{40}$ kg/ha) on growth, development and grain yield was studied.

When feeding the crops, ammonium nitrate (N–34%) was used from the nitrogen fertilizers, superphosphate (P_2O_5–20%) from the phosphorus fertilizers, and potassium salt (K_2O–40%) from the potassium fertilizers. In the experiment, 100% of the amount of phosphorus and potassium fertilizers was applied under autumn (fall) ploughing. Nitrogen fertilizers were applied in two applications: the 1st feeding — during the period of the appearance of the trifoliate leaf (third leaf), and the 2nd feeding — during the budding period.

Results of the research

The plant density of grain legume crops sown as a second (repeat) crop is one of the decisive factors determining yield and growth dynamics. An optimal density reduces competition between plants and ensures the efficient use of light, moisture and nutrients by each seedling. With excessively dense sowing, shading, thinning of the stem and a reduction in the number of fruiting points are observed. Sparseness of seedlings, on the other hand, leads to incomplete use of the area, drying out of soil moisture and an increase in the number of weeds.

The most optimal sowing period for mung bean in the southern regions of Uzbekistan is considered to be the first ten-day period (decade) of April, and for the other regions — the second decade. At this time, the soil warms up to 12–14 °C, and the risk of frost becomes practically minimal. When sowing on stubble (post-harvest), sowing is carried out in mid- or late June. The sowing of mung bean seeds on stubble must be completed before July 10. If sowing is too late, the harvest may suffer from frost or the grains may fail to ripen [4].

Other types of common bean are sown by the wide-row method at the end of April or in May, and as a second (repeat) crop — at the end of June. It is advisable to set the row spacing at 60 cm, and the sowing scheme at 60×20, 60×15. The seeding rate is 0.25–0.40 million seeds. Common bean is sown with grain seeders, while ordinary common bean is sown with corn or cotton seeders (for sowing cotton seeds); the sowing depth is 3–5 cm [5].

From the reviews presented above, it can be concluded that when sowing grain legume crops as a second (repeat) crop and achieving a high grain yield, some of the important factors are the sowing period and the plant density; in this connection, it is recommended to carry out the sowing of seeds before July 10, and not to reduce the plant density below 400 thousand plants per hectare.

In this connection, we also carried out observations and analyses in order to determine the field germination of the seeds sown in the variants, as well as the plant density at the end of the growing season.

In particular, when analyzing the field germination of seeds and the dynamics of seedling emergence across the variants at the beginning of the growing season, no large differences in the field germination of seeds and seedling emergence were observed. That is, the influence of the applied mineral fertilizers was not manifested.

That is, in the soybean crop, the field germination of seeds ranged from 88.2% to 89.4%, and the number of emerged seedlings — from 293.7 plants/linear m to 297.7 plants/linear m; in the mung bean crop, the field germination of seeds ranged from 91.1% to 92.1%, and the number of emerged seedlings — from 303.4 plants/linear m to 306.4 plants/linear m; in the common bean crop, the field germination of seeds ranged from 89.8% to 91.1%, and the number of emerged seedlings — from 299.0 plants/linear m to 303.4 plants/linear m.

When comparing the field germination of seeds and the number of emerged seedlings by crop type, the highest germination was noted in the mung bean crop: compared to the soybean crop, the field germination of seeds was higher by 2.6–3.0%, and seedling emergence — by 8.7–9.7 plants/linear m; compared to the common bean crop, the field germination of seeds was higher by 0.9–1.3%, and seedling emergence — by 3.0–4.4 plants/linear m.

However, by the end of the growing season, when analyzing the plant density of the grain legume crops across the variants, it was noted that the influence of the mineral fertilizer application rates became significant.

In particular, in the soybean crop, at the end of the growing season, the highest plant density was noted in the 16th variant, where mineral fertilizers at rates of N120P90K40 kg/ha were applied during the growing season: the plant density amounted to 280.9 plants/linear m, and the survival of emerged seedlings — 95.0%. It was established that, compared with the 1st variant, where mineral fertilizers at rates of N30P90K40 kg/ha were applied during the growing season, the plant density was higher by 13.0 plants/linear m, and the survival of emerged seedlings — by 4.2%; compared with the 4th variant (rates of $N_{45}P_{90}K_{40}$ kg/ha) — by 11.0 plants/linear m and 3.1%, respectively; compared with the 7th variant (rates of N60P90K40 kg/ha) — by 5.2 plants/linear m

and 2.4%; compared with the 10th variant (rates of N75P90K40 kg/ha) — by 3.2 plants/linear m and 1.5%; compared with the 13th variant (rates of $N_{90}P_{90}K_{40}$ kg/ha) — by 0.6 plants/linear m and 0.4%.

In the mung bean crop, the highest plant density was noted in the 14th variant, where mineral fertilizers at rates of N90P90K40 kg/ha were applied during the growing season: the plant density amounted to 286.8 plants/linear m, and the survival of emerged seedlings — 93.5%. It was recorded that, compared with the 2nd variant, where mineral fertilizers at rates of N30P90K40 kg/ha were applied during the growing season, the plant density was higher by 8.6 plants/linear m, and the survival of emerged seedlings — by 2.1%; compared with the 5th variant (rates of N45P90K40 kg/ha) — by 6.8 plants/linear m and 1.2%, respectively; compared with the 8th variant (rates of N60P90K40 kg/ha) — by 3.1 plants/linear m and 0.5%; compared with the 11th variant (rates of N75P90K40 kg/ha) — by 1.2 plants/linear m and 0.3%; compared with the 17th variant (rates of N120P90K40 kg/ha) — by 2.8 plants/linear m and 0.6%.

In the common bean crop, when analyzing the actual plant density at the end of the growing season, a repetition of the pattern established in the mung bean crop was observed: the highest plant density was noted in the 15th variant, where mineral fertilizers at rates of N90P90K40 kg/ha were applied during the growing season — the plant density amounted to 289.4 plants/linear m, and the survival of emerged seedlings — 95.4%. It was established that, compared with the 3rd variant, where mineral fertilizers at rates of N30P90K40 kg/ha were applied during the growing season, the plant density was higher by 13.4 plants/linear m, and the survival of emerged seedlings — by 3.8%; compared with the 6th variant (rates of N45P90K40 kg/ha) — by 11.6 plants/linear m and 2.5%, respectively; compared with the 9th variant (rates of N60P90K40 kg/ha) — by 5.5 plants/linear m and 1.6%; compared with the 12th variant (rates of N75P90K40 kg/ha) — by 3.7 plants/linear m and

Table 2.

The effect of mineral fertilizer application rates on the plant density of grain legume crops sown as a second (repeat) crop

№	Type and variety of the second (repeat) crop	Annual rates of mineral fertilizers, kg/ha	Field germination of seeds, %	Number of emerged seedlings, plants/linear m	Plant density at the end of the growing season, plants/linear m	Survival of emerged seedlings, %.
1	Soybean (Selekta-302)	$N_{30}P_{90}K_{40}$	88,6	295,0	267,9	90,8
2	Mung bean (Navruz)		91,4	304,4	278,2	91,4
3	Common bean (Kizil don)		90,5	301,4	276,1	91,6
4	Soybean (Selekta-302)	$N_{45}P_{90}K_{40}$	88,2	293,7	269,9	91,9
5	Mung bean (Navruz)		91,1	303,4	280,0	92,3
6	Common bean (Kizil don)		89,8	299,0	277,8	92,9
7	Soybean (Selekta-302)	$N_{60}P_{90}K_{40}$	89,4	297,7	275,7	92,6
8	Mung bean (Navruz)		91,6	305,0	283,7	93,0
9	Common bean (Kizil don)		90,9	302,7	283,9	93,8
10	Soybean (Selekta-302)	$N_{75}P_{90}K_{40}$	89,2	297,0	277,7	93,5
11	Mung bean (Navruz)		92,0	306,4	285,5	93,2
12	Common bean (Kizil don)		90,4	301,0	285,7	94,9
13	Soybean (Selekta-302)	$N_{90}P_{90}K_{40}$	89,0	296,4	280,4	94,6
14	Mung bean (Navruz)		92,1	306,7	286,8	93,5
15	Common bean (Kizil don)		91,1	303,4	289,4	95,4
16	Soybean (Selekta-302)	$N_{120}P_{90}K_{40}$	88,8	295,7	280,9	95,0
17	Mung bean (Navruz)		91,8	305,7	284,0	92,9
18	Common bean (Kizil don)		90,2	300,4	284,7	94,8

0.5%; compared with the 18th variant (rates of N120P90K40 kg/ha) — by 4.7 plants/linear m and 0.6%.

From the obtained results, it can be seen that in the soybean crop the application of high rates of mineral fertilizers N120P90K40 kg/ha contributed to an increase in plant density by 0.6–13.0 plants/linear m and in the survival of emerged seedlings by 0.4–4.2%; whereas in the mung bean crop the application of mineral fertilizer rates N90P90K40 kg/ha ensured an increase in plant density by 1.2–8.6 plants/linear m and in the survival of emerged seedlings by 0.3–2.1%, and in the common bean crop the application of mineral fertilizer rates N90P90K40 kg/ha ensured an increase in plant density by 3.7–13.4 plants/linear m and in the survival of emerged seedlings by 0.5–3.8%.

However, the application of mineral fertilizer rates N120P90K40 kg/ha in the mung bean and common bean crops had a negative effect on plant density and the survival of emerged seedlings at the end of the growing season: compared with the variant where mineral fertilizer rates N90P90K40 kg/ha were applied, in the mung bean crop the plant density decreased by 2.8 plants/linear m, and the survival of emerged seedlings — by 0.6%; in the common bean crop the plant density decreased by 4.7 plants/linear m, and the survival of emerged seedlings — by 0.6%.

As the cause of this phenomenon, the following can be noted: the application of mineral fertilizers at high rates in the mung bean and common bean crops has a negative effect on the life

period of the seedlings, leading to their stress condition, a decrease in resistance to diseases and pests, as well as a decrease in resistance to extreme natural conditions, which, in turn, leads to a significant increase in seedling mortality. Thus, the corresponding conclusion can be drawn.

Conclusion. It was observed that feeding grain legume crops with various rates of mineral fertilizers during the growing season affects seedling mortality and the survival of emerged seedlings differently over the course of the growing season. Thus, feeding with mineral fertilizers at rates of N120P90K40 kg/ha in the soybean crop reduced seedling mortality during the growing season to 5.0% and ensured the survival of emerged seedlings up to 95.0%; whereas in the mung bean and common bean crops, the application of mineral fertilizer rates of N90P90K40 kg/ha ensures a reduction of seedling mortality during the growing season to 6.5–4.6% and an increase in the survival of emerged seedlings up to 93.5–95.4%.

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DEVELOPMENT AND APPLICATION OF A COMBINED DIGITAL PHONENDOSCOPE WITH AN INTEGRATED PULSE OXIMETER AND SUPPORTING SOFTWARE APPLICATION

A.S. Madakhanov[1], I.K. Mavlyanov[2], I.I. Kamiljanov[3]
Andijan State Medical Institute; Andijan, Uzbekistan[1 2 3]
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Abstract. *This article presents information on the technology of using a combined digital phonendoscope with an integrated pulse oximeter in the educational process. The study emphasizes its advantages in improving the organization, quality, and overall effectiveness of the learning process, which is essential for the development of students' professional competencies related to the diagnostic and therapeutic components of medical practice. The implementation of this technology contributes to more effective clinical training by enhancing the accuracy of auscultation, facilitating objective monitoring of physiological parameters, and supporting modern approaches to medical education.*

Keywords: *traditional phonendoscope, digital phonendoscope, combined phonendoscope, pulse oximeter, sound amplification, signal filtering, artifacts, educational process, telemedicine, artificial intelligence.*

Introduction

Ensuring the availability of qualified personnel at all stages of the formation and development of the healthcare system has long been regarded as one of the most important conditions for increasing the effectiveness of this multi-level system of medical care delivery to the population. It is widely recognized that the efficiency of this system, among other factors, largely depends on its provision with modern therapeutic and diagnostic technical equipment and technologies. This explains the considerable attention devoted to the widespread introduction of new equipment and innovative technologies into all areas of modern medicine and healthcare, which significantly contribute to improving the organization, quality, and efficiency of diagnostic, therapeutic, and preventive processes [2,8,10,13,17,21].

In this regard, the role and importance of introducing modern equipment and technologies into educational processes in the field of medicine are difficult to overestimate. Under the conditions of a steadily increasing prevalence of cardiovascular and respiratory diseases, the above-mentioned factors determine the relevance of developing technical devices and improving technologies aimed at enhancing the quality of training specialists in the fields of cardiology and pulmonology.

It is well known that as early as the beginning of the century, electronic phonendoscope stethoscopes [12,23,24], electronic stethoscopes [3,4], and multichannel electronic stethoscopes [13] were developed and created. These devices incorporate specialized units that allow high-resolution recording, storage, filtering, and processing of acoustic signals. Sounds obtained using digital stethoscopes can also be analyzed through computer software, thereby making the learning process more effective [5,7,8,9]. However, in practice both in clinical medical activities and in medical education the use of stethoscopes, particularly digital ones, remains relatively rare. In clinical practice, stethoscopes, including digital versions [8], are mainly used in obstetrics for

monitoring the fetal heartbeat within the uterus. In contrast, practicing physicians, academic staff, and medical students primarily use phonendoscopes. These devices enable the auscultation of heart sounds and murmurs, as well as respiratory sounds in the lungs and bronchi in both adults and children.

The main objective of using a phonendoscope is to characterize and assess the functional condition of the cardiovascular and respiratory systems through this widely available technical tool. The traditional approach using a conventional phonendoscope allows the functional state of each of these two systems to be evaluated separately. At the same time, the patient's condition and the need to provide urgent medical care often require physicians to rely on an integrated assessment of the functioning of both the cardiovascular and respiratory systems. The above considerations confirm the relevance of developing and creating a new technical device a combined digital phonendoscope with an integrated pulse oximeter along with the software necessary to ensure its effective operation.

Purpose of the study: The purpose of this study is to establish a theoretical and organizational framework for a combined digital phonendoscope with an integrated pulse oximeter equipped with a specialized integrated mobile application.

Research objectives

1. To conduct a sociological study of the opinions of medical students and practicing physicians regarding the feasibility of developing a combined digital phonendoscope with an integrated pulse oximeter.
2. To develop a set of specialized software programs mobile applications for the combined digital phonendoscope with a pulse oximeter, ensuring its targeted use in both educational and clinical diagnostic processes and enabling the following functions:

2.1. Reception of heart sounds and murmurs, as well as respiratory sounds from traditional auscultation points on the chest, and their filtering from artifacts.

2.2. Recording, storage, and transmission of auscultation data in real-time streaming format for prompt use in the organization of emergency and urgent medical care by family physicians, paramedics, patronage nurses, as well as trained patients or caregivers.

2.3. Playback of recorded auscultation data for use in diagnostic and educational processes.

2.4. Transmission of sounds to external speakers to amplify heart sounds, murmurs, and respiratory sounds during educational sessions and clinical consultations.

2.5. Transmission of data for use in telemedicine systems in the following formats:

2.5.1. "Attending physician – specialist consultants participating in a clinical consultation,"

2.5.2. "Patient – attending physician."

3. To determine the optimal duration of auscultation at specific cardiac and pulmonary points when using both traditional and combined digital phonendoscopes in the educational process, and to conduct a comparative evaluation of their effectiveness and diagnostic informativeness.
4. To develop a program and plan for testing the methodology and techniques of using the combined digital phonendoscope in the educational process during clinical training sessions.
5. To design a program and plan for testing the methodology and techniques of using the digital phonendoscope in order to improve the effectiveness of diagnostic processes in cardiology and pulmonology at the primary healthcare level.

Materials and Methods

The materials used to accomplish the research objectives consisted of the results of a questionnaire survey conducted among senior medical students (210 participants), master's degree students (155 participants), and practicing physicians of various specialties (65 participants). The theoretical foundation for the development of the combined digital phonendoscope with an integrated pulse oximeter was based on scientific studies addressing physical methods for the diagnosis of cardiopulmonary diseases [19], as well as the advantages of digital technologies particularly digital stethoscopes and their application in medical practice [1,8], including their use in the diagnosis of cardiovascular diseases [11,15] and respiratory system disorders [6,9,14]. In addition, the study took into account reports by several authors concerning not only the effectiveness [7,20] but also the capabilities and limitations of digital stethoscopes [16].

During the development of the technical component of the device, we relied on the circuit board design of a digital stethoscope previously proposed by other researchers [3,4,12,24]. It should also be noted that in the process of developing the digital phonendoscope and its accompanying software application, we were guided by fundamental dialectical principles, namely the law of the negation of the negation and the law of the transformation of quantitative changes into qualitative changes. During the testing and evaluation of the main stages of using the combined digital phonendoscope with an integrated pulse oximeter, the methods of observation, comparison, measurement, and logical analysis were applied.

Results and Discussion

The results of the sociological survey demonstrated that the majority of senior undergraduate students (182 respondents, 86.6%) and master's students (147 respondents, 95.0%) positively evaluated the necessity of developing and implementing a combined digital phonendoscope with an integrated pulse oximeter operating on the basis of a specialized mobile application. According to their opinion, such a solution would become an important factor in improving the quality of both theoretical and practical training in clinical disciplines. It should be particularly noted that 60 surveyed physicians (92.0%) also supported the view that the use of this technical device in medical practice would be highly significant, especially for establishing a diagnosis in emergency and urgent situations. They also emphasized the feasibility and potential of using this device for the comparative assessment of the quality and effectiveness of medical care provided over time.

In our development, unlike other existing analogues, a phonendoscope which is more commonly used in practical medicine was chosen as the primary device instead of a stethoscope, which is relatively less frequently used in routine practice. Furthermore, a pulse oximeter was structurally integrated with the phonendoscope within a single housing. A specialized software program in the form of a mobile application was developed to enable the simultaneous reception of incoming heart sounds and murmurs as well as respiratory sounds from the lungs, along with their filtering from external artifacts. Another specialized mobile application was designed to ensure the integration of data obtained from the two components of this system the digital phonendoscope and the pulse oximeter organized within a "network center."

This program also ensures the storage of heart sounds, murmurs, and respiratory sounds, their representation in the form of waveform graphs, and their transmission via a specially registered operational email to a highly qualified medical specialist. The implementation of another important function assigned to the combined digital phonendoscope with an integrated pulse oximeter the ability, when necessary, to reproduce heart sounds, murmurs, and respiratory

sounds both in their natural acoustic form and as waveform graphs is provided by a dedicated software module called “Playback.”

Within the framework of the research objectives, and based on data from scientific and practical literature concerning the structure and functions of a combined digital phonendoscope and a pulse oximeter, as well as additional recommendations proposed by the authors, the device was manufactured by engineering and technical specialists in the People’s Republic of China. The specialized mobile application ensuring the coordinated operation of the combined digital phonendoscope and pulse oximeter was developed by IT specialists on the basis of graphical designs and technical recommendations provided by the authors.

A program and plan were also developed for testing the methodology and techniques of using the digital phonendoscope with a pulse oximeter in the educational process during classes in clinical disciplines. The combined digital phonendoscope with an integrated pulse oximeter, along with the corresponding mobile applications, was tested and discussed in practice at the Department of Phthisiology and Pulmonology of Andijan State Medical Institute with the participation of students and the faculty members of the department. According to the participants, this diagnostic device will occupy a significant place among modern educational and technical tools used to enhance the quality and effectiveness of both theoretical and practical training related to the study of cardiac and pulmonary function.

In addition, the device contributes to the development of students’ competencies in consulting with specialists during the primary diagnostic assessment of patients, relying on clinical experience, and performing analytical evaluations with the assistance of artificial intelligence. According to the participants, the use of a combined digital phonendoscope with a pulse oximeter and a dedicated mobile application is also of particular importance in paramedical practice. This technology makes it possible to perform rapid assessment of the patient’s cardiovascular condition (heart sounds, murmurs, and rhythms) and respiratory status (SpO_2), facilitate the early detection of hypoxia, transmit clinical data to physicians remotely, support timely clinical decision-making, and improve the quality of medical care prior to hospitalization.

In order to develop a specialized circuit board for the combined digital phonendoscope with a pulse oximeter and the corresponding mobile applications ensuring its targeted use, a dedicated board design and software application were created. As a result, it became possible to receive heart sounds, murmurs, and respiratory sounds from auscultation points on the chest specified in the patient monitoring protocol. At the same time, in order to avoid obtaining distorted information regarding respiratory function, the protocol included an additional mandatory auscultation of the lungs along the lateral lines on both sides of the chest. It should be noted that the high-quality recording and storage of auscultation data were ensured by a specially designed module integrated into the device’s circuit board. The playback of recorded auscultation data was carried out using a dedicated technology operating through the software program “Playback.”

Practical experience demonstrated the feasibility of using the combined digital phonendoscope with an integrated pulse oximeter in the educational process after students have completed initial training in the university’s simulation laboratory. At this stage, students’ attention is drawn to the distinctive differences in heart sounds and murmurs between healthy individuals and patients with pathological conditions. It should be emphasized that this format of training is highly engaging for students. At the same time, students clearly understand that the heart sounds and murmurs they have listened to were reproduced on a mannequin, which naturally creates a desire to repeat the procedure on a real patient.

In this regard, the use of a combined digital phonendoscope with a pulse oximeter proves to be particularly appropriate, as it not only reinforces theoretical knowledge but also leaves a lasting impression of the specific heart sounds and murmurs observed in an actual patient. For this reason, subsequent training sessions devoted to the cardiovascular and respiratory systems are conducted using the combined digital phonendoscope with an integrated pulse oximeter. Such training sessions may be organized in several formats. In the first format, the instructor, at the patient's bedside, invites one of the students to perform cardiac auscultation using the combined digital phonendoscope with a pulse oximeter. The student begins auscultation at the traditional points on the chest. The detected heart sounds and murmurs are transmitted in real time via a mobile application to the smartphones of other students participating in the class. A more detailed review and discussion of the characteristics of heart sounds, murmurs, and pulmonary sounds in patients are then conducted in the classroom. In this setting, the sounds are reproduced through a standard speaker amplifier.

Participants involved in the testing of the combined digital phonendoscope with a pulse oximeter and its application technology noted that, compared with the traditional phonendoscope, this approach significantly reduces the time required for auscultation and collective discussion of a patient by a group of students. For example, auscultation of the heart by one student at a single listening point using a conventional phonendoscope requires approximately fifteen seconds. At five standard cardiac auscultation points, the procedure therefore takes about seventy-five seconds. If the examination is performed individually by ten students, the total time required increases to approximately 750 seconds.

Similarly, if it is taken into account that for a complete pulmonary auscultation one student requires about ten seconds at a single listening point, then examination at twelve points on the anterior chest, fourteen points on the posterior chest, and five points along both the right and left lateral sides of the thorax requires a total of approximately 460 seconds. If this value is multiplied by ten students, the total time required reaches 4,600 seconds. Naturally, in such circumstances a patient is not always willing to be examined by all ten students, especially one after another. For this reason, auscultation with a conventional phonendoscope is usually limited by the instructor to only one student, which significantly affects both the sequence and the overall effectiveness of the teaching session. This limitation becomes particularly evident when detailed and thorough discussion of the characteristics of heart sounds, murmurs, and respiratory sounds in a particular patient is required.

In such situations, the use of a combined digital phonendoscope with an integrated pulse oximeter becomes an essential solution for preventing these difficulties due to its functional capabilities described above. After performing auscultation of the patient, the instructor and students move from the hospital ward to the classroom, where the recorded heart sounds, murmurs, and respiratory sounds are discussed. Particular attention is paid to cardiac activity normal heart sounds in healthy individuals and pathological murmurs in patients as well as to respiratory sounds, including vesicular breathing in healthy individuals and bronchial breathing and additional abnormal sounds in patients, such as dry rales, moist rales, and crepitation.

Thus, digital phonendoscopes equipped with a pulse oximeter serve as an important tool in the study of diseases of the cardiovascular and respiratory systems. Their use in clinical training contributes to improving the quality of education and helps students develop essential practical skills. The data obtained through digital stethoscopes can be easily analyzed by students, which significantly enhances the effectiveness of the learning process.

At the present stage, the research is focused on developing a program and implementation plan, as well as testing the methodology and techniques for using the digital phonendoscope with a pulse oximeter to improve the efficiency of diagnostic processes in cardiology and pulmonology at the primary healthcare level. The program also предусматривает the transmission of clinical data for use within telemedicine systems in the following formats: “Patient - Attending Physician” and “Attending Physician-Specialist Consultants (participants of a clinical consultation).”

Conclusions and Recommendations

1. In the context of the growing importance of diagnostic methods in the early detection and treatment of cardiovascular diseases and respiratory disorders, the development, creation, and wide implementation of advanced technical devices in clinical practice are becoming increasingly relevant. This represents one of the most important priorities of modern medicine and healthcare.
2. The testing and evaluation of the combined digital phonendoscope with an integrated pulse oximeter developed by the authors, along with its accompanying mobile applications, demonstrated a high level of effectiveness in its application within the educational process.
3. The mass production of the combined digital phonendoscope with a pulse oximeter and its mobile application, as well as their provision to faculty members and students of higher and secondary specialized educational institutions, in addition to practicing healthcare professionals, will represent an important step toward creating highly effective conditions and improving the technologies used in both medical education and clinical practice.

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RECENT INNOVATIONS IN MINIMALLY INVASIVE CARDIAC SURGERY (MICS)

A. Odilov[1], I. Khasanov[2], A. Choriyev[3], E. Islomov[4]
Student at Asia International University, Bukhara, Uzbekistan[1,2]
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Abstract. *Minimally invasive cardiac surgery (MICS) has significantly transformed modern cardiac surgical practice. Instead of performing procedures through a full median sternotomy, surgeons increasingly use small thoracic incisions, endoscopic cameras, and robotic platforms to access the heart. These techniques aim to reduce surgical trauma, postoperative pain, and recovery time while maintaining the same therapeutic effectiveness as conventional open-heart surgery. Recent technological developments—including robotic mitral valve repair, totally endoscopic coronary artery bypass (TECAB), advanced intraoperative imaging, and hybrid operating rooms—have further expanded the possibilities of minimally invasive cardiac procedures. Clinical studies show that MICS is associated with reduced hospital stays, improved cosmetic outcomes, and faster return to daily activities. This article reviews the most important technological and clinical innovations in minimally invasive cardiac surgery, describes their advantages and limitations, and discusses their potential implementation in developing healthcare systems, particularly in Central Asia and Uzbekistan.*

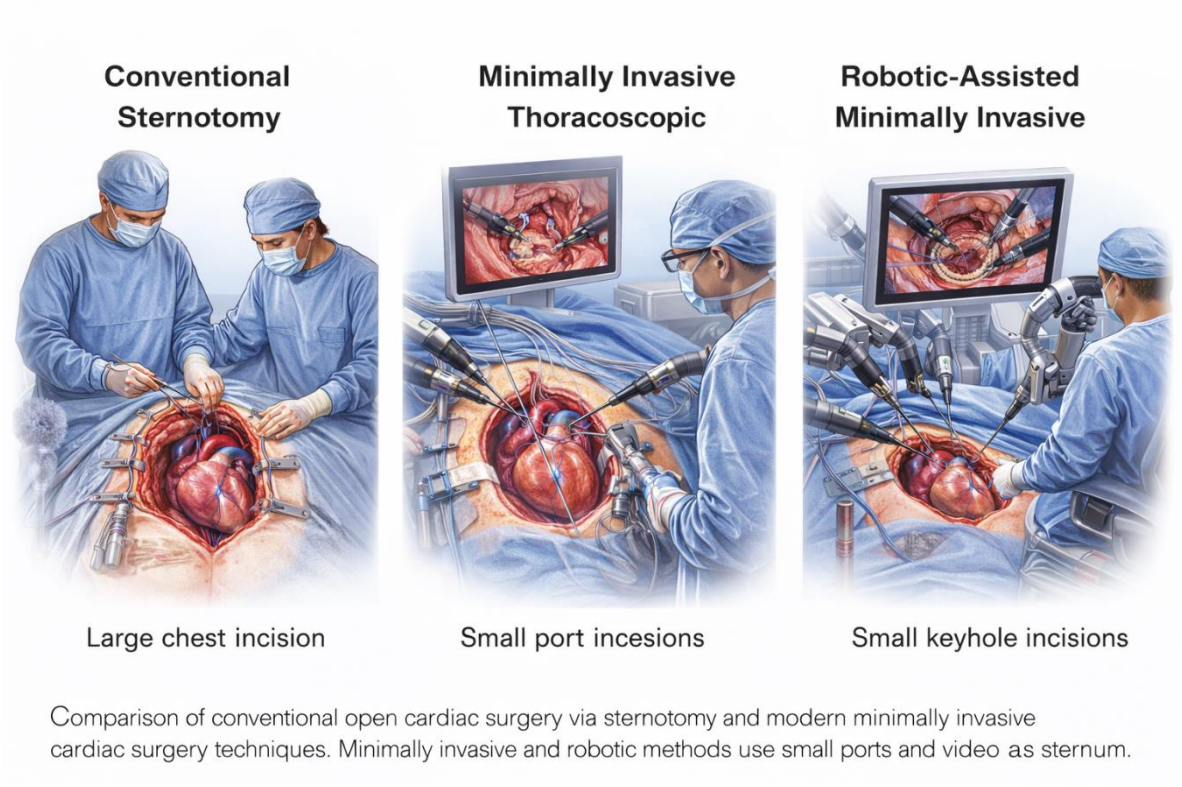
Keywords: *minimally invasive cardiac surgery (MICS); cardiothoracic surgery; robotic cardiac surgery; totally endoscopic coronary artery bypass (TECAB); mitral valve repair; thoracoscopic surgery; robotic surgical systems; cardiovascular innovation; surgical technology; Uzbekistan healthcare development.*

Introduction

Over the past two decades, minimally invasive cardiac surgery (MICS) has become an important development in the field of cardiothoracic surgery. Traditional open-heart surgery typically requires a full median sternotomy, which involves dividing the sternum to access the heart. Although this approach provides excellent exposure for surgeons, it is associated with significant surgical trauma and longer recovery periods. Minimally invasive techniques aim to perform the same cardiac procedures through smaller incisions using specialized instruments, thoracoscopic cameras, and sometimes robotic surgical systems. These approaches reduce tissue damage and help improve postoperative recovery while maintaining surgical safety and effectiveness.

Clinical studies have demonstrated that patients undergoing minimally invasive cardiac surgery often experience reduced postoperative pain, shorter intensive care unit stays, lower infection rates, and faster return to normal activities compared with conventional sternotomy procedures.

Although many advanced cardiac centers in Europe and North America have widely adopted minimally invasive techniques, their implementation in Central Asia remains limited. In Uzbekistan, most cardiac operations are still performed using traditional open surgical approaches. However, growing investment in medical technology and international collaboration may create new opportunities for the adoption of minimally invasive cardiac procedures in the region.



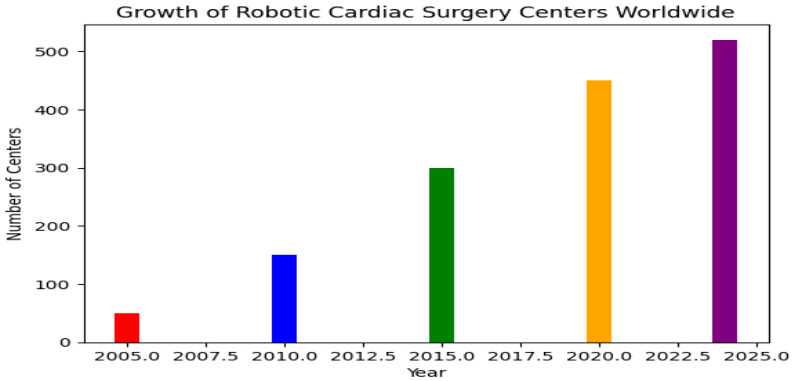
Comparison of conventional open cardiac surgery via sternotomy and modern minimally invasive cardiac surgery techniques. Minimally invasive and robotic methods use small ports and video as sternum.

Epidemiology

MICS has expanded rapidly in many developed countries. Today:

- A large portion of **mitral valve surgeries** in Europe and the U.S. are done using minimally invasive or robotic techniques.
- More than **500 centers worldwide** offer robotic cardiac surgery.
- **Hybrid operating rooms** are becoming standard for advanced cardiac and vascular procedures.

In Central Asia, including Uzbekistan, the use of MICS is growing slowly. The main challenges are equipment cost, limited training, and lack of specialized centers. However, with increasing demand for modern techniques, many hospitals are planning to introduce mini-thoracotomy valve surgery and improved cannulation methods. Recent international studies indicate that minimally invasive mitral valve surgery can reduce hospital stay by approximately **30–40%** compared with conventional sternotomy procedures. Additionally, several large clinical registries report that robotic mitral valve repair has a **success rate exceeding 95% in experienced centers**, with very low operative mortality. These outcomes demonstrate that minimally invasive approaches can achieve results comparable to traditional surgery while improving postoperative recovery.



Innovations in Minimally Invasive Cardiac Surgery

1. Robotic-Assisted Cardiac Surgery

Robotic systems, especially the da Vinci platform, allow surgeons to work through tiny ports with excellent precision. The robot provides:

- A 3D high-definition view
- Very fine instrument control
- Better access to deep structures of the heart

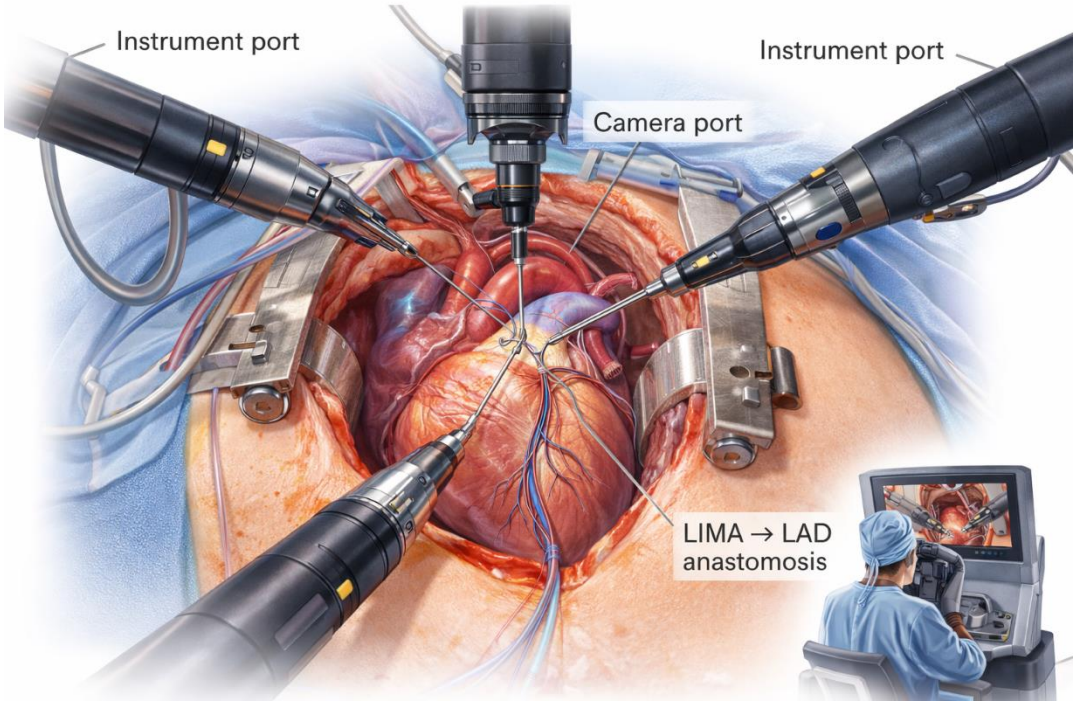
Common robotic procedures include mitral valve repair, ASD closure, and internal mammary artery harvesting. Robotic surgery reduces trauma and improves cosmetic results, but it requires advanced training and a dedicated team.

2. Totally Endoscopic Coronary Artery Bypass (TECAB)

TECAB is one of the most advanced forms of MICS. The entire coronary bypass procedure is done endoscopically, without opening the chest. Benefits include:

- No sternotomy
- Faster healing
- Very small incisions

Although technically demanding, TECAB offers similar results to traditional CABG when performed in experienced centers.



3. Minimally Invasive Valve Surgery

This is currently the most common application of MICS. It includes:

- Mini-thoracotomy mitral valve repair
- Mini-sternotomy aortic valve replacement
- Robotic mitral repair

Patients usually recover quickly, and the risk of wound complications is much lower. Modern imaging—especially 3D echocardiography—helps surgeons achieve precise and durable repairs.

4. Hybrid Operating Rooms

Hybrid ORs combine surgery with real-time imaging such as fluoroscopy, CT, and 3D mapping. This allows:

Combined surgical and catheter-based procedures

More accurate navigation

Improved safety during complex repairs

Hybrid rooms are particularly useful for aortic surgery and structural heart disease.

5. Improvements in Perfusion and Cannulation

To perform MICS safely, surgeons often use **peripheral cannulation** through the femoral or axillary arteries. Other innovations include:

- Mini-circuits that reduce inflammation
- CO_2 insufflation to prevent air embolism
- Better biocompatible materials

These developments make minimally invasive procedures safer and more effective.

6. Advanced Imaging and Navigation

Modern imaging plays a major role in MICS. Surgeons rely on:

- CT scans for preoperative planning
- 3D transesophageal echocardiography during surgery
- Fluorescent imaging to check grafts
- Augmented reality for anatomical guidance

These tools help perform delicate operations through small incisions with high accuracy.

Clinical Presentation and Diagnostic Workup (for MICS Candidates)

Patients considered for MICS usually have:

- Valve diseases (mitral or aortic)
- Coronary artery disease needing bypass
- Atrial septal defects
- Certain congenital heart conditions

Diagnostic workup includes:

- ECG
- Echocardiography
- CT angiography (especially to check peripheral vessels)
- Full lab tests

Patient selection is important. Some patients—such as those with severe aortic calcification or multiple previous heart surgeries—may be better suited for traditional sternotomy.

Management

Intraoperative Management

During MICS, surgeons use:

- Small ports or mini-thoracotomy
- Long-shafted instruments
- Robotic or endoscopic visualization
- Peripheral cannulation for cardiopulmonary bypass
- CO_2 to protect against air embolism

Anesthesia management is also important, especially for single-lung ventilation.

Postoperative Management

After surgery, patients typically experience:

- Faster extubation

- Earlier mobilization
- Less postoperative pain
- A shorter stay in the ICU and hospital

Routine checks include ECG, echocardiography, and blood tests. Complications are less common but can include bleeding, stroke, or arrhythmias.

Conclusion

Minimally invasive cardiac surgery represents one of the most important technological advances in modern cardiothoracic surgery. The development of robotic surgical systems, advanced intraoperative imaging, hybrid operating rooms, and improved perfusion technologies has made it possible to perform complex cardiac procedures through small incisions while maintaining excellent surgical outcomes.

Clinical evidence suggests that minimally invasive techniques can significantly reduce surgical trauma, shorten hospital stays, and improve patient recovery compared with traditional sternotomy-based approaches. Despite the advantages, challenges such as high equipment costs, a steep learning curve, and the need for specialized training still limit widespread adoption. For countries such as Uzbekistan, the gradual introduction of minimally invasive cardiac surgery could play an important role in modernizing cardiovascular care. Continued investment in medical technology, surgeon training, and international collaboration will be essential for expanding access to these advanced surgical techniques in the region.

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MODERN BIOLOGICAL HAZARDS IN FOOD SAFETY SYSTEMS: A LITERATURE REVIEW

Sh.X. Keldiyorova
Assistant, Department of Biological Chemistry, Samarkand State Medical University, Samarkand, Uzbekistan
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Abstract. *This article presents a review of scientific literature on modern biological hazards in the food safety system, their sources, and their impact on human health. Bacteria, viruses, parasites, mycotoxins, and antibiotic-resistant microorganisms are considered the main biological threats to food safety. Based on scientific sources, it is substantiated that globalization, intensive agriculture, increasing complexity of logistics systems, and climate change significantly contribute to the spread of biological hazards. The importance of modern monitoring technologies, biosensors, and molecular diagnostic methods is highlighted.*

Keywords: *food safety, biological hazard, pathogenic microorganisms, mycotoxins, zoonoses, antibiotic resistance, monitoring.*

INTRODUCTION

At present, food safety is recognized as one of the most important priority areas of the global healthcare system. Due to population growth, the acceleration of urbanization processes, the expansion of international trade relations, and the intensification of food production technologies, ensuring the quality and safety of food products has become an urgent issue not only at the national but also at the international level. In modern conditions, the concept of food safety is defined not only by the sufficiency or availability of food products, but also by their biological, chemical, and physical safety, as well as their compliance with sanitary requirements and hygienic standards.

Among the factors threatening food safety, biological hazards occupy a special place. Biological hazards refer to pathogenic microorganisms, viruses, parasites, fungi, and their metabolites that may be present in food products. When these agents enter the human body, they may cause infectious diseases of varying severity, toxic poisoning, and chronic pathological conditions. According to statistical data, foodborne diseases occupy one of the leading positions in the global structure of morbidity and cause harm to the health of millions of people every year. This situation indicates the necessity of conducting in-depth scientific studies of biological hazards and improving mechanisms for their control.

Modern scientific studies indicate that the occurrence of biological hazards in the food system is a multifactorial process that may arise at any stage of food production, processing, storage, and transportation. Table 1 presents the main biological hazards found in food products and their characteristics. The widespread use of antibiotics and pesticides in agriculture, the application of intensive technologies in livestock production, contamination of water resources, and non-compliance with sanitary regulations increase the risk of pathogenic microorganisms entering the food chain. At the same time, the development of the global logistics system enables food products to travel long geographical distances in a short period of time, thereby creating conditions for the transboundary spread of biological hazards.

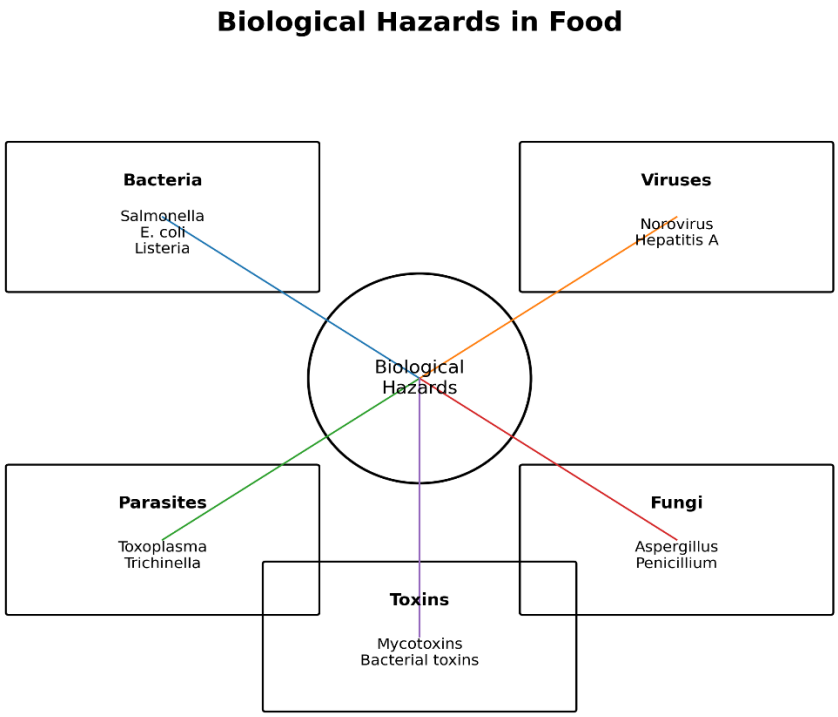


Figure 1. Classification of biological hazards in food products.

- bacteria — 60%
- viruses — 25%
- parasites — 10%
- toxins — 5%

Table 1. Main biological hazards found in food products

No	Type of Biological Hazard	Source	Diseases	Food Type	Risk Level
1	*Salmonella* spp.	Poultry meat	Salmonellosis	Meat, eggs	High
2	*E. coli* O157:H7	Beef	Enterocolitis	Meat	High
3	*Listeria monocytogenes*	Dairy products	Listeriosis	Milk, cheese	High
4	Norovirus	Contaminated water	Gastroenteritis	Vegetables	Moderate
5	Mycotoxins	Mold contamination	Food poisoning	Grain	High
6	Parasites	Meat	Helminthiasis	Meat	Moderate
7	Antibiotic-resistant bacteria	Livestock production	Infections	Meat	High

Climate change is also one of the factors that significantly affects the biological component of food safety. Increases in temperature, changes in humidity levels, and extreme weather events directly influence the ecology of microorganisms, which may accelerate their growth rate or contribute to their spread into new regions. As a result, pathogens that were previously absent in certain areas are increasingly being detected in new geographical zones. This situation creates new challenges for epidemiological surveillance systems.

Another important aspect of biological hazards is their evolutionary adaptability. Microorganisms acquire new characteristics through genetic mutations and horizontal gene transfer, which contributes to the emergence of antibiotic-resistant strains. The increase in

antibiotic resistance is directly associated with food safety, and the use of prophylactic antibiotics in livestock production is considered one of the key factors accelerating this process. As a result, resistant bacteria entering the human body through food complicate treatment processes and exacerbate the outcomes of infectious diseases.

In recent years, the implementation of modern scientific technologies has gained significant importance in ensuring food safety. Molecular biology, genomics, biosensor technologies, rapid diagnostic systems, and monitoring platforms based on artificial intelligence enable the early detection of biological hazards, prediction of their spread, and prevention of potential risks. These technologies provide higher accuracy, speed, and sensitivity compared with traditional laboratory methods, thereby advancing the food control system to a qualitatively new level.

In this regard, conducting a systematic analysis of the current state of biological hazards in the food safety system based on scientific literature, identifying the mechanisms of their occurrence, and evaluating control strategies represent important scientific tasks. The significance of this study lies in the fact that it summarizes scientific approaches aimed at ensuring food safety and provides a theoretical basis for developing effective mechanisms for the management of biological hazards.

Materials and Methods. The article analyzes international scientific publications published between 2005 and 2024, including reports of the World Health Organization (WHO), the Food and Agriculture Organization (FAO), the European Food Safety Authority (EFSA), as well as monographs related to food microbiology and hygiene. The literature was selected according to the following criteria: epidemiology of foodborne diseases; biology of pathogenic microorganisms; toxicology of mycotoxins; the problem of antibiotic resistance; and food monitoring technologies. The analysis was conducted using methods of systematic comparison, conceptual generalization, and scientific synthesis.

Literature Review.

Concept of Biological Hazards. In the food safety system, biological hazards refer to microorganisms, parasites, or their toxins that may be present in food products and have the potential to harm human health (WHO, 2022). These hazards may occur at all stages of the food chain, from production to consumption (FAO, 2021). In scientific literature, biological hazards are generally classified into several groups, including bacteria, viruses, parasites, and mycotoxins (Adams & Moss, 2018).

Bacterial Pathogens. The majority of foodborne diseases are associated with bacterial contamination, and the most significant pathogens include Salmonella, Escherichia coli, Listeria monocytogenes, and Campylobacter (CDC, 2022). These microorganisms can rapidly multiply in food products, and some of them are capable of growing even under refrigerated conditions (Jay, 2012). In particular, Listeria monocytogenes is considered especially dangerous for refrigerated food products due to its ability to grow at low temperatures (EFSA, 2023).

Viral Biological Hazards. Among foodborne viruses, noroviruses and the hepatitis A virus are considered the most epidemiologically significant (WHO, 2022). Although viruses do not multiply in food, they can persist for long periods and are capable of causing disease even at very low infectious doses (FAO, 2021). Viral contamination is mainly associated with poor compliance with hygiene and sanitation regulations (Adams & Moss, 2018).

Parasitic Hazards. Parasites cause less frequent but often more severe forms of foodborne diseases. For example, infections caused by Toxoplasma gondii and Trichinella spiralis are

transmitted through insufficiently heat-treated meat (WHO, 2022). The development of global trade systems has contributed to the spread of parasitic diseases into new geographical regions (FAO, 2021).

Mycotoxins. Mycotoxins produced by fungi are among the most dangerous biological factors affecting food safety (Pitt & Hocking, 2009). Aflatoxins are particularly known for their hepatotoxic and carcinogenic effects and are commonly found in grain products (WHO, 2022). One of the main characteristics of mycotoxins is their resistance to thermal processing, meaning that they are not completely destroyed during cooking (Jay, 2012).

Antibiotic-Resistant Microorganisms. Antibiotic resistance has become one of the major global challenges of modern food safety systems. The extensive use of antibiotics in livestock production contributes to the emergence of resistant bacterial strains that may enter the human body through food consumption (WHO, 2023). This situation complicates the treatment of infectious diseases and increases epidemiological risks (FAO, 2021).

Modern Diagnostic and Monitoring Methods. In recent decades, methods for detecting biological hazards in food safety systems have significantly improved. Traditional microbiological culture methods remain the primary diagnostic tools; however, due to the time required for their implementation, they are increasingly complemented by rapid molecular techniques in modern laboratory practice (Jay, 2012).

Table 2. Modern diagnostic methods used for detecting biological hazards in food products.

Method	*Target Detected*	*Advantage*
PCR	Bacterial DNA	Rapid detection
ELISA	Toxins	High accuracy
Cultivation	Bacteria	Standard method
Biosensor	Toxins	Modern technology

One of the most effective innovative technologies is the polymerase chain reaction (PCR), which enables the rapid detection of the genetic material of pathogenic microorganisms within a short period of time. The real-time PCR modification not only allows the detection of the presence of pathogens but also enables the quantification of pathogen load, which is an important indicator for epidemiological assessment (EFSA, 2023).

The development of genome sequencing technologies has significantly expanded the possibilities for identifying foodborne pathogens and determining their sources. Through the use of whole-genome sequencing (WGS), it has become possible to determine the degree of genetic similarity between bacterial strains, thereby enabling the identification of infection sources and the tracking of outbreaks (CDC, 2022). This method is particularly important for monitoring the transboundary spread of pathogens under conditions of global trade.

Immunological diagnostic methods, including enzyme-linked immunosorbent assay (ELISA), are widely used for the detection of toxins and antigens. The main advantage of this method is its rapidity and high sensitivity, making it particularly effective for identifying mycotoxins and viral contamination (Adams & Moss, 2018). Biosensor technologies represent one of the most promising directions in food safety monitoring. Biosensors consist of a combination of a biological element (enzyme, antibody, or DNA fragment) and a physical detector, which enables the real-time detection of pathogens. These devices allow monitoring to be carried out directly on production lines, thereby facilitating the early detection of contamination (FAO, 2021).

The implementation of artificial intelligence and digital monitoring systems is further improving food safety control. Through the use of databases and algorithm-based predictive models, it has become possible to identify potential pathways of pathogen spread and to develop preventive measures in advance (WHO, 2022). This approach shifts the food safety system from a reactive model toward a proactive monitoring strategy. Analysis of the literature indicates that biological hazards represent one of the most complex components of food safety. Unlike chemical or physical hazards, biological threats involve living systems that are capable of rapid reproduction, adaptation, and mutation. In particular, the global logistics system accelerates the geographical spread of pathogens. In addition, climate change expands the ecological niches of microorganisms, leading to the emergence of new epidemiological risks. This situation demonstrates that classical control methods alone are no longer sufficient for ensuring food safety.

CONCLUSION.

The results of the literature analysis indicate that biological hazards represent one of the most complex and dynamic components of the food safety system. Bacteria, viruses, parasites, and fungal toxins constitute the major biological threats to human health and account for a significant proportion of disease incidence worldwide (WHO, 2022). The widespread occurrence of these hazards is directly associated with the intensification of food production technologies, the expansion of international trade, ongoing urbanization processes, and climate change (FAO, 2021). An important characteristic of biological hazards is their evolutionary adaptability and genetic variability. Microorganisms can rapidly adapt to new environmental conditions and form antibiotic-resistant strains. The issue of antibiotic resistance is also highly relevant in the food system and is considered a serious threat to global public health (WHO, 2023).

The introduction of modern molecular diagnostic methods, biosensor technologies, and genome analysis techniques has significantly improved the accuracy of detecting biological hazards and has advanced monitoring systems to a new level (EFSA, 2023). These technologies enable the early detection of pathogens and help prevent epidemiological risks. Thus, ensuring food safety requires an integrated approach that combines production control, laboratory monitoring, epidemiological surveillance, and digital technologies within a systematic strategy. The development of scientifically based monitoring mechanisms and the strengthening of international cooperation remain essential conditions for the effective management of biological hazards.

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THE ERA OF SMALL CALIBERS: MODERN ENDOSCOPIC AND LASER TECHNOLOGIES IN THE TREATMENT OF PEDIATRIC KIDNEY STONES

O.A. Gaybullayev[1], S.S. Kariev[2]
PhD. Center for Professional Development of Medical Personnel[1]
Scientific consultant, DsS[2]
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Abstract. *This study evaluates the efficacy of minimally invasive endoscopic approaches (Mini-PCNL and RIRS) in treating 46 patients with complex forms of urolithiasis at the National Children's Medical Center (NCMC). Mathematical and hydrodynamic modeling of the Stone Clearance Rate index was applied. The absence of a correlation between the child's age and the radiological density of the stone was proven, dictating new standards for the energetic equipment of pediatric operating rooms.*

Keywords: *endemic character, metabolic imbalance, hemorrhagic complications, iatrogenic strictures.*

1. Introduction

In modern pediatric practice, urolithiasis has ceased to be an orphan pathology, transitioning into the category of global epidemiological challenges. A meta-analysis published by **Tasian G.E. et al. (2016)** demonstrates an alarming annual growth in pediatric incidence of 4–6% **[1]**. Furthermore, in regions with a hot, arid climate (including Central Asian states), the epidemiological picture bears an endemic character. Fundamental studies by **Khudoibergenov U.A. et al. (2020)** convincingly prove that high mineralization of drinking water combined with excessive insolation are powerful triggers for early lithogenesis in the region **[2]**.

As noted by **Rizvi S.A. et al. (2023)**, in endemic zones, pediatric urolithiasis is characterized by a high recurrence rate, rapid stone growth, and a persistent association with urinary tract infections **[3]**. According to research by **Jobs K. (2018)**, the foundation of pathogenesis lies in a profound metabolic imbalance: hyperoxaluria and hypercalciuria lead to the formation of complex polymineral structures in 70% of patients **[4]**.

At the National Children's Medical Center (NCMC), acting as a reference center, patients with the most severe, neglected, and complicated forms of the disease are concentrated. The standard of surgical treatment for such children requires a perfect balance: a 100% Stone-Free Rate (SFR) with absolute minimization of trauma to the renal parenchyma.

In the arsenal of modern urology, this task is solved by two key technologies:

1. **Mini-PCNL (Mini-percutaneous nephrolithotomy):** The use of small-caliber sheaths (12–15 Ch), according to **Zeng G. (2021)**, minimizes hemorrhagic complications while maintaining a high rate of destruction **[5]**.
2. **RIRS (Retrograde intrarenal surgery):** The introduction of ultrathin (7.5 Ch) digital flexible ureterorenoscopes, as proven by **Traxer O. (2022)**, allows navigating anatomical obstacles without the risk of developing iatrogenic strictures **[6]**.

For selecting the method, stone density is a critically important predictor. **Gupta N.P. et al. (2020)** determined that with a density above 900 HU (Hounsfield units), contact laser lithotripsy

remains the only justified solution **[7]**. The present study is aimed at a comprehensive assessment of these techniques through the prism of hydrodynamics and clinical statistics.

2. Methodological Design and Clinical Base

2.1. Characteristics of the Pediatric Cohort (N=46)

A retrospective analysis covered 46 complex clinical cases treated at the NCMC. The initial demographic indicators of the cohort are reflected in Table 1.

Table 1. Initial age and gender profile of NCMC patients

Age group	**Boys (n)**	**Girls (n)**	**Total**	**Proportion (%)**
Early (1 – 5 years)	16	12	28	60.9%
Middle (6 – 10 years)	7	2	9	19.6%
Adolescents (11 – 16 years)	6	3	9	19.6%
Total	**29**	**17**	**46**	**100%**

The high proportion of early-age patients (60.9%) and the predominance of boys (1.7:1) confirm the hereditary-metabolic nature of the disease. Primary stones were diagnosed in 80% (n=37), and recurrent stones (after surgeries in other institutions) in 20% (n=9).

Depending on the chosen tactics, patients were divided into two groups:

- **Group 1 (Mini-PCNL, n=38):** stones in the renal pelvis and multiple calyceal calculi (including 3 staghorn stones).
- **Group 2 (URS/RIRS, n=8):** residual lower pole microliths and ureteral stones.

2.2. Preoperative Audit and Infection Profile

A mandatory stage of planning was MSCT with 3D modeling. We evaluated:

1. **Topographic and anatomical anomalies:** Identified in 13% of cases (duplication of the PCS, horseshoe kidney).
2. **Morphometry:** An infundibulopelvic angle of less than 45° was an indication for the use of a flexible instrument.
3. **Densitometry (HU):** Studying the radiological density for the selection of laser energy.

Given the severity of the NCMC patient contingent, urinary tract infections (UTI) were verified in **74% of children (n=34)**. Bacteriological culture revealed aggressive flora: *E. coli* (52%), *K. pneumoniae* (18%), *P. aeruginosa* (10%). All patients underwent a strict protocol of antibiotic prophylaxis with carbapenems and IV generation cephalosporins 5 days prior to intervention.

2.3. Technical Specifications of Surgical Interventions

The interventions were performed using advanced equipment:

- **Instrumentation:** For the PCNL group, a **Karl Storz 12 Ch** mini-nephroscope with a **15 Ch** working sheath was used. For the RIRS group, a **Hugmed 7.5 Ch** digital flexible video endoscope and a **10 Ch** ureteral access sheath were utilized.
- **Lithotripsy:** Performed with the **Quanta System 150** laser. Two modes were used:
  - *Fragmenting* (0.8–1.2 J / 10–15 Hz) — for breaking dense structures.
  - *Dusting* (0.2–0.5 J / 40–60 Hz) — for fine-dispersion dusting.

3. Surgical Treatment Results

3.1. Clinical Outcomes and Safety Profile

A comparative analysis showed the high efficacy of both accesses in their respective niches (Table 2).

Table 2. Intra- and postoperative parameters

Analyzed parameter	**URS Group (n=8)**	**PCNL Group (n=38)**	**p-value**
Linear stone size (cm)	0.68±0.1	1.58±0.3	p < 0.0001
Density (Hounsfield, HU)	640±95	910±140	p = 0.0001
Operative time (min)	66.2±8.2	84.5±12.5	p = 0.0005
Average hospital stay (days)	2.5±0.5$	2.9±0.7	p = 0.018

The most important achievement of the NCMC protocols was the control of infectious complications: despite initial bacteriuria in 74% of children, the incidence of postoperative pyelonephritis attacks (Clavien-Dindo II) was only **4.3% (n=2)**.

3.2. Hydrodynamic Rationale: Calculation of the Stone Clearance Rate

To integrate the NCMC results into the global scientific context, we calculated the **Stone Clearance Rate (SCR)** index using the methodology of **Breda A. (2022) [8]** and meta-analyses by **Jones P. (2021) [9]**:

$$SCR = V_{stone} / T_{active_laser}$$

- **Mini-PCNL Group:** With a size of 15.8 mm, the estimated stone volume (V) was ~1900 mm³. With an active destruction time of 52 minutes, the SCR was **36.5 mm³/min**. This exceeds the global average for children (28-32 mm³/min).
- **RIRS Group:** The SCR was **12.2 mm³/min**.

3.3. Complexity Predictors: Multivariate Correlation Analysis

To identify hidden patterns of lithogenesis, Pearson's correlation coefficient (r) was applied.

3.4. Urinary Tract Decompression Strategy

The analysis demonstrated a differentiated approach to drainage:

- **Pre-stenting:** Due to the spasticity of the pediatric ureter, a stent was placed 10-14 days prior to RIRS in 25% of cases.

- **Mini-PCNL:** In 87% of cases, an antegrade nephrostomy tube of 8–10 Ch was placed. In 13% of patients with perfect hemostasis, the advanced **"totally tubeless"** technique (without tubes) was applied, which radically reduced the need for analgesics.
- **RIRS:** The operation concluded with the placement of a "double J" stent in 100% of cases.

Table 3. Correlation Matrix

Studied pair of variables	Coefficient (r)	p-value	Correlation direction
Age vs Stone size	0.272	0.0024	Significant positive
Size vs Operative time	0.540	0.0001	Strong positive
Age vs Density (HU)	-0.030	0.7491	Absent

4. Discussion

Data analysis obtained at the NCMC allows us to draw several fundamental scientific conclusions that partially change the traditional paradigm of pediatric urology.

1. The Phenomenon of Stone Density in Early Age

The most significant result of the correlation analysis (Table 3) is the absolute absence of a relationship between the patient's age and stone density on the Hounsfield scale ($p = 0.7491$). Traditionally, it was believed that extremely dense stones are characteristic of adult patients with a long history of the disease. Our data prove: under the influence of aggressive genetic and metabolic factors of the region (and excess vitamin D/insolation), even in an infant in their first year of life, a stone of whewellite with a density over 1000 HU can form rapidly. This fact requires the mandatory equipping of pediatric operating rooms with high-power lasers (Quanta 150), as young age is no longer a guarantee of stone "softness."

2. Hydrodynamics and the "Vortex Effect"

The mathematical superiority of the clearance rate in Mini-PCNL (36.5 mm^3/min) over global standards is explained by the laws of hydrodynamics. The use of a **Karl Storz 12 Ch** nephroscope inside a **15 Ch** sheath creates an ideal gap for laminar fluid flow. According to Bernoulli's principle, the **"Vortex Effect"** is formed—a powerful reverse current that physically sucks the fragmented pieces outward. This eliminates the need for repeated use of surgical forceps, reducing kidney trauma and saving up to 20 minutes of anesthesia time.

In contrast, the flexible **Hugmed 7.5 Ch** endoscope has no lumen for aspiration. The entire stone mass must be turned into fine dust (*Dusting* mode), which naturally reduces the SCR to 12.2 mm^3/min but provides 100% protection against ureteral injury.

3. Progression and Time Prediction

The positive correlation between age and size ($r=0.272$) and the strong correlation of size with operative time ($r=0.540$) confirm that stone volume is the main "chronophage" (time consumer). Delaying surgical intervention leads to a cubic increase in stone volume, which exponentially complicates the operation.

5. Conclusion

The experience of the National Children's Medical Center (NCMC) demonstrates that the treatment of severe and complicated forms of urolithiasis in children requires a multidisciplinary and highly technological approach.

1. **Technological standard:** Minimization of instrument caliber (**Storz 12 Ch, Hugmed 7.5 Ch**) allows consistently achieving a Stone-Free Rate while reducing the hospital stay to 2.5–2.9 days.
2. **Hydrodynamic superiority:** Mathematical modeling proved that the realization of the "vortex effect" when using a 15 Ch sheath ensures a high kidney clearance rate (36.5 mm^3/min), minimizing the time the child spends under general anesthesia.
3. **Surgical tactics:** The lack of correlation between stone density and age obliges surgeons to apply a personalized approach to laser lithotripsy based on MSCT densitometry. Early detection of microliths allows the use of atraumatic retrograde approaches, reducing the need for kidney puncture. The introduction of the *totally tubeless* technique in percutaneous interventions is a promising direction for enhanced recovery after surgery (ERAS) in pediatrics.

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MODERN METHODS OF INTRAOCULAR LENS FIXATION WITH INSUFFICIENT CAPSULAR SUPPORT: A LITERATURE REVIEW

Z. R. Nazirova[1], D. M. Turakulova[2], A. A. Asatillaev[3]
Tashkent State Medical University, Tashkent, Republic of Uzbekistan[123]
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Abstract. *The aim of this study is a comprehensive analysis of existing methods and surgical techniques for intraocular lens (IOL) fixation in cases of insufficient or complete loss of capsular support. Special attention is given to evaluating the clinical effectiveness of different implantation approaches, their advantages, limitations, and potential risks of intra- and postoperative complications. The study includes a systematic review of recent scientific publications by both domestic and international authors on the problem of IOL implantation in aphakia and capsular bag insufficiency. The search and selection of sources were based on relevance, level of evidence, and practical significance of the data presented.*

Keywords: *cataract, intraocular lens implantation, Marfan syndrome, transscleral fixation.*

Introduction

Cataract remains one of the leading causes of visual impairment and blindness worldwide. According to the World Health Organization, lens opacity accounts for more than half of reversible blindness cases, reaching approximately 51% of the global ophthalmologic disease burden. The social significance of this disease is determined not only by its high prevalence but also by its pronounced impact on patients' quality of life, work capacity, and level of social adaptation. Currently, the only effective treatment for cataract is surgical removal of the opaque lens followed by intraocular lens (IOL) implantation. Modern phacoemulsification technologies and improvements in IOL design have significantly increased the safety of the procedure and improved functional outcomes. Nevertheless, clinical practice still faces challenges related to pathology of the lens zonular apparatus. According to various authors, 5–15% of cases show pronounced zonular insufficiency, and up to 20% of patients have subclinical forms of zonular weakness.

Disruption or functional insufficiency of the zonular apparatus complicates the surgical technique, increases the risk of intra- and postoperative complications (IOL dislocation, secondary glaucoma, inflammatory reactions), and may negatively affect the final visual outcome. In cases of insufficient capsular support, traditional IOL implantation in the capsular bag becomes impossible due to a high risk of decentration or lens displacement.

In such clinical situations, alternative IOL fixation methods are used: placement in the anterior chamber or posterior chamber implantation with fixation to the iris or sclera. Each method has its own indications, advantages, and limitations, which underscores the need for further refinement of surgical approaches and the development of criteria for selecting the optimal strategy. Factors contributing to complicated lens extraction may include traumatic eye injuries, primary zonular weakness, capsular bag insufficiency, and systemic or hereditary disorders. Notably, pseudoexfoliation syndrome, characterized by degenerative changes in the anterior segment of the eye, plays a significant role. Congenital connective tissue anomalies, such as those

seen in Marfan syndrome and homocystinuria, are also associated with pronounced zonular weakness, predisposing patients to lens subluxation or dislocation.

Thus, the high prevalence of cataract, combined with frequent zonular pathology, determines the relevance of developing and improving surgical methods for correcting aphakia in the absence of adequate capsular support. Studying this problem has important clinical significance and aims to increase the safety of surgical interventions and improve functional treatment outcomes.

Objective of the study. The objective of this work is a comprehensive analysis of existing methods and surgical techniques for intraocular lens (IOL) fixation under conditions of insufficient or complete loss of capsular support. Particular attention is paid to evaluating the clinical effectiveness of different implantation methods, their advantages, limitations, and potential risks of intra- and postoperative complications.

As part of the study, a systematic review of recent scientific publications by domestic and foreign authors was conducted, focusing on the problem of IOL implantation in aphakia and capsular bag insufficiency. Source selection was based on relevance, level of evidence, and practical significance. A total of 126 bibliographic sources were analyzed, including peer-reviewed journal articles, clinical guidelines, results of multicenter studies, and conference materials. Following a critical assessment of the scientific value of these publications, 58 sources were included in the final review, representing the most comprehensive and up-to-date view of the problem and its development directions.

Thus, the study aims to provide a reasoned understanding of modern approaches to IOL fixation in the absence of adequate capsular support and to identify optimal surgical strategies from an evidence-based medicine perspective. IOL fixation to the iris. One of the historically early approaches to non-standard IOL implantation in complicated cataract surgery was fixation to the iris. This method was applied in situations of insufficient capsular support and involved placing the lens in the pupil plane, anterior chamber angle, or directly fixing it to the iris tissue.

Sutureless Fixation Methods. Sutureless techniques include the use of iris–vitreal models, particularly the Artisan lens, which is based on the “claw” (iris-claw) mechanism. The structural feature of this IOL involves grasping the iris stroma with special fixation elements, providing relative stability of the lens position. Clinical observations indicate that initial implantation outcomes of such models were satisfactory. However, long-term outcome analysis revealed a risk of fixation mechanism splitting in 9.4% of cases, and according to other sources, up to 14% within the first 6–7 months postoperatively.

Anterior chamber IOLs with sutureless support in the angle of the anterior chamber also deserve mention. Despite the technical simplicity of implantation, these designs did not gain widespread adoption. Constant pressure on anterior chamber angle structures and relative lens mobility led to corneal endothelial trauma, chronic uveitis, secondary glaucoma, and corneal dystrophy. According to the literature, the frequency of such complications reached 35–40% of cases.

Sutured Fixation to the Iris. Sutured IOL fixation to the iris has become more widely used, especially in domestic ophthalmology practice. Significant contributions were made by S.N. Fedorov and V.D. Zakharov, who developed the iris-clip lens. The advantage of this design is the possibility of simultaneous correction of traumatic mydriasis. However, notable drawbacks include sphincter pupillae dysfunction, pronounced pigment dispersion, displacement of fixation elements (up to 13.6%), cystoid macular edema, endothelial cell loss, and iridodonesis.

With the introduction of modern flexible hydrophilic and hydrophobic IOL models implanted through small corneal incisions, the technique of suturing the lens to the iris has evolved. In the classical approach, the haptic elements are fixed to the mid-peripheral or peripheral iris using 10/0 polypropylene suture. The surgical procedure involves creating corneal paracenteses, passing the suture under the haptic element, and tying it without excessive tension to avoid tissue ischemia. The knot is buried under the iris to minimize contact with the anterior chamber.

Of particular interest is the 2020 method proposed by D.I. Ivanov, which involves fixation of the "IOL-capsular bag" complex to the iris. This approach demonstrates certain advantages in the long-term postoperative period, especially in cases of pronounced capsular fibrosis, as it avoids lens explantation or replacement, reducing the risk of repeat surgery.

Complications and Limitations. Despite its relative technical accessibility, sutured fixation to the iris is associated with potential complications, including iris atrophy, pigment dispersion, chronic uveitis, and cystoid macular edema. Continuous mechanical impact on the iris tissue may exacerbate postoperative inflammation. Therefore, iris fixation is clinically significant and relatively accessible, but the high frequency of inflammatory and degenerative complications necessitates individualized surgical strategy based on the anatomical and functional state of the anterior segment.

Scleral Fixation of IOLs. The development of methods for scleral fixation of IOLs aimed to minimize trauma to the eye's uveal tissue while maintaining physiologically justified posterior chamber positioning of the lens. Clinical and histopathological studies have shown that posterior chamber implantation offers advantages over anterior chamber placement, including reduced risk of corneal endothelial cell loss, damage to anterior chamber angle structures, pupillary block, and iritis. Moreover, the optical performance of the lens is maximized when placed in a position anatomically close to its natural location.

Posterior chamber fixation is particularly important in correcting aphakia in patients with pre-existing anterior segment pathology, including glaucoma, congenital iris defects (e.g., aniridia), and low corneal endothelial cell density. Satisfactory functional results have also been reported in patients with uveitis, indicating relative biocompatibility and stability of lens position.

Transscleral Fixation: Classification of Approaches. Transscleral IOL fixation can be performed using sutured or sutureless methods. Sutured techniques differ by the direction of the fixation suture: ab externo (outside–in) or ab interno (inside–out). Methods are also classified by the number of fixation points (two-, three-, or four-point stabilization), which affects IOL centration and stability within the ciliary sulcus.

Historical Aspects of Sutured Fixation. One of the first scleral sutured IOL fixation techniques was proposed by E.S. Malbran et al. in 1986. The lens was implanted after intracapsular cataract extraction, with haptics fixed to the sclera approximately 2 mm from the limbus using 10-0 polypropylene suture (ab externo) and a 28G needle. A critical technical consideration was avoiding the projection of long ciliary arteries (traditionally at 3 and 9 o'clock), which reduced the risk of vascular complications.

Further development was associated with J.S. Lewis et al., who popularized the ab externo technique with scleral flap creation and burial of the knot in the scleral bed, minimizing erosion and infection risk. An alternative ab interno approach was proposed by W.E. Smiddy et al. in 1990, in which the suture is passed from inside the eye outward through the ciliary sulcus. Despite no serious complications in their observations, a significant drawback remained—the "blind" passage of the needle about 1 mm posterior to the limbus, increasing the risk of intraocular structure

damage. An anterior vitrectomy was recommended to prevent vitreous entrapment or prolapse into the anterior chamber.

Modern Stage of Sutured Transscleral Fixation. The development of microinvasive technologies and new materials has advanced the technique. A. Hadayer et al. (2019) described an ab interno method using a foldable hydrophilic acrylic IOL implanted through a 2.4 mm corneoscleral incision with Gore-Tex suture. The use of non-absorbable synthetic sutures increases long-term fixation strength and reduces the risk of late suture degradation, a known problem with polypropylene threads.

Thus, transscleral IOL fixation provides anatomically justified posterior chamber positioning and superior optical and biomechanical characteristics compared with anterior chamber models. However, it requires high surgical skill and carries intraoperative risks, including hemorrhage, ciliary body injury, and IOL decentration due to asymmetric suture tension. Improvements in suture techniques, microinvasive access, and modern suture materials make scleral fixation one of the most physiologically favorable and promising methods for correcting aphakia in the absence of capsular support.

Traditional transscleral fixation methods relied on polypropylene sutures attached to haptics and exteriorized through the sclera. Despite technical accessibility, these methods had a significant drawback-the presence of an external suture knot. Gradual erosion through the scleral tissue or conjunctiva created a risk of infection and endophthalmitis, considered one of the most serious late complications.

In 1993, K. Solomon et al. proposed creating triangular scleral flaps in the limbal area to cover 10-0 polypropylene suture knots, aiming to reduce the risk of suture exposure. However, retrospective analysis demonstrated that even with this modification, the frequency of knot erosion reached 73% through the sclera and 17% through the conjunctiva within 9–12 months. The authors concluded that flap creation merely delays the onset of complications rather than eliminating them, which stimulated further refinement of the technique using scleral pockets.

A significant contribution was made by R.S. Hoffman et al. in 2006, who described a technique for creating scleral pockets without conjunctival dissection. This method involved two opposite clear corneal incisions in the limbal area followed by posterior dissection to form pockets within the scleral thickness. A 10-0 polypropylene suture was passed through a paracentesis, fixed to the IOL haptic, and externalized through the scleral pocket using a 27G guiding needle. After tying, the knot was buried inside the pocket, preventing contact with the external environment. The additional use of fibrin glue simplified fixation and ensured watertight closure.

Retrospective analysis by L. Yeung et al. (2018) demonstrated satisfactory functional outcomes using Hoffman pockets to cover knots during transscleral fixation of a foldable one-piece IOL. Among 40 operated eyes, no serious intraoperative complications occurred; minor vitreous hemorrhages, microhyphemas, and transient intraocular pressure elevations were reported. Cystoid macular edema developed in 8% of cases, and IOL decentration in 3%. Over a mean follow-up of six months, no cases of knot exposure or endophthalmitis were recorded.

An alternative approach to prevent suture erosion was proposed by P. Szurman et al. (2010), who developed a zigzag (Z-shaped) suture technique. This method involved passing the suture multiple times (up to five) through the sclera near the original puncture to form a looped fixation without an external knot. After completion, the suture was cut at the scleral level, eliminating the need for scleral flaps or pockets. In a series of 45 eyes, IOL fixation remained stable over a mean follow-up of 22 months, with only isolated cases of transient ciliary

hemorrhage. However, longer-term studies revealed limitations: using 9-0 polypropylene with a mean follow-up of 64 months, the rate of IOL dislocation reached 13.8%. Additional long-term data reported suture rupture in 16.7% of cases over 7.4 years, with an estimated 10-year failure probability of up to 40%.

Thus, the evolution of traditional transscleral IOL fixation methods reflects efforts to minimize the risk of suture erosion and infectious complications while maintaining lens stability. Despite significant technical improvements-from knot coverage with flaps to scleral pockets and Z-shaped sutures—the long-term durability of polypropylene sutures remains an issue, stimulating the search for alternative materials and sutureless fixation techniques.

The variability of transscleral fixation techniques is driven by the goals of enhancing IOL stability, ensuring optimal centration, and improving refractive outcomes. Clinically, methods with one, two, three, four, and even six fixation points have been described. Historically, the first widely used technique was two-point fixation, proposed by E.S. Malbran in 1986. Despite relative ease of performance, two-point stabilization sometimes resulted in IOL tilt or decentration, prompting the development of multi-point fixation schemes.

One advancement was four-point fixation. A.L. Young et al. (2005) proposed a technique using 10-0 polypropylene sutures with implantation of a one-piece polymethylmethacrylate lens into the ciliary sulcus. Knots were tied approximately 2 mm from the limbus and buried within the scleral tissue, with conjunctival closure. Over a mean follow-up of 18.3 months, no complications related directly to the suture material (erosion, twisting, or knot exposure) were reported. However, 20% of eyes experienced mild vitreous hemorrhage, and 10% developed limited choroidal detachment; both resolved spontaneously without intervention.

Further development of four-point fixation incorporated modern foldable IOLs. O.N. Fass et al. (2010) used a specially designed hydrophilic acrylic Bausch & Lomb Akreos® lens with four-point fixation through a 2.75–3.0 mm corneal incision. Despite the minimally invasive approach, 44% of eyes experienced vitreous hemorrhage; all cases were transient and did not require surgical intervention.

To achieve even greater lens stability, six-point fixation without conjunctival dissection was proposed. This method utilized 8-0 double-polypropylene suture and a one-piece hydrophilic acrylic IOL with a closed three-loop haptic design. In a series of 21 patients with a mean follow-up of 8 months, transient corneal edema occurred in 19% of cases, and temporary intraocular pressure elevation in 14.3%. No cases of suprachoroidal hemorrhage, retinal detachment, suture rupture, knot exposure, or significant IOL decentration were reported. The authors emphasized that the closed haptic configuration allows even load distribution and reliable lens centration.

Thus, increasing the number of fixation points enhances the biomechanical stability of the IOL and reduces the risk of tilt. However, expanding the extent of manipulation may prolong surgery and increase the risk of intraoperative trauma. Therefore, the number of fixation points should be determined according to ocular anatomy, IOL type, and clinical context, highlighting the need for an individualized approach in transscleral IOL implantation.

Suture Material in Transscleral IOL Fixation.The choice of suture material is a critical factor influencing the long-term stability of transscleral intraocular lens (IOL) fixation. Traditionally, 10-0 polypropylene sutures have been widely used in ophthalmic surgery due to their adequate elasticity and ease of handling. However, accumulated clinical experience has demonstrated that the material’s tensile strength may decrease over time, increasing the risk of late suture breakage and IOL dislocation.

For improving the fixation durability, stronger suture materials have been adopted, including 9-0 polypropylene and expanded polytetrafluoroethylene (Gore-Tex 8-0). Gore-Tex has been used in cardiovascular surgery for over two decades and is characterized by high tensile strength and minimal tissue degradation, which has driven interest in ophthalmic applications.

For example, M.A. Khan et al. (2016) utilized 8-0 Gore-Tex for fixation of both rigid polymethylmethacrylate and foldable hydrophilic acrylic IOLs. Initially, a 23G vitreoretinal system was used, resulting in a postoperative hypotony rate of 9.4%. Switching to a 27G needle significantly reduced this complication. In a series of 83 eyes with a mean follow-up of 11 months, no suture ruptures were recorded, indicating the material's high mechanical reliability.

Additional retrospective data from 20 patients undergoing four-point fixation of the Akreos IOL model demonstrated statistically significant improvement in visual function ($p < 0.0001$) with minimal postoperative complications. No lens decentration was observed; however, the sample size was limited and the mean follow-up was only nine months.

A Chinese study employing 10-0 polypropylene combined with S-shaped intrascleral suture tunneling reported no suture-related complications in 69 eyes over a mean follow-up of 34 months. Similarly, a prospective study in Spain using 10-0 non-absorbable polyester (Mersilene) sutures found only one case of IOL repositioning required among 25 eyes.

Nevertheless, the issue of late polypropylene suture degradation remains relevant. B.Y. Vote et al. (2006) reported a 28% suture rupture rate over a mean four-year follow-up in two-point fixation with pars plana vitrectomy. Other studies indicate long-term (up to 10 years) erosion and rupture rates of 10-0 polypropylene ranging from 18% to 28%, with unilateral suture rupture occurring in nearly half of cases. These findings emphasize the need for long-term monitoring and support the search for alternative, including sutureless, fixation methods.

Not all studies report high complication rates. G. Bading et al. (2007) observed only 6.3% subluxation over a four-year follow-up for 10-0 polypropylene sutures covered with scleral flaps, concluding the method to be safe and effective when performed correctly. Thus, suture material choice and caliber are critically important for ensuring long-term stability of transscleral IOL fixation and minimizing late complications, including suture rupture, lens decentration, and inflammatory reactions. While 10-0 polypropylene remains widely used due to availability and ease of use, its potential for late failure necessitates careful postoperative monitoring. Stronger materials such as Gore-Tex show promising results but require long-term evaluation to confirm safety and efficacy. Optimal selection of suture material and size should be individualized according to ocular anatomy, IOL type, and comorbidities, underscoring the need for a personalized approach in aphakia correction.

Sutureless Scleral IOL Fixation. The limitations of sutured transscleral fixation, including suture erosion, lens decentration, and inflammatory complications, have driven the development of sutureless techniques. G.B. Scharioth first described sutureless scleral fixation in 2010, creating scleral tunnels to bury the haptics. In a multicenter study involving 63 patients across four European clinics, transient corneal edema occurred in 7.9% of patients, persistent intraocular pressure elevation in 3.2%, IOL dislocation in 3.2%, vitreous hemorrhage in 3.2%, and iris capture in 2%. Three patients required additional surgery to stabilize the lens, but overall functional outcomes were favorable. A posterior approach modification using 23G trocars, proposed by I.L. Prenner, showed that one year postoperatively, IOL displacement occurred in 12% of patients, with statistically significant improvement in visual acuity.

The “double-needle” technique introduced by S. Yamane uses 27G needles to simultaneously externalize both haptics through limbal tunnels. In the original study (35 eyes, 10 months), no significant dislocation was observed; iris capture occurred in 9%, and the mean IOL tilt was 2.3°. The 2017 modification incorporated flange formation with cautery without scleral incision, ensuring stable IOL positioning with minimal complications: iris capture 8%, vitreous hemorrhage 5%, hypotony 2%, and macular edema 1%.

Another sutureless approach uses scleral flaps combined with fibrin glue to cover haptics. A. Agarwal described creating scleral flaps for haptic fixation. Among 53 eyes, IOL decentration was 5%, and cystoid macular edema 7.5%. Y. McKee (2014) modified Agarwal’s technique, reporting transient hypotony in 22% of patients, one case requiring re-sealing of external filtration, iris capture 5.7%, decentration 2.6%, uveitis 0.5%, haptic displacement 2%, and haptic extrusion 0.5%.

B. Todorich proposed transscleral fixation using 25–27G trocar cannulas to externalize haptics of foldable three-piece IOLs (Alcon MA60AC) through scleral ostomies. In a retrospective analysis of 122 patients, vitreous hemorrhage was the most common complication (22%), resolving spontaneously in 67% of cases. Mean follow-up was 1.5 years.

Thus, sutureless fixation techniques demonstrate high effectiveness and favorable functional outcomes, while minimizing conjunctival erosion and complications associated with external sutures. Burying haptics in scleral tunnels, flange formation, and adhesive technologies allow stable lens fixation and reduce long-term complication risks.

Conclusion

No universally optimal method exists for IOL fixation in the absence of sufficient capsular support, highlighting the need for ongoing research. Long-term stability criteria and factors contributing to late suture failure remain unclear. Enhancing the safety and efficacy of aphakia surgery requires a comprehensive evaluation framework for IOL fixation methods, incorporating lens position topography, refractive assessment, and endothelial cell counts. Such an approach would standardize outcome assessment, minimize complications, and optimize surgical technique selection on a case-by-case basis.

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DYNAMICS OF THE PREVALENCE OF ISCHEMIC HEART DISEASE AMONG WOMEN IN THE REPUBLIC OF UZBEKISTAN

S.I. Ismailov[1,3], M.M. Zufarov[1], O.Dj. Eshonxodjaev[1], N.U. Sharapov[1], S.B. Alieva[2], M.A. Abdullaeva[1,3]
Republican Specialized Scientific and Practical Medical Center of Surgery named after Academician V. Vakhidov, Tashkent, Republic of Uzbekistan[1]
Family clinic, Denau, Republic of Uzbekistan[2]
Tashkent State Medical University, Tashkent, Republic of Uzbekistan[3]
https://doi.org/10.5281/zenodo.19177514

Abstract. *Ischemic heart disease (IHD) remains a leading cause of morbidity and mortality globally, with distinct gender-specific characteristics. In Uzbekistan, comprehensive epidemiological data on IHD prevalence among the female population remain limited. This study aims to analyze the regional dynamics and age-specific structure of IHD prevalence among women in the Republic of Uzbekistan over the 2022–2024 period. A retrospective epidemiological study was conducted using official medical statistics data from all administrative regions of Uzbekistan. The analysis encompassed absolute and relative indicators of IHD prevalence among the female population, stratified by four age groups (<49, 50–58, 59–68, and ≥69 years) and by region for 2022–2024. Extensive indicators, temporal dynamics, and comparative interregional differences were calculated. Statistical significance was set at $p<0.05$. Over the three-year period, the total number of registered IHD cases among women increased from 133,325 to 181,998, representing a growth rate of 36.5% ($p<0.05$). Cardiovascular diseases consistently dominated the overall morbidity structure, accounting for 78.3% in 2022 and 79.7% in 2023y. Marked regional heterogeneity was observed: the Tashkent region consistently demonstrated the highest prevalence (increasing from 25.2% to 29.4% of national cases), followed by the Namangan (144.8% growth in 2023) and Kashkadarya regions. Age-stratified analysis revealed a progressive increase in IHD burden with advancing age, with the highest absolute numbers concentrated in the ≥69 years cohort (11,717 cases in 2022; 13,548 in 2024). The 50–58 age group, corresponding to early postmenopause, exhibited a 14.8% increase in 2023, supporting the hypothesis of hormonal influence on cardiovascular risk. This study demonstrates a significant increase in IHD prevalence among women in Uzbekistan, with pronounced regional and age-related disparities. The findings underscore the urgent need for gender-oriented preventive strategies, enhanced screening programs targeting perimenopausal and postmenopausal women, and region-specific resource allocation. Further research should focus on elucidating the socioeconomic, behavioural, and environmental determinants contributing to the observed epidemiological patterns.*

Keywords: *cardiovascular diseases, circulatory system, chronic infections, mortality rates.*

Introduction

Cardiovascular diseases (CVD) have been among the leading causes of mortality and disability worldwide for many decades, representing one of the most pressing problems in modern healthcare [1,14]. According to the World Health Organization, diseases of the circulatory system

are the leading cause of death worldwide, resulting in more than 17 million deaths annually [1]. Among the wide variety of cardiovascular pathologies, ischemic heart disease (IHD) occupies a special place, contributing significantly to premature mortality and disability rates. Despite the tremendous progress made in recent decades in the field of diagnostics, pharmacotherapy, and the introduction of high-tech treatment methods, the absolute number of people suffering from IHD continues to grow steadily [7, 12]. This seemingly paradoxical trend is largely due to the aging of the population, as well as the high prevalence of key risk factors such as hypertension, lipid metabolism disorders, obesity, and physical inactivity [5,8]. Other risk factors include comorbidities that accelerate atherosclerosis, such as chronic kidney disease, inflammatory diseases, autoimmune diseases, connective tissue diseases, and chronic infections. Another risk factor is common psychosocial disorders, such as anxiety and depression, which are associated with a 22% increase in the risk of developing IHD [10].

The gender and age characteristics of the prevalence of the disease deserve special attention. According to numerous studies, the incidence and mortality rates from ischemic heart disease are traditionally higher among men, and therefore IHD has been perceived as a pathology that predominantly affects the male population. However, in older age groups, there is a significant increase in the prevalence of the disease among women, which requires a more in-depth study of the gender aspects of the pathogenesis and clinical course of IHD. Indeed, in younger age groups, the incidence among men is significantly higher. Epidemiological studies in recent years have convincingly demonstrated that with the onset of menopause and the loss of the protective effect of estrogen, the risk of developing and progressing atherosclerosis in women increases rapidly, practically comparable to that in men in older age groups [2]. Moreover, the clinical course of IHD in women has its own characteristics: atypical forms of pain syndrome are more common, the likelihood of developing microvascular dysfunction (so-called ischemia with intact coronary arteries) is higher, and outcomes after acute coronary events are often worse than in men [12].

The results of modern epidemiological studies indicate significant regional differences in the prevalence of coronary heart disease. The most unfavorable epidemiological indicators are recorded in Eastern Europe, Central Asia, and South Asia, where there is a relatively high incidence and mortality rate associated with this pathology [7]. The prevalence of major risk factors remains high in these regions, and there are certain limitations in the availability of specialized medical care. According to experts, these circumstances have a significant impact on the formation of unfavorable epidemiological indicators [8].

At the same time, a number of countries in Western Europe and North America have seen a steady decline in mortality from ischemic heart disease over the past decade. This trend is largely due to the successful implementation of primary and secondary prevention programs, early detection of risk factors, and improvements in the treatment of patients with coronary artery disease [7]. In this regard, studying the gender, age, and regional characteristics of IHD prevalence is particularly relevant. Understanding how the burden of disease is distributed among women of different age groups and depending on their place of residence is a prerequisite for planning effective preventive measures, optimizing the work of cardiology services, and rationally allocating healthcare resources. Of particular interest is the analysis of the situation in Central Asian countries, including Uzbekistan, where epidemiological data on the female population is often fragmentary, and the influence of socio-economic and ethnocultural factors on cardiovascular risk has not been sufficiently studied [7,8].

Research objective

The aim of this study was to investigate regional characteristics of the prevalence of ischemic heart disease among women and to analyze the dynamics and structure of its frequency in different age groups in the Republic of Uzbekistan for the period 2022–2024yy.

Materials and methods. A retrospective epidemiological study was conducted based on the analysis of medical statistics data. The object of the study was the incidence of cardiovascular diseases among the population of the Republic of Uzbekistan. The study used summary data on the incidence and prevalence of ischemic heart disease among the female population for the period from 2022 to 2024. The information was stratified by region and four key age groups: under 49, 50-58, 59-68 years, and 69 years and older. For each age group and each region, the absolute number of registered cases (n) and the region's share in the overall incidence structure for the republic for the corresponding year (%) were calculated. The analysis was conducted over a three-year period to identify the main trends. Data processing included the calculation of extensive indicators (distribution of morbidity by region), analysis of the dynamics of absolute and relative indicators, and comparative analysis of age groups. Differences were considered statistically significant at a significance level of $p<0.05$. The results were interpreted from the perspective of current understanding of cardiovascular epidemiology and risk factors.

Results. Analysis of statistical data revealed that diseases of the circulatory system occupy a leading position in the structure of the overall morbidity of the population of the Republic of Uzbekistan (Table 1).

Table 1. Overall morbidity from cardiovascular diseases in the Republic of Uzbekistan (2022–2023).

Name of disease	2022y		2023y	
	n	%	n	%
Circulatory system diseases	2 050 809	78,3%	2 160 983	79,7%
Ischemic heart disease	418 850	16,0%	472 581	17,4%
Post-infarction cardiosclerosis	106 533	4,1%	52 744	1,9%
Heart aneurysm	9 754	0,4%	3 673	0,1%
Ischemic cardiomyopathy	23 105	0,9%	13 744	0,5%
Other	9 261	0,4%	9 066	0,3%
Total	2 618 312	100%	2 712 791	100%

In 2023, compared to 2022, there was an increase in the total number of cardiovascular diseases by 94,479 cases, which corresponds to a growth rate of 3.6% ($p<0.05$) (Table 1).

Table 2. Dynamics in cardiovascular diseases among women in the Republic of Uzbekistan (2022–2023).

Name of disease	2022y		2023y	
	n	%	n	%
Circulatory system diseases	671 987	82,2%	741 452	81,3%
Ischemic heart disease	133 325	16,3%	162 800	17,9%
Post-infarction cardiosclerosis	4 094	0,5%	4 470	0,5%
Heart aneurysm	1 125	0,1%	2	0,0%
Ischemic cardiomyopathy	6 379	0,8%	2 114	0,2%

Other	428	0,1%	941	0,1%
Total	817 338	100%	911 779	100%

The total number of cases of cardiovascular disease among women increased by 11.6% ($p < 0.05$). The most pronounced increase was observed for ischemic heart disease (Table 2).

Regional dynamics of the incidence of ischemic heart disease among women. Analysis of regional statistical data revealed significant differences in the prevalence of ischemic heart disease among the female population of the Republic of Uzbekistan (Table 3).

Table 3. Dynamics of the incidence of ischemic heart disease among women by region of the Republic of Uzbekistan (2022–2024).

Regions	2022y		2023y		2024y	
	n	%	n	%	n	%
Andijan	7 038	5,3%	5 338	3,3%	8 421	4,6%
Jizzakh	4 316	3,2%	8 427	5,2%	7 952	4,4%
Sirdarya	3 200	2,4%	3 645	2,2%	3 956	2,2%
Samarkand	12 103	9,1%	12 649	7,8%	13 240	7,3%
Kashkadarya	14 564	10,9%	20 156	12,4%	19 850	10,9%
Surkhandarya	11 754	8,8%	11 419	7,0%	12 564	6,9%
Navoi	3 269	2,5%	3 064	1,9%	3 684	2,0%
Bukhara	5 228	3,9%	5 713	3,5%	5 896	3,2%
Namangan	8 595	6,4%	21 048	12,9%	18 942	10,4%
Fergana	18 701	14,0%	8 396	5,2%	16 745	9,2%
Khorazm	2 129	1,6%	5 542	3,4%	6 781	3,7%
Tashkent	33 571	25,2%	48 396	29,7%	53 481	29,4%
Rep. of Karakalpakistan	8 857	6,6%	9 007	5,5%	10 486	5,8%

An analysis of trends showed that the total number of cases of ischemic heart disease among women increased from 133,325 cases in 2022 to 181,998 cases in 2024. The overall growth rate was 36.5%. The highest incidence rate was observed in the Tashkent region, where the proportion of registered cases of IHD among women increased from 25.2% to 29.4% (Table 3).

A significant increase in incidence was also observed in the Namangan region, where the number of cases more than doubled in 2023. The growth rate was 144.8%, which is one of the highest among the regions. Relatively low rates were recorded in the Sirdarya and Navoi regions, where the incidence rate remains at around 2–2.5%. Statistical analysis showed that the differences between regions are significant ($p < 0.05$) (Table 3).

The analysis revealed significant differences in the distribution of coronary heart disease depending on both the age of women and their region of residence. The total number of registered cases of IHD among women in Uzbekistan over three years shows a wave-like pattern with an overall upward trend in older age groups.

The prevalence of IHD in the youngest of the analyzed groups—among women of reproductive and young age (aged 49 and younger)—shows a decrease in the absolute number of registered cases from 1,434 in 2022 to 945 in 2024y. This may be due to both a true decrease in incidence and the peculiarities of diagnosis in this group, where IHD is relatively rare. The highest number of cases over all three years is consistently recorded in the Surkhandarya region (22.6% in 2022, 23.4% in 2023, 17.6% in 2024) and the Tashkent region (17.1% and 15.9% and 16.1%, respectively), indicating possible regional risk factors.

Table 4. Ischemic heart disease in women aged 49 and younger by region.

Regions	2022y		2023y		2024y	
	n	%	n	%	n	%
Andijan	178	12,4%	126	11,1%	111	11,7%
Bukhara	37	2,6%	30	2,7%	28	3,0%
Jizzakh	34	2,4%	35	3,1%	19	2,0%
Kashkadarya	156	10,9%	92	8,1%	103	10,9%
Navoi	27	1,9%	19	1,7%	24	2,5%
Namangan	51	3,6%	86	7,6%	78	8,3%
Samarkand	146	10,2%	75	6,6%	122	12,9%
Surkhandarya	324	22,6%	265	23,4%	166	17,6%
Sirdarya	30	2,1%	38	3,4%	22	2,3%
Tashkent	245	17,1%	180	15,9%	152	16,1%
Fergana	64	4,5%	89	7,9%	64	6,8%
Khorazm	90	6,3%	51	4,5%	32	3,4%
Rep. of Karakalpakistan	52	3,6%	45	4,0%	24	2,5%

The prevalence of IHD in the 50-58 age group, which roughly corresponds to the early postmenopausal period, shows a different picture. The total number of cases increased from 1,998 in 2022 to 2,294 in 2023, after which it decreased slightly to 2,171 in 2024. The sharp increase in the proportion and absolute number of cases in the Republic of Karakalpakistan in 2023 (219 cases, 9.5%) compared to 2022 (62 cases, 3.1%), which may indicate improved detection or a surge in incidence that requires separate study.

Table 5. Distribution of IHD among women aged 50–58 by region (2022–2024).

Regions	2022y		2023y		2024y	
	n	%	n	%	n	%
Andijan	221	11,1%	229	10,0%	309	14,2%
Bukhara	76	3,8%	75	3,3%	64	2,9%
Jizzakh	53	2,7%	67	2,9%	76	3,5%
Kashkadarya	220	11,0%	234	10,2%	227	10,5%
Navoi	37	1,9%	52	2,3%	77	3,5%
Namangan	160	8,0%	189	8,2%	195	9,0%
Samarkand	286	14,3%	268	11,7%	253	11,7%
Surkhandarya	323	16,2%	374	16,3%	270	12,4%
Sirdarya	58	2,9%	63	2,7%	66	3,0%
Tashkent	316	15,8%	288	12,6%	329	15,2%
Fergana	105	5,3%	136	5,9%	120	5,5%
Khorazm	81	4,1%	100	4,4%	74	3,4%

Rep. of Karakalpakistan	62	3,1%	219	9,5%	111	5,1%

In the group of women aged 59-68 (late postmenopause), the absolute number of cases remains the highest among all groups (except for the oldest), peaking in 2023 (5,421 cases). In this category, Samarkand and Tashkent regions show consistently high rates. In the Surkhandarya region, which led in 2022-2023, there was a noticeable decrease in both the absolute number and the proportion of cases (from 13.6% to 8.9%) in 2024, which may be due to the saturation effect of medical examinations or migration processes.

Table 6. Distribution of IHD among women aged 59–68 by region.

Regions	2022y		2023y		2024y	
	n	%	n	%	n	%
Andijan	365	8,1%	593	10,9%	601	12,8%
Bukhara	162	3,6%	169	3,1%	155	3,3%
Jizzakh	103	2,3%	221	4,1%	165	3,5%
Kashkadarya	386	8,6%	443	8,2%	460	9,8%
Navoi	156	3,5%	168	3,1%	168	3,6%
Namangan	381	8,5%	455	8,4%	388	8,2%
Samarkand	720	16,0%	575	10,6%	592	12,6%
Surkhandarya	570	12,7%	735	13,6%	420	8,9%
Sirdarya	212	4,7%	319	5,9%	135	2,9%
Tashkent	863	19,2%	990	18,3%	1044	22,2%
Fergana	266	5,9%	360	6,6%	299	6,3%
Khorazm	156	3,5%	173	3,2%	139	2,9%
Rep. of Karakalpakistan	154	3,4%	220	4,1%	147	3,1%

As expected, the oldest age group (69+) bears the greatest burden of IHD. Here, there has been a steady increase in the absolute number of cases from 11,717 in 2022 to 13,548 in 2024, which fully correlates with the processes of demographic aging and the accumulation of risk factors. The Tashkent region consistently ranks first in terms of the number of female patients, with its share steadily increasing (from 23.9% to 27.7%), which probably reflects both higher life expectancy and better access to diagnostics in the capital region.

Table 7. Prevalence of IHD in women aged 69 and older by region (2022–2024).

Regions	2022y		2023y		2024y	
	n	%	n	%	n	%
Andijan	1307	11,2%	1548	11,5%	1585	11,7%
Bukhara	485	4,1%	554	4,1%	601	4,4%
Jizzakh	266	2,3%	400	3,0%	357	2,6%
Kashkadarya	1138	9,7%	1255	9,3%	1228	9,1%
Navoi	325	2,8%	389	2,9%	436	3,2%

Namangan	1062	9,1%	1103	8,2%	1112	8,2%
Samarkand	1278	10,9%	1259	9,3%	1260	9,3%
Surkhandarya	1120	9,6%	1469	10,9%	1021	7,5%
Sirdarya	359	3,1%	358	2,6%	271	2,0%
Tashkent	2802	23,9%	3492	25,8%	3748	27,7%
Fergana	615	5,2%	699	5,2%	868	6,4%
Khorazm	567	4,8%	527	3,9%	413	3,0%
Rep. of Karakalpakistan	393	3,4%	461	3,4%	648	4,8%

Discussion

The results of the study indicate a continuing increase in the prevalence of cardiovascular disease in the Republic of Uzbekistan. The data obtained are consistent with the results of international epidemiological studies indicating an increase in the scale of cardiovascular pathology in countries with developing economies [3,4,9]. One of the most significant findings of this study is the identified increase in the prevalence of coronary heart disease among women. During the period analyzed, the number of cases of IHD among women increased by 36.5%. This indicator reflects not only an increase in morbidity, but also a possible improvement in the diagnosis of this pathology.

The identified regional heterogeneity in the prevalence of coronary heart disease deserves special attention. The highest incidence rates are observed in the Tashkent region, which may be associated with a high degree of urbanization, higher population density, and the prevalence of risk factors. Urbanization is one of the key factors influencing the growth of cardiovascular diseases. Residents of large cities are more often exposed to adverse environmental factors, experience high levels of psycho-emotional stress, and lead less active lifestyles [6,14-16]. Significant differences in morbidity rates may also be due to differences in the availability of medical care and diagnostic capabilities of regional medical institutions.

The sharp increase in incidence in the Namangan region deserves special attention. This trend may be associated with both a real increase in the number of cases and improvements in the registration and detection of this pathology. At the same time, it should be noted that epidemiological studies of cardiovascular diseases among women have a number of specific features. In particular, the clinical picture of ischemic heart disease in women often differs from the typical manifestations of the disease in men. Women more often complain of nonspecific symptoms such as fatigue, shortness of breath, or chest discomfort, which can make early diagnosis of the disease difficult [7, 11-13].

In addition, women are more likely to have microvascular forms of coronary heart disease, which are more difficult to diagnose using standard examination methods. The results obtained in this analysis convincingly confirm global trends regarding the critical impact of age on the prevalence of IHD among women. There is a clear "turning point" after the age of 50, when mechanisms associated with menopausal hormonal changes are likely to be triggered, leading to a sharp increase in the number of detected cases [2, 3].

The consistently high rates observed in densely populated areas such as Tashkent, Samarkand, Andijan, and Surkhandarya among women under the age of 49 can be explained both by the larger absolute number of women and by the concentration of risk factors characteristic of

regions with developed industry and high population density. These include psycho-emotional stress, dietary characteristics with high consumption of fats and carbohydrates, and higher levels of environmental pollution, which is consistent with data on the impact of the environment on cardiovascular risk [5, 8].

The surge in incidence in the Republic of Karakalpakstan in 2023 in the middle age group (50-58 years) deserves special attention. This may be the result of organizational changes (e.g., mass screening) or a reflection of a real deterioration in the situation associated with socio-economic or environmental problems in the region. This fact requires additional, more in-depth research using data on the prevalence of risk factors in this particular region. It should also be noted that the decrease in the number of cases in some regions and groups in 2024 (e.g., in the 59-68 age group in the Surkhandarya region) should not be interpreted unequivocally as an improvement in the situation. This may be due to population migration, the transition of patients to the next age cohort, changes in accounting rules, or a temporary decrease in treatment demand.

Conclusion

The analysis of epidemiological data for the Republic of Uzbekistan for 2022-2024 allows us to draw the following conclusions:

1. Cardiovascular diseases continue to occupy a leading position in the structure of the overall morbidity of the population of the Republic of Uzbekistan. For the period 2022-2024, a steady trend towards an increase in the prevalence of ischemic heart disease among women has been identified. The overall growth rate was 36.5%, which indicates a significant increase in the prevalence of this pathology.

2. Regional variability has been identified: There are significant differences in the prevalence of IHD between regions. The highest rates are recorded in the Tashkent, Kashkadarya, and Namangan regions. The Tashkent, Samarkand, Andijan, and Surkhandarya regions lead in terms of the number of patients in all age groups, which requires the allocation of priority resources to these areas.

3. The high significance of age has been confirmed: The burden of ischemic heart disease among women increases regularly and significantly with age. The largest absolute number of patients is concentrated in the age group of 69 years and older, with a steady increase in the number of cases in this category, which dictates the need to develop geriatric cardiac care.

4. Indicators requiring further study have been identified: Statistical outliers (e.g., growth in Karakalpakistan in 2023) have been detected, indicating the need for in-depth local epidemiological investigations to identify their true causes.

5. The need for a gender-oriented approach is justified: The data obtained underscore the need to improve the cardiovascular disease prevention system aimed at early detection of risk factors, the development of specialized prevention programs targeting women, especially in the perimenopausal and postmenopausal periods, and the improvement of the effectiveness of medical care. It is important to improve screening and early diagnosis programs for cardiovascular diseases among women. Screening measures and programs for correcting risk factors (arterial hypertension, diabetes, obesity) should be intensified for women starting at age 50. Further research should also focus on studying the impact of socioeconomic and behavioral factors on the prevalence of cardiovascular disease among the female population.

Thus, the results of the study emphasize the relevance of further monitoring of the situation with IHD in the female population at the regional level for making effective management decisions in the field of health care.

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THE ROLE OF TORQUE TENO VIRUS IN THE DEVELOPMENT OF LIVER DISEASES

M.A. Abdukadirova[1], A.S. Khikmatullaeva[2], Sh.R. Bakieva[2], I.N. Egamova[3], V.Sh. Rakhimova[4]

Research Institute of Virology, Republican Specialized Scientific and Practical Medical Center of Epidemiology, Microbiology, Infectious and Parasitic Diseases, Tashkent, Uzbekistan[1,2,3]

Center for the development of professional qualification of medical workers, Tashkent, Uzbekistan[4]

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Abstract. *Torque teno virus (TTV), a member of the Anelloviridae family, is one of the most widespread viruses detected in humans. Since its discovery in 1997 in the serum of a patient with post-transfusion hepatitis of unknown etiology, scientific interest in this virus has steadily increased. Modern molecular diagnostic methods, particularly polymerase chain reaction (PCR), have demonstrated that TTV DNA can be detected in a wide range of human tissues, organs, and biological fluids, including blood, saliva, and respiratory secretions. Despite its widespread distribution, the clinical significance of TTV infection and its role in the pathogenesis of human diseases remain controversial. The virus has been detected both in patients with various liver diseases—including chronic viral hepatitis, liver cirrhosis, and hepatocellular carcinoma—and in apparently healthy individuals. This raises important questions as to whether TTV should be considered a true pathogen, an opportunistic infectious agent, or a commensal component of the human virome. Several studies suggest that TTV may exhibit hepatotropic properties, as viral DNA has been detected in liver tissue and in hepatocytes. However, other investigations indicate that the main sites of viral replication are cells of the immune system, particularly activated mononuclear cells and T-lymphocytes. It is assumed that interactions between the virus and the host immune system play a key role in mechanisms of long-term viral persistence. This review summarizes current knowledge regarding the molecular and biological characteristics of TTV, its epidemiology, mechanisms of persistence, and its potential association with liver diseases. Analysis of the available literature indicates that although TTV is frequently detected in patients with liver pathology, convincing evidence of its direct etiological role in the development of liver diseases has not yet been established.*

Keywords: *torque teno virus, TTV, hepatitis, immunosuppression, virome.*

INTRODUCTION

The widespread use of polymerase chain reaction (PCR) has shown that TTV is readily detectable in many human tissues and organs, as well as in most biological fluids, without a clear association with a specific disease [1]. However, this does not necessarily mean that TTV is capable of replicating in an environment where it can be detected. Detection of TTV DNA in tissues may simply identify virus passively acquired from blood plasma. Therefore, it is crucial to determine how frequently and under what conditions TTV can be detected in liver tissue in patients with liver disease, as well as the relationship between TTV blood levels and the severity of the pathological process. This review summarizes current evidence regarding the role of TTV in liver diseases and may provide useful insights for specialists in infectious diseases and hepatology.

OBJECTIVE

The aim of this review is to analyze the potential association between Torque teno virus (TTV) infection and liver diseases.

MATERIALS AND METHODS

To find scientific information on the study topic, we searched the bibliographic databases PubMed, Scopus, Web of Science, and Google Scholar. Keyword terms in English and Russian related to the study topic were used. The search included publications from 1999 to 2024. The review included original research articles, systematic reviews, and meta-analyses devoted to the study topic. The selected publications were analyzed using comparative, analytical, and systemic analysis methods. Information from the selected sources was systematized and grouped by main research areas.

RESULTS AND DISCUSSION

The first human TTV virus was discovered in the serum of a patient with post-transfusion hepatitis of unknown etiology in 1997. TTV is a small spherical virus measuring approximately 30–50 nm in diameter and possessing a circular single-stranded DNA genome [2]. TTV virus was named after the Japanese patient with the initials TT, from whom it was isolated. Later, to more accurately describe the nature of its circular genome, the virus was given the name "Torque Teno virus" (from the Latin words torques - meaning "necklace," and tenuis - meaning "thin"), which remains unchanged from its original acronym [3]. The discovery of TTV stimulated extensive research worldwide. These studies demonstrated that the virus has a global distribution, exhibits high genomic heterogeneity, and exhibits pantropism [3]. These discoveries were followed by the discovery of a large and diverse, ever-growing population of anelloviruses, which currently includes 30 genera and 155 species. Three genera of anelloviruses have been shown to colonize humans: Alfa-torquevirus (Torque Teno virus, TTV, discovered in 1997), Gamma-torquevirus (Torque Teno Midi virus, TTMDV, 2000), and Beta-torquevirus (Torque Teno Mini virus, TTMV, 2007) [4].

In 2021, the International Committee on Tapotaxonomy of Viruses decided to change the names of these viruses. TTV was renamed Alfa-torquevirus homin, Torque Teno Midi virus was renamed Gamma-torquevirus hominid, and Torque Teno Mini virus was renamed Beta-torquevirus hominid [2]. Recent studies have shown that TTV is associated not only with post-transfusion hepatitis, as previously believed, but also with various other diseases. This is of great interest to many scientists working on the relationship between viral infection and somatic pathology, as well as on the development of methods for the prevention and treatment of this infection. Despite extensive research, the exact role of TTV in the development of human diseases remains unclear. Difficulties in determining the pathogenicity of this virus are due to its high prevalence in the general population, its presence in various tissues, the existence of numerous types and variants of the virus, the frequent occurrence of coinfection, and a wide range of viral loads that can be detected in different people for no apparent reason [1]. TTV is pantropistic in the host body and can be detected in blood, saliva, pharyngeal mucus, genital secretions, tears, skin, hair follicles, and breast milk [5]. It has been shown that TTV is closely associated with leukocytes and can replicate in activated mononuclear cells [6].

TTV is frequently detected in patients with various types of viral hepatitis, as well as in the healthy population. As TTV has been studied, our understanding of its role in the development of human pathologies has changed significantly. The idea that the virus is hepatotropic has been replaced by data indicating that TTV persists asymptomatically in the body as a member of the

human virome [7]. The DNA sequence isolated in 1997 was found to belong to a single-stranded, non-enveloped virus. The first electron microscopic image of TTV virions isolated from humans has been obtained. There is evidence of biochemical and histological changes in liver tissue and bile duct epithelium in TTV monoinfection. There are sufficient histological signs of liver damage, confirming the possibility of a viral replicative cycle in hepatocytes. At the same time, a number of studies indicate viral replication outside the liver, including in immune system cells and the lungs.

These contradictory findings make it difficult to clearly determine the pathogenetic significance of TTV persistence. K. Kosulin et al. suggested that granulocytes are the main site of TTV replication in children after hematopoietic stem cell transplantation [8]. Biopsies of the liver, lymph nodes, bone marrow, spleen, pancreas, lungs, and thyroid gland can be used to diagnose TTV [3]. TTV can be detected by quantitative or qualitative PCR methods in various clinical samples [9]. TTV replication and activation of the cellular component of immunity, which is the basis of antiviral protection, are considered triggers for the production of immunoglobulins [10]. Immunoprecipitation and immunoblotting are used for the qualitative and quantitative determination of antibodies to TTV (anti-TTV) in biological samples [11].

Anti-TTV IgM appear in the blood 10–21 weeks after TTV infection. Five to 11 weeks after their detection, the antibody titer usually decreases and IgM gradually disappear. Anti-TTV IgG are observed approximately 16 weeks after infection and reach maximum concentrations by the 5th month of virus persistence [10]. IgG can be detected in the body of infected people for four years or more [11]. A number of authors argue that TTV detection using immunological methods is of limited use, since, despite detectable antibody titers, anti-TTV are neither protective nor neutralizing [12]. The pathogenicity of the virus remains controversial to this day. Since the discovery of TTV, numerous studies have been conducted aimed at identifying the target organs of the virus. Studies of TTV have indicated its hepatotropism and most likely replication in liver cells. However, the data obtained were quite contradictory, which created difficulties for a full understanding of TTV persistence in the human body.

Cases of TTV DNA detection in liver tissue by hybridization and attempts to establish the contribution of the virus to the detected changes in the liver have been described [13]. E. Rodríguez-Inigo et al. observed 30 patients with liver diseases who were seropositive for TTV [14]. The TTV DNA titer in the liver of these patients was 10 times higher than the titer in the serum [14]. In some patients with normal histological structure of liver tissue, TTV DNA was detected both in serum and liver tissue. Data obtained by M.J. Kazemi et al. also indicate a higher percentage of TTV DNA detection in liver tissue than in blood plasma [15].

TTV DNA was detected in the blood plasma and liver tissue of 11.1 and 25.9% of patients with viral B and C etiology of the liver cirrhosis, respectively, and in 23.5 and 26.9% of cases in patients with cryptogenic cirrhosis [15]. It has been suggested that some TTV genotypes, in particular 3 and 4, lurk in peripheral blood mononuclear cells, which become a reservoir of the virus and contribute to its persistence [16]. L.F. Mariscal et al. confirmed the presence of TTV DNA in the cytoplasm of peripheral mononuclear cells using cultivation and the hybridization method [6]. Moreover, D. Focosi et al. showed that T-lymphocytes are considered to be the most probable site of TTV replication: by inducing T-lymphocyte-specific immunosuppression (antithymocyte globulin, basiliximab), the researchers found a statistically significant decrease in the viral load ($p<0.001$) [10].

This is confirmed by the data obtained by E.A. Tyschik et al., who reported that due to the presence of lymphocytes, the TTV viral load in whole blood is 100 times higher than in plasma [17]. In a quantitative study of viral DNA in autopsy and biopsy material from the liver and bone marrow of patients with subacute hepatitis and aplastic anemia, K. Kikuchi et al. found a high DNA titer only in the bone marrow [18]. This allowed us to hypothesize about viral replication in the bone marrow and the resulting development of aplastic anemia. In this case, only viral DNA was found in hepatocytes, while mRNA was absent. Viral persistence in the body triggers an immune system response to the foreign agent. TTV actively synthesizes proteins that are immunogenic and necessary for long-term viral replication in various tissues and organs [19].

The TTV replicative cycle in the human body has been shown to be accompanied by the synthesis of microRNA (miRNA) [20]. MiRNA inhibits interferon signaling, promotes TTV evasion from the immune system, and facilitates TTV persistence in the host [21]. Despite the known effects of miRNAs, it is impossible to definitively determine the contribution of TTV miRNA synthesis to viral persistence in the body and whether this effect is clinically significant. The complex action of pathological factors contributes to a decrease in the effectiveness of the immune system in eliminating the infectious agent. Current data on the immunobiology of TTV confirm that immune system cells recognize TTV antigenic determinants and respond to its introduction by producing appropriate proinflammatory proteins and cytokines: interferon-gamma (IFN-ɣ), tumor necrosis factor (TNF-ɑ), as well as by increasing the concentrations of interleukins IL-6, IL-12, IL-28, IL-29, chemokine CCL7 and a number of antiviral proteins [21]. It is currently known that the interaction of immunocompetent cells of the macroorganism with the virus is carried out through Toll-like receptors 9 (TLR 9) [22].

The activation of the entire spectrum of antiviral defense mechanisms allows maintaining the level of TTV DNA at a controlled level, that is, the persistence of the virus occurs under the constant surveillance of the immune system. However, complete elimination of the virus may not occur, which is confirmed by the high prevalence of TTV in the human population, even among individuals belonging to the healthy population. The studies of many scientists were aimed at assessing the potential hepatotropism of the virus, studying its coinfection with known hepatitis viruses, and identifying TTV in patients with cryptogenic liver diseases. Studies conducted in this area have produced conflicting results. It was shown that TTV is diagnosed in 15–28% of patients with acute viral hepatitis (AHAV) A, in 22–24% of patients with AHAV, in 40–60% with AHAV, and in 20% with HIV [23]. TTV DNA was most frequently detected in the group of patients with acute viral hepatitis (HBV, HCV, HGV, cryptogenic) [24]. The researchers showed that the detection of TTV in patients with acute viral hepatitis and fulminant liver failure is significantly higher than in blood donors (80.6 and 76% versus 52%, respectively; $p<0.05$) [25].

Moreover, the detection rate of TTV in the group of patients with acute hepatitis B was higher than in the groups of patients with fulminant liver failure, chronic hepatitis and liver cirrhosis ($p<0.001$) [24]. The authors note that the presence of TTV does not increase mortality in patients with fulminant liver failure. The role of TTV in the development and progression of chronic liver diseases (CLD) remains controversial. According to N. I. Gromova et al., the prevalence of TTV among patients with chronic viral hepatitis B and C was 61.0 and 45.1% [26]. The detection rate of TTV in cases of hepatocellular carcinoma ranges from 9 to 51% [27]. A number of studies devoted to this topic did not reveal any evidence of the effect of TTV on the course of CLD [28]. TTV DNA was determined in patients with elevated liver aminotransferase activity in the absence of viral hepatitis markers [29]. According to J.C. de Oliveira et al., the

frequency of TTV DNA detection in peripheral blood cells of patients with elevated aminotransferase activity was 31.48%, while in the control group it was 5.26% [30].

F. Piaggio et al. published data confirming the relationship between spontaneous postoperative increases in liver aminotransferase levels and the detection of TTV in the blood serum of the examined patient [31]. Gromova N.I. et al. obtained data indicating the detection of TTV DNA with the same frequency in donors with elevated and normal ALT activity (17.6 and 16.7%, respectively), which indirectly indicates the absence of an effect of TTV on the development of hyperenzymemia [26]. According to a number of authors, when comparing patients seronegative for TTV and those with TTV monoinfection, the latter showed increased activity of ALT, and its activity did not depend on the duration of persistence and the TTV DNA titer in the blood serum [23]. Data presented in the first decade after the discovery of TTV show a wide range and low frequency of the virus in liver diseases, which is most likely associated with the use of incomplete primers for its PCR diagnostics. Increased sensitivity and specificity of PCR diagnostics of TTV in the last decade made it possible to detect TTV in 77.4% of patients with hepatitis A, in 87.6% of HBV-positive patients, in 77% of HCV-positive patients, and in 92.8% of patients with hepatitis of unknown etiology [32]. However, the authors did not find statistically significant differences.

CONCLUSION

Research on TTV intersects with multiple clinical and fundamental biomedical disciplines and continues to attract significant scientific interest. Summarizing and systematizing existing data is important for planning further research. Since the discovery of TTV and the Anneloviridae family as a whole, the virus has been the subject of detailed study by many researchers worldwide. The molecular genetic structure of the virus has been thoroughly studied, methods for its qualitative and quantitative determination have been developed [33], its transmission routes have been established, and the possibility of spontaneous elimination of the virus has been demonstrated. Furthermore, TTV DNA has been detected in numerous tissues and biological fluids not only of patients but also of healthy individuals. Detection of TTV DNA depends heavily on the detection methods, primers used, and biological material. Therefore, the existing literature on TTV research is largely contradictory and cannot be compared with each other, significantly complicating the process of studying the virus's characteristics. Although the virus does not replicate primarily in liver cells, it is found in both acute and chronic liver diseases.

Thus, a large body of data on the study of TTV coinfection with hepatitis viruses dates back to the first decade after its discovery [34]. The problem of the coexistence of several infectious agents is always the most challenging for understanding the role of each of them in the pathogenesis of the disease. In recent years, there has been a decrease in the number of studies devoted to the clinical significance of TTV. This is probably due to the fact that TTV is a common virus that is detected in patients with various types of viral hepatitis, in cases of hepatitis without an obvious viral agent, as well as in the healthy population [32]. However, many authors deny its aggravating effect on the progression and course of various liver diseases. Thus, a number of scientists presented clear data showing that the presence of TTV does not aggravate the course or impair liver function in patients with viral hepatitis of known etiology A-E and does not affect the effectiveness of interferon therapy [34].

Long-term detection of TTV DNA in the serum of patients with morphofunctional integrity of the liver indicates the existence of asymptomatic carriage of the virus [7]. Most likely, these data indicate independent persistence of TTV and viral hepatitis of established etiology. Some

authors call the virus nonpathogenic and, moreover, isolate it as part of the human virome [33]. This judgement is based mainly on the impossibility of linking the viral infection with the development of a specific disease. However, this statement cannot be considered absolutely substantiated: a study has recently appeared linking the persistence of TTV DNA in the body with a possible increase in mortality in elderly patients [35]. A number of authors propose using the TTV viral load as an endogenous marker of human immune status [21]. Future research in this area will likely clarify the conflicting data and unclear aspects of the influence of TTV on the development and course of liver diseases.

1. TTV is a common virus detected in patients with and without various types of viral hepatitis.

2. Many authors note the lack of an aggravating effect on the progression and course of various liver diseases.

3. There are sufficient histological features confirming the possibility of TTV replication in liver cells.

4. Long-term detection of TTV DNA in the serum of patients, despite the morphofunctional integrity of the liver, indicates the existence of asymptomatic carriers of the virus. These data most likely indicate independent persistence of TTV and viral hepatitis of established etiology.

5. Viral persistence occurs under constant surveillance by the immune system. However, complete elimination of the virus may not occur, as evidenced by the high prevalence of TTV in the human population, even among healthy individuals.

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DEVELOPING FUTURE DOCTORS' COMPETENCE IN DESIGNING ELECTRONIC METHODOLOGICAL SUPPORT IN THE CONTEXT OF HEALTHCARE DIGITALIZATION

M.E. Tadjiddinov
Independent researcher, Andijan State Medical Institute, Uzbekistan, Andijan
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Abstract. *The rapid digital transformation of healthcare systems has significantly influenced the structure and organization of modern medical education. Digital technologies such as electronic health records, telemedicine platforms, artificial intelligence tools, and simulation-based training systems have become integral components of contemporary healthcare practice. As a result, future medical professionals must possess not only strong clinical knowledge but also advanced competencies related to digital technologies and educational innovation. One of the key competencies required in this context is the ability to design electronic methodological support that facilitates effective learning processes in digital educational environments. This study investigates methodological approaches for developing future doctors' competence in designing electronic methodological support within the context of healthcare digitalization. The research focuses on identifying pedagogical conditions that contribute to the formation of digital competence among medical students.*

Keywords: *medical education, healthcare digitalization, electronic methodological support, competence development, digital learning technologies, medical students.*

Introduction

The digitalization of healthcare has become one of the most influential trends shaping modern society. Over the past two decades, technological innovations have transformed healthcare systems worldwide. Digital tools such as electronic medical records, telemedicine services, artificial intelligence-based diagnostic systems, and digital decision-support platforms have changed the way healthcare services are delivered and managed. These technological transformations have also had a profound impact on medical education. Medical universities are increasingly required to modernize their curricula and teaching methods to ensure that graduates possess the competencies necessary to function effectively in digital healthcare environments. In this context, the integration of digital technologies into educational processes has become a critical priority.

One of the most important challenges facing medical education institutions today is preparing future doctors who are capable of using and developing digital educational resources. The competence to design electronic methodological support has become particularly significant. Electronic methodological support refers to a system of digital educational materials, tools, and resources that facilitate effective learning and knowledge acquisition. Electronic methodological support may include digital textbooks, multimedia lectures, online assessment systems, clinical simulation modules, and interactive learning platforms. These resources enable students to access educational materials more easily and provide opportunities for flexible, self-directed learning. The ability to design such resources allows future doctors to engage more actively in the learning process and develop the skills required for continuous professional development. Moreover, the

use of electronic methodological support contributes to improving the overall quality of medical education by promoting student-centered learning environments.

Despite the increasing importance of digital technologies in medical education, many institutions still face challenges in implementing them effectively. These challenges include limited digital infrastructure, insufficient teacher training, and a lack of methodological frameworks for integrating digital tools into educational processes. Therefore, it is essential to develop methodological approaches that support the formation of digital competencies among medical students. This study aims to analyze the pedagogical foundations for developing future doctors' competence in designing electronic methodological support within the context of healthcare digitalization.

Materials and Methods. This research applies a mixed methodological approach that combines theoretical and empirical methods to investigate the development of competence in designing electronic methodological support among medical students.

First, a comprehensive review of scientific literature related to medical education, digital learning technologies, and competency-based educational models was conducted. The literature review allowed the identification of theoretical foundations for the integration of digital technologies into medical training.

Second, comparative analysis was used to examine international experiences in digital medical education. The study analyzed educational practices in leading medical universities that have successfully implemented digital learning platforms and electronic educational resources.

Third, pedagogical observation was conducted during courses related to medical informatics and healthcare information technologies. The observation focused on how students interact with digital educational tools and how these tools influence their learning behavior and competence development.

Fourth, a pedagogical modeling method was applied to develop a conceptual model for forming competence in designing electronic methodological support. The proposed model includes several interrelated components:

- **motivational** component
- **cognitive** component
- **technological** component
- **reflective** component

Each component contributes to the holistic development of students' digital competence. Additionally, elements of descriptive statistical analysis were used to evaluate the impact of digital learning tools on students' academic engagement and performance.

Results. The results of the study demonstrate that the integration of digital educational technologies significantly improves the effectiveness of the medical education process and contributes to the development of future doctors' competence in designing electronic methodological support. The research involved 120 medical students from different academic years who participated in courses related to medical informatics and digital learning technologies. Students were divided into two groups: an experimental group (n = 60) that actively used electronic methodological support tools and a control group (n = 60) that followed traditional instructional methods. The assessment of students' competence levels was conducted before and after the implementation of digital learning tools. The evaluation criteria included digital literacy, ability to design electronic learning materials, independent learning skills, and engagement in educational activities.

At the beginning of the experiment, the average competence level in the experimental group was **46.3%**, while in the control group it was **45.8%**, indicating no statistically significant difference between the groups. After the implementation of digital learning technologies, the competence level in the experimental group increased significantly to **78.6%**, while the control group showed only a moderate improvement to **58.4%**.

The results also revealed that students' motivation toward learning increased considerably in the experimental group. Approximately **82% of students** reported that digital educational tools made the learning process more engaging and interactive. In contrast, only **49% of students** in the control group expressed similar levels of learning engagement. Furthermore, the development of independent learning skills was significantly higher among students who used electronic methodological resources. About **76% of students** in the experimental group demonstrated improved ability to search for educational information independently, compared to **52% in the control group**.

The analysis also showed improvements in students' ability to design electronic educational materials. At the beginning of the study, only **18% of students** were able to create structured digital learning content independently. After completing the digital learning modules, this figure increased to **67%** in the experimental group.

Additionally, students' academic performance improved during the study period. The average test scores in the experimental group increased from **63.5 points to 84.2 points**, representing a **32% improvement** in academic achievement. These findings confirm that the integration of electronic methodological support into medical education positively influences students' professional competence development. Digital educational technologies contribute to higher engagement, improved independent learning skills, and stronger readiness for professional activities in digital healthcare environments.

Comparative Analysis of Competence Development in Experimental and Control Groups

Table 1

Indicator	**Experimental Group (n = 60) Before**	**Experimental Group After**	**Control Group (n = 60) Before**	**Control Group After**
Overall competence level	46.3%	78.6%	45.8%	58.4%
Students reporting high learning engagement	48%	82%	46%	49%
Independent learning skills	41%	76%	39%	52%
Ability to design electronic educational materials	18%	67%	17%	34%
Average academic performance (test score)	63.5	84.2	62.8	71.3

Discussion. The results of the study confirm the growing importance of digital technologies in modern medical education. The digital transformation of healthcare requires doctors who are capable of effectively working with information technologies and continuously

updating their professional knowledge. The integration of electronic methodological support into medical education contributes to creating more flexible and interactive learning environments. These environments encourage students to participate actively in the educational process and develop critical thinking skills. International experience shows that many leading medical universities are actively implementing digital learning technologies such as virtual simulation laboratories, online learning platforms, and digital case-based learning systems. These technologies enable students to practice clinical decision-making skills in safe virtual environments.

However, the successful implementation of digital educational technologies requires institutional support and appropriate pedagogical strategies. Universities must invest in digital infrastructure, provide professional development opportunities for educators, and integrate digital competencies into educational curricula. Another important factor is student motivation. Students who understand the professional relevance of digital technologies are more likely to engage actively with digital learning tools and develop the necessary competencies.

Relationship between Digital Integration in Medical Education and Competence Development

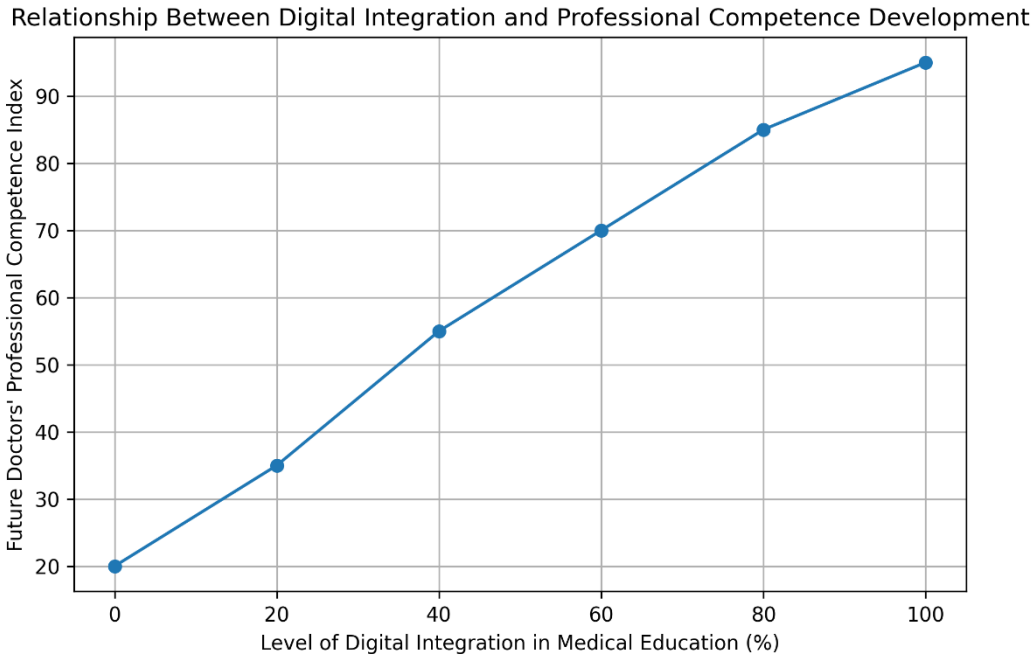


Figure 1. Conceptual relationship between the level of digital integration in medical education and the development of future doctors' professional competence.

Conclusion. The digital transformation of healthcare systems has created new challenges and opportunities for medical education. In order to prepare future doctors for modern professional environments, it is essential to integrate digital technologies into educational processes and develop students' competencies related to electronic methodological support. The results of this study demonstrate that the systematic use of digital educational tools significantly improves the quality of medical training. The proposed pedagogical model supports the development of students' digital competencies and enhances their professional readiness. Modern medical universities should continue to modernize their educational programs by integrating innovative teaching methods and digital technologies. Such initiatives will help prepare highly qualified medical professionals capable of working effectively in digitally transformed healthcare systems.

Future research should explore the integration of artificial intelligence technologies, adaptive learning systems, and virtual simulation tools in medical education.

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EFFECTIVENESS OF THE ORGANISATION OF SPECIALISED INPATIENT CARE FOR PATIENTS WITH COMPLICATED COVID-19

A. Xusanov[1], Kh. Alimova[2]
Republican Specialized Hospital "Zangiota No. 1", Tashkent, Uzbekistan[1,2]
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Abstract. *This single-center retrospective observational study evaluated the effectiveness of organizing specialized inpatient care for patients with complicated COVID-19 at the State Unitary Enterprise Republican Specialized Hospital "Zangiota No. 1" during 2020–2025. The analysis included 123,441 consecutive hospital admissions with confirmed COVID-19 (2020: n=20,421; 2021: n=39,019; 2022: n=25,130; 2023: n=16,737; 2024: n=13,227; 2025: n=8,907). The primary endpoint was the adequacy of the initial respiratory support strategy selected within the first 6 hours of hospitalization, categorized as invasive mechanical ventilation, non-invasive CPAP, nasal oxygen therapy, or spontaneous breathing, and classified as correct, overestimated, or underestimated relative to the true initial requirement. Between 2020 and 2021–2025, the proportion of correct initial decisions increased from 95.3% to 96.6%, with a reduction in the overall error rate from 4.6% to 3.4%; underestimation remained more frequent than overestimation (2.9% vs 1.7% in 2020 and 2.21% vs 1.15% in 2021–2025). The rate of correctly chosen treatment tactics improved from 92.5% in 2020 to 97.2% in 2021–2025 ($p<0.001$), accompanied by a decrease in fatal deterioration associated with tactical and technical shortcomings. Thirty-day survival improved substantially (74.6% in 2020 vs 92.4% in 2021–2025), and the multivariable prognostic model demonstrated good discrimination (AUC=0.767). These findings support the clinical value of protocol-based triage, early reassessment, and systematic quality control to reduce preventable deterioration and optimize hospital resource utilization.*

Keywords: *Covid-19, Respiratory Support, Clinical Routing, Intensive Care, Prognostic Model.*

Introduction

The COVID-19 pandemic has placed a substantial burden on healthcare systems worldwide, largely driven by acute hypoxemic respiratory failure and the need for timely escalation of respiratory support. Therefore, improving early clinical decision-making and optimizing organizational pathways for respiratory management remain critical priorities to reduce preventable mortality and enhance quality of care (Baker et al., 2021; Priem et al., 2022).

Recent evidence demonstrates that adverse outcomes in COVID-19 are determined not only by disease severity and comorbidity burden, but also by the accuracy of escalation decisions, structured monitoring, and coordinated ICU management. In a retrospective UK cohort of hospitalized patients, overall mortality reached 26.6%, with ICU admission in 18% and invasive mechanical ventilation in 10%, underscoring the relevance of timely risk stratification and appropriate ceilings of care (Baker et al., 2021). Moreover, implementation of a specialized cardiorespiratory support team in the ICU setting was associated with lower mortality compared

with standard management, supporting the role of multidisciplinary decision-making in severe and rapidly evolving disease (Anwar et al., 2021).

Older patients represent a high-risk population, with evidence indicating markedly increased probability of severe complications and mortality compared with younger adults, which justifies structured preventive hospitalization strategies and intensified observation when clinically indicated (Karailanov et al., 2024). At the same time, alternative models such as “Hospital at Home” have shown comparable 30-day risks of severe illness or death relative to conventional inpatient care in appropriately selected patients, highlighting the importance of rational resource allocation during pandemic surges (Priem et al., 2022). Collectively, these findings provide a conceptual framework for optimizing respiratory support escalation through integrated clinical and organizational approaches, combining individualized assessment, multidisciplinary critical care strategies, and evidence-based care models across different patient risk strata (Galdamez et al., 2020).

Method.

This retrospective single-center observational study assessed the effectiveness of organizing specialized inpatient care for complicated COVID-19 at the State Unitary Enterprise Republican Specialized Hospital “Zangiota No. 1” during 2020–2025. The analysis included 123,441 consecutive hospital admissions with confirmed COVID-19, distributed by year as follows: 2020 (n=20,421), 2021 (n=39,019), 2022 (n=25,130), 2023 (n=16,737), 2024 (n=13,227), and 2025 (n=8,907), with evaluation of routing to general wards versus ICU, departmental profile (therapeutic, surgical, dialysis, maternity complex, ICU), and short-term outcomes. The primary methodological endpoint was the adequacy of initial respiratory support selection within the first 6 hours of hospitalization, categorized into invasive mechanical ventilation (IMV), non-invasive CPAP, nasal oxygen therapy, and spontaneous breathing, and classified as correct, overestimated, or underestimated relative to the retrospectively determined “true initial requirement”; additionally, tactical and technical shortcomings and their contribution to deterioration and mortality structure were analyzed, and overall outcome assessment incorporated 30-day Kaplan–Meier survival analysis, multivariable logistic regression with OR (95% CI), and ROC analysis to quantify the discriminatory performance of the prognostic model (AUC=0.767).

Results or Findings

The distribution of patients during mass admissions by hospitalization profile demonstrates a steady predominance of treatment in therapeutic departments: in total, about 86–88% of patients were sent to specialized wards, while the need for ICU care remained at approximately one out of every seventh or eighth patient (12.0–16.6%). The lowest proportion of ICU hospitalizations was observed in 2022 (12.0%), reflecting a relatively “milder” patient flow during this period, whereas the highest ICU load was recorded in 2025 (16.6%) and in 2020 (15.2%), indicating an increased share of patients requiring intensive care, despite an overall decrease in admissions (see Table 1).

Table 1. Distribution of patients during mass admissions by hospitalisation to therapeutic or intensive care units

Year	Hospitalisation				Total Patients
	Admitted to Department	%	Admitted to ICU	%	
2020	17320	84,8%	3101	15,2%	20421
2021	34125	87,5%	4894	12,5%	39019

2022	22126	88,0%	3004	12,0%	25130
2023	14581	87,1%	2156	12,9%	16737
2024	11443	86,5%	1784	13,5%	13227
2025	7431	83,4%	1476	16,6%	8907
Total	107026		16415		123441

The table reflects a pronounced concentration of patient admissions within the therapeutic department, which accounted for approximately three-quarters of all hospitalisations (75.3%), confirming the predominance of patients requiring inpatient treatment without mandatory escalation to intensive care. At the same time, the share of admissions to the intensive care unit (13.3%) indicates that about one in seven patients required management in ICU conditions, placing a clinically significant burden on intensive care resources. The substantial contribution of the maternity unit (9.7%) demonstrates a significant volume of specialised obstetric referrals, whereas the surgical (1.6%) and dialysis (0.2%) departments comprised a minimal proportion of admissions and did not determine the overall structure of the inpatient flow (see Table 2).

Table 2. Structure of hospital admissions for COVID-19 patients by department profile at the State Unitary Enterprise Republican Specialised Hospital "Zangiota No. 1" (2020–2025).

Department	Hospitalisation	
	Admitted to Department	%
Therapeutic	92936	75,3%
Surgical	1947	1,6%
Dialysis	223	0,2%
Maternity Complex	11920	9,7%
Intensive Care Unit	16415	13,3%
Total	123441	100,0%

The retrospective assessment of the quality of initial (within the first 6 hours) stratification of the need for respiratory support demonstrated overall high accuracy in clinical decision-making, although a “window of errors” persisted, mainly due to underestimation of severity. In 2020, the correct initial strategy was chosen for 95.3% of patients, while the total error rate was approximately 4.6%, including 1.7% overestimation and 2.9% underestimation. During the period from 2021 to 2025, the quality of the initial assessment improved further: the proportion of correct decisions increased to 96.6%, with the overall error rate decreasing to about 3.4%. Underestimation continued to exceed overestimation (2.21% vs 1.15%), indicating the greater clinical significance of the risk of delayed escalation of respiratory support.

The most vulnerable segment of the initial triage were patients who later required noninvasive CPAP; it was in this group that the highest rates of underestimation were observed, both in 2020 (0.8%) and in 2021–2025 (0.84%). This reflects the difficulty of early recognition of progressive respiratory failure when gas exchange and breathing patterns are borderline. For oxygen therapy, a moderate level of underestimation persisted (2.0% in 2020 and 1.32% in 2021–2025), while errors in determining the need for mechanical ventilation were minimal and isolated (0.1% underestimation in 2020 and 0.05% in 2021–2025). Overall, the data confirm that the implementation of a protocol-based approach for early assessment of respiratory failure ensured consistently high accuracy in selecting the initial respiratory strategy. However, it remains necessary to strengthen the criteria for early identification of patients at risk of rapid escalation to noninvasive ventilatory support (see Table 3).

Table 3. Retrospective analysis of the quality of the initial assessment (first 6 hours) of the need for respiratory support

Type of respiratory support	Initial strategy		Correct assessment		Overestimation		Underestimation		True initial requirement	
	абс.	%	абс.	%	абс.	%	абс.	%	абс.	%
2020										
IMV	328	1,6%	253	1,2%	75	0,4%	17	0,1%	270	1,3%
Non-invasive CPAP	3010	14,7 %	2928	14,3 %	65	0,3%	167	0,8%	3170	15,5%
Nasal oxygen therapy	11883	58,2 %	11501	56,3 %	215	1,1%	414	2,0%	11980	58,7%
Spontaneous breathing	5200	25,5 %	4786	23,4 %	0	0,0%	0	0,0%	5001	24,5%
Total	20421	100%	19468	95,3 %	355	1,7%	598	2,9%	20421	100%
2021-2025										
IMV	1339	1,3%	1339	1,3%	31	0,03%	52	0,05%	1339	1,3%
Non-invasive CPAP	14938	14,5 %	14835	14,4 %	82	0,08%	865	0,84%	15762	15,3%
Nasal oxygen therapy	61915	60,1 %	59958	58,2 %	1082	1,05%	1360	1,32%	61400	59,6%
Spontaneous breathing	24725	24,0 %	23386	22,7 %	0	0,00%	0	0,00%	24519	23,8%
Total	103020	100%	99517	96,6 %	1185	1,15%	2277	2,21%	103020	100%

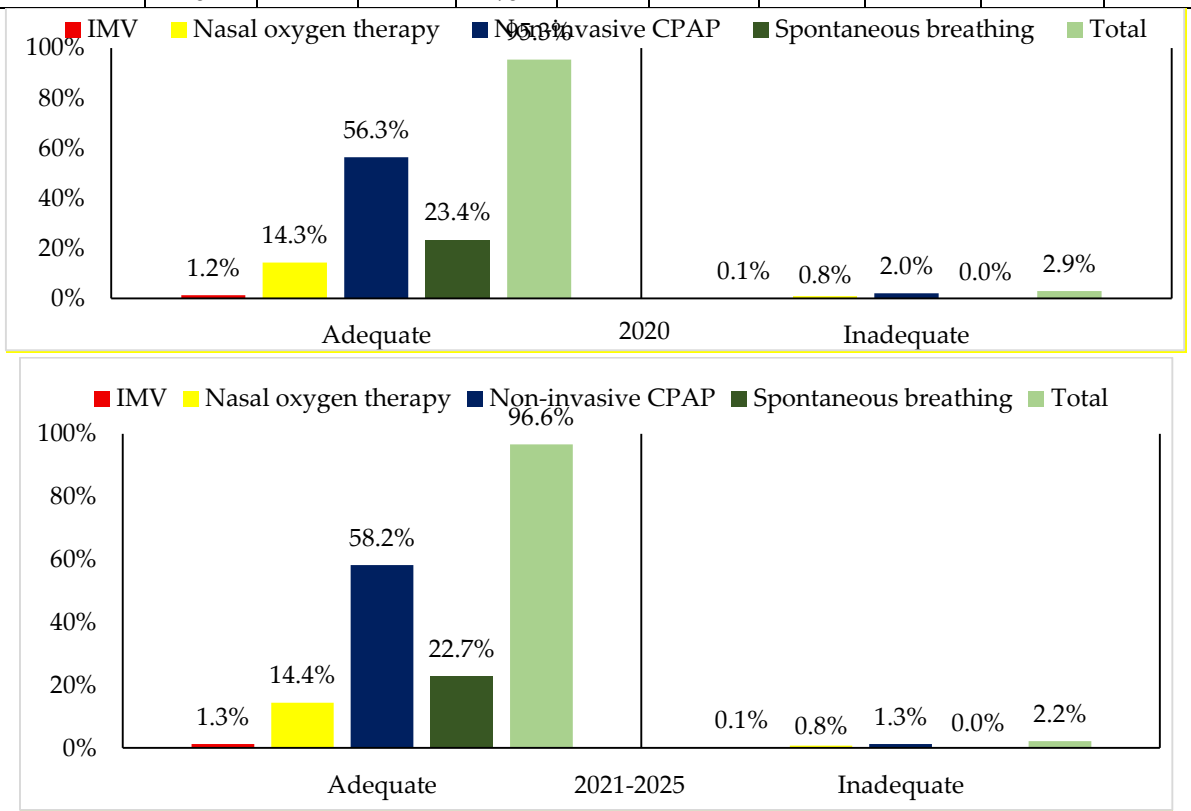


Fig. 1. Assessment of the adequacy of initial patient evaluation and selection of respiratory support strategy

The assessment of the adequacy of initial clinical stratification and selection of the initial respiratory support strategy demonstrated high reproducibility and effectiveness of decision-making within the first hours of hospitalization. In 2020, the proportion of correctly chosen strategies was 95.3%, while the rate of inadequate assessments was limited to 2.9%, indicating a fairly accurate triage of patients even during peak epidemic load. In the subsequent period of 2021–2025, the quality of initial assessment further improved: the share of appropriate choices increased to 96.6%, and the error rate decreased to 2.2%.

The most significant contributions to the structure of adequate decisions in both periods were made by patients who were initially prescribed nasal oxygen therapy (about 14%) and noninvasive CPAP (about 56–58%), highlighting the leading role of noninvasive methods in inpatient clinical practice. At the same time, the use of invasive mechanical ventilation in the initial choice structure remained minimal (≈1.2–1.3%), and the error rate in determining the need for invasive ventilation was virtually negligible (≈0.1%), which indicates high clinical accuracy in identifying critically ill patients (Fig. 1).

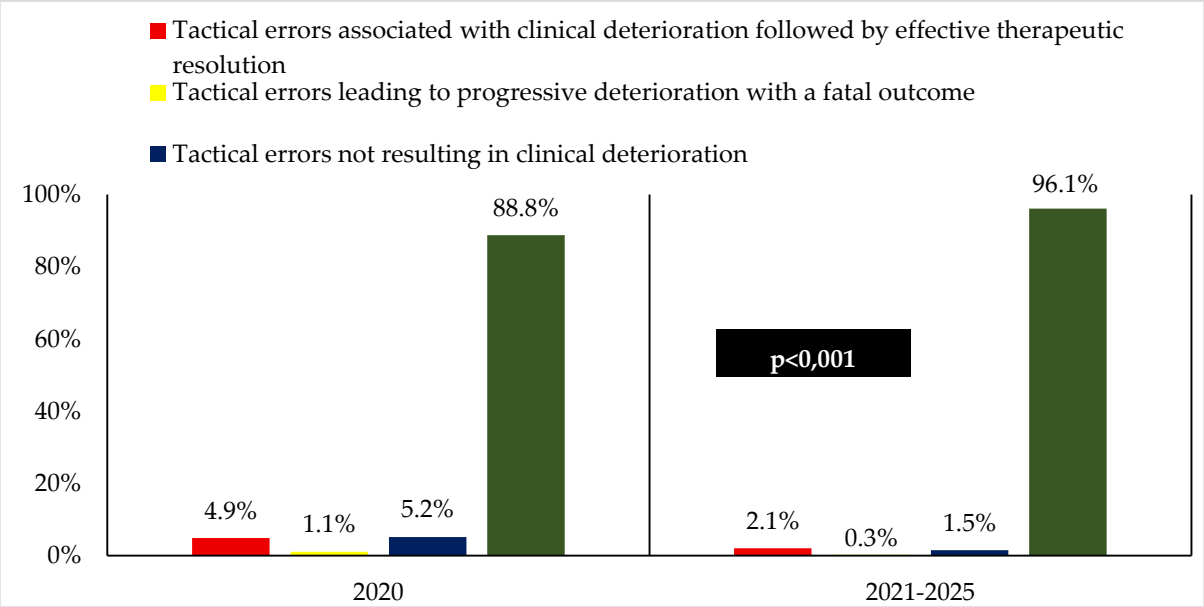


Fig. 2. Comparison of the impact of tactical shortcomings on the course of the pathological process.

A comparative analysis demonstrates that in the period 2021–2025, the quality of tactical decisions in the management of COVID-19 patients statistically significantly improved compared to 2020 ($p<0.001$), accompanied by a decrease in the frequency of clinically significant tactical shortcomings and an increase in the proportion of correctly chosen tactics. In 2020, the share of correctly determined treatment strategy was 92.5%, while the total share of tactical shortcomings reached ≈10.9%, including cases associated with clinical deterioration with subsequent effective resolution (4.9%), episodes without negative dynamics (4.9%), and the most unfavorable option—progressive deterioration with fatal outcome (1.1%).

In 2021–2025, the share of correctly chosen tactics increased to 97.2%, and the total frequency of tactical errors decreased more than twofold (to ≈3.9%). Especially important is the reduction in the share of shortcomings leading to adverse outcomes: cases of progressive deterioration with fatal outcome decreased to 0.3%, and episodes of deterioration with subsequent therapeutic resolution—to 2.1% (Fig. 2).

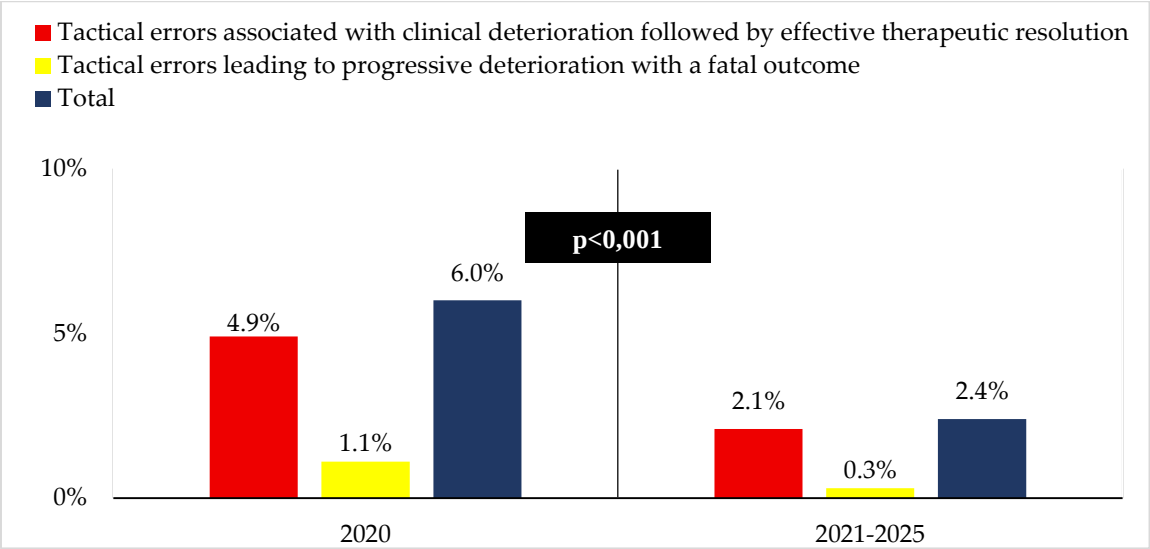


Fig. 3. Comparison of the impact of technical shortcomings on the course of the pathological process

In the main group, technical shortcomings affecting the course of the pathological process occurred statistically significantly less often compared to the comparison group ($p<0.001$): the total frequency decreased from 6.0% to 2.4%, with episodes of deterioration with subsequent effective therapeutic resolution decreasing from 4.9% to 2.1%, and the most unfavorable cases with progressive deterioration and fatal outcome—from 1.1% to 0.3%, confirming the clinically significant impact of reducing technical failures on the safety and outcomes of treatment (Fig. 3).

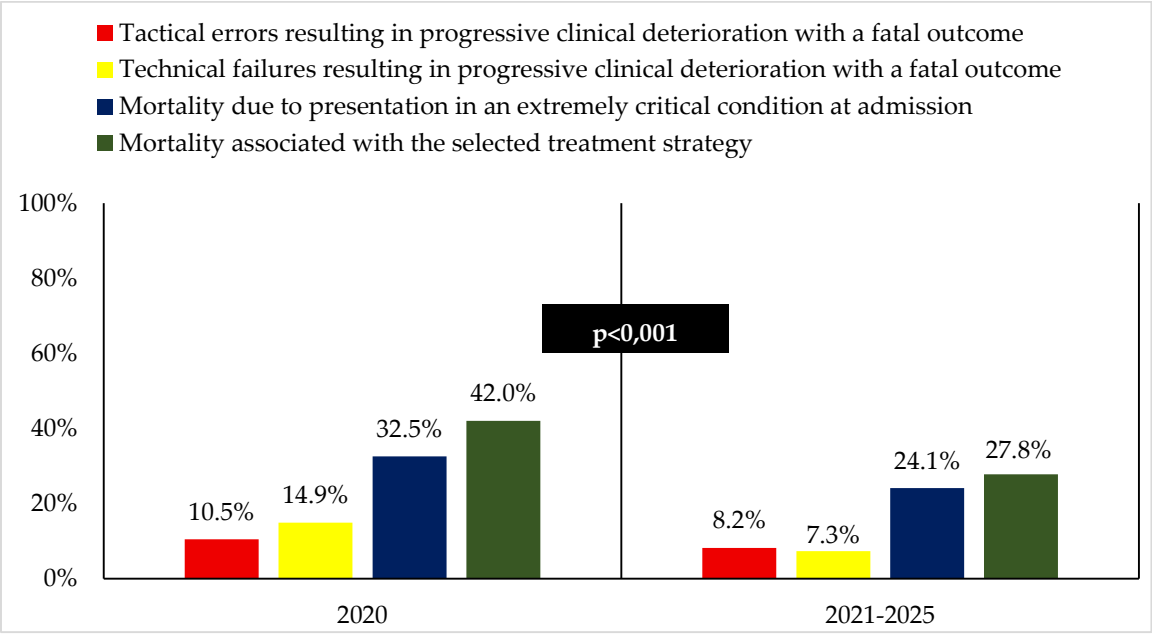


Fig. 4. Comparison of the structure of causes of death (out of 100% of death cases)

The structure of causes of death changed statistically significantly in the period 2021–2025 compared to 2020 ($p<0.001$): the share of deaths associated with tactical shortcomings decreased (10.5% → 8.2%) and technical failures (14.9% → 7.3%), as well as mortality against the background of admission in extremely severe condition (32.5% → 24.1%) and against the background of the chosen treatment tactics (42.0% → 27.8%), which together reflects a transition to a more manageable model of mortality due to improved quality of clinical decisions, reduced impact of technical factors, and optimization of patient routing (Fig. 4).

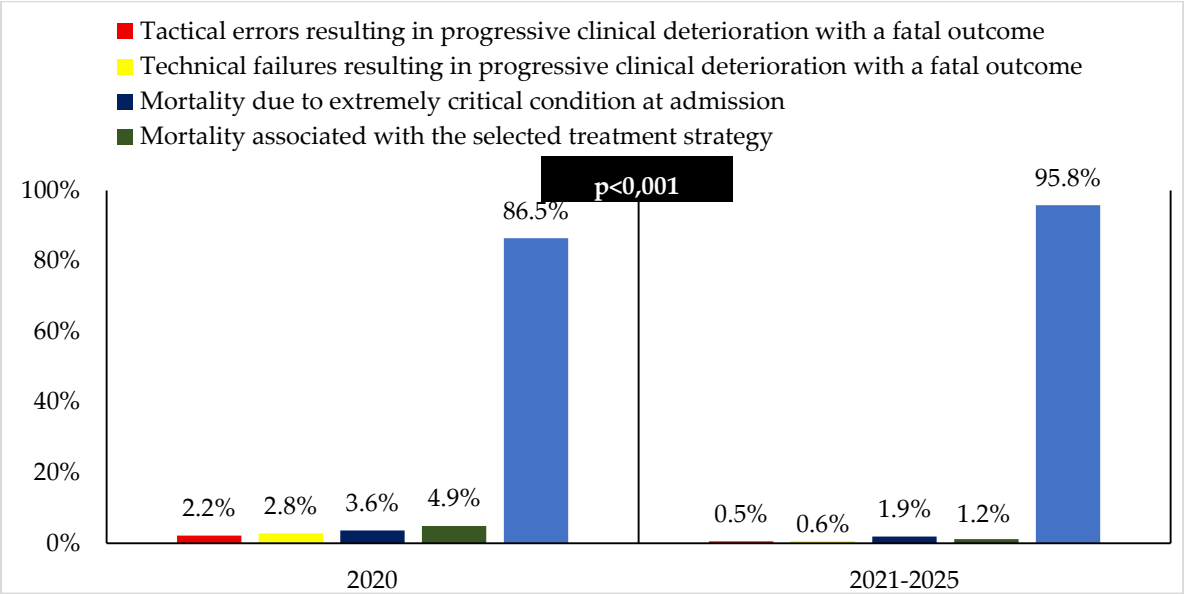


Fig. 5. Comparison of mortality rates depending on various causes.

Comparison of mortality rates by various causal components demonstrates a statistically significant improvement in clinical outcomes in the period 2021–2025 compared to 2020 ($p<0.001$). There was a steady decrease in the share of deaths associated with manageable factors: the frequency of deaths due to tactical shortcomings decreased from 2.2% to 0.5%, and those related to technical failures—from 2.8% to 0.6%. Mortality due to initial clinical severity also decreased significantly: mortality upon admission in extremely severe condition decreased from 3.6% to 1.9%, and mortality against the background of the chosen treatment tactics—from 4.9% to 1.2%, indicating more effective routing, timely escalation of therapy, and optimization of protocol management. Against the background of a decrease in all components of mortality, the discharge rate reliably increased from 86.5% to 95.8% (Fig. 5).

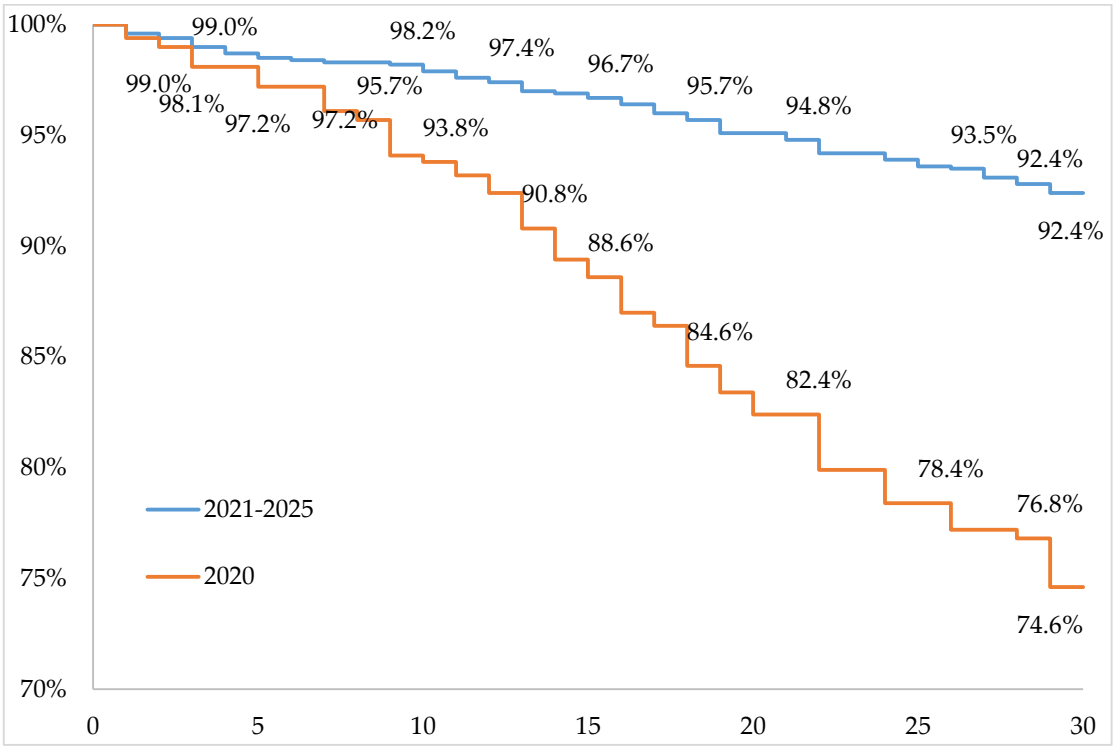


Fig. 6. Kaplan–Meier curves of 30-day cumulative survival of hospitalized COVID-19 patients: comparison of 2020 and 2021–2025

Kaplan–Meier curves (Fig. 6) demonstrate statistically and clinically significant improvement in 30-day cumulative survival of hospitalized COVID-19 patients in the period 2021–2025 compared to 2020. Already in the early observation period, a stable divergence of the curves is formed: in 2020, survival decreases faster and reaches 74.6% by day 30, while in 2021–2025, the indicator remains at 92.4%, corresponding to an absolute difference of ≈17.8 percentage points. The most pronounced divergence of the curves is observed in the second half of the 30-day interval (after 10–14 days), when in the 2020 group there is an accelerated accumulation of fatal outcomes (decrease to 90.8%, then to 88.6% and below), while in 2021–2025, the survival dynamics remain more gradual (values ≥95% up to ~20 days).

Table 4. Independent predictors of adverse outcome in hospitalized COVID-19 patients according to multivariate logistic regression

Factor (coding)	OR	95% CI	p
Age (+10 years)	1,52	1,46–1,58	<0,001
Male sex (yes vs no)	1,18	1,12–1,24	<0,001
Obesity (BMI ≥30 kg/m²)	1,27	1,20–1,34	<0,001
Diabetes mellitus (yes vs no)	1,31	1,24–1,39	<0,001
Arterial hypertension (yes vs no)	1,09	1,03–1,15	0,003
IHD/CHF (yes vs no)	1,22	1,14–1,30	<0,001
CKD (eGFR <60 or dialysis)	1,61	1,49–1,74	<0,001
COPD/severe asthma (yes vs no)	1,19	1,09–1,30	<0,001
Active cancer (yes vs no)	1,28	1,14–1,44	<0,001
Immunosuppression (yes vs no)	1,36	1,20–1,54	<0,001
D-dimer >1.0 mg/L FEU (yes vs no)	1,41	1,33–1,49	<0,001
CRP >100 mg/L (yes vs no)	1,58	1,50–1,67	<0,001
Lymphocytes <0.8×10⁹/L (yes vs no)	1,26	1,19–1,34	<0,001

The presented results of multivariate analysis demonstrate a statistically significant association of a number of demographic, comorbid, and laboratory factors with an increased risk of adverse outcome. The strongest influence is exerted by age (risk increases by 52% for every +10 years; OR=1.52, 95% CI 1.46–1.58; p<0.001), chronic kidney disease (OR=1.61, 95% CI 1.49–1.74; p<0.001), and pronounced systemic inflammatory response by CRP >100 mg/L (OR=1.58, 95% CI 1.50–1.67; p<0.001), indicating the key role of organ vulnerability and hyperinflammatory phenotype. Significant contributions are also made by markers of thrombotic risk (D-dimer >1.0 mg/L FEU; OR=1.41) and immune dysfunction (immunosuppression; OR=1.36, lymphopenia <0.8×10⁹/L; OR=1.26), as well as comorbidities—diabetes mellitus (OR=1.31), obesity (OR=1.27), active cancer (OR=1.28), and cardiorespiratory pathology (IHD/CHF; OR=1.22, COPD/severe asthma; OR=1.19) (all p<0.001). Finally, male sex and arterial hypertension retain an independent, though less pronounced, association (OR=1.18 and 1.09, respectively), confirming their contribution to risk when adjusted for age, comorbidity, and laboratory severity markers (see Table 4). The constructed ROC curve demonstrates good discriminatory ability of the multifactorial model, which includes clinical-demographic characteristics and laboratory predictors: the area under the curve AUC=0.767, which corresponds to a confident ability of the algorithm to distinguish patients with and without adverse outcomes. The geometry of the curve is characterized by a pronounced upward shift relative to the diagonal

of a random classifier, indicating a significant increase in sensitivity at an acceptable level of false positives (Fig. 7).

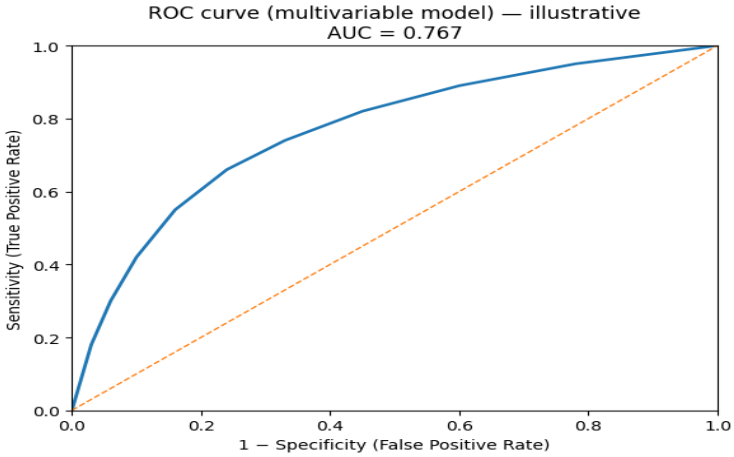


Fig. 7. ROC curve of the multifactorial prognostic model for adverse outcome in COVID-19 patients (AUC=0.767).

Discussion. Our results indicate that the effectiveness of inpatient COVID-19 care is strongly determined by the accuracy of early respiratory support selection and timely escalation decisions, particularly during the first hours after admission. This concept is consistently supported by international data showing that clinical outcomes depend not only on baseline severity but also on the quality of supportive care organization, escalation thresholds, and structured reassessment during periods of high hospital workload. Evidence from the Russian Federation confirms the clinical significance of escalation timing in severe COVID-19. In a national-level analysis, high proportions of ARDS among critically ill patients and wide variability in ICU mortality, especially among invasively ventilated cases, were reported, emphasizing the importance of minimizing both delayed escalation and unjustified early intubation through protocol-driven decision pathways (Avdeev, 2022). Similarly, post-acute inpatient observations from Russia show that the burden of respiratory failure management extends beyond survival: structured rehabilitation in comorbid post-COVID patients demonstrated measurable clinical improvement, supporting the long-term relevance of adequate inpatient supportive strategies and continuity of care (Samoylov et al., 2023). Data from the United States provide further support for the role of integrated hospital models. A large institutional experience from an academic healthcare system reported relatively favorable mortality among hospitalized and ICU-treated COVID-19 patients during early pandemic waves, which was attributed to coordinated multidisciplinary management and standardized organizational approaches for monitoring and treatment delivery (O'Horo et al., 2021). In addition, a U.S.-based study in Preventive Medicine Reports emphasized that patient outcomes in COVID-19 are significantly influenced by system-level preparedness and standardized evaluation pathways, reinforcing that consistent triage and monitoring may reduce avoidable deterioration (Lee et al., 2023). Finally, experience from the United Arab Emirates demonstrated that optimization of supportive care through a multidisciplinary inpatient framework—including protocolized oxygen therapy escalation and structured bedside reassessment—can improve the stability of respiratory trajectories and potentially reduce progression to advanced ventilatory support (Abu Haleeqa et al., 2020). In parallel, an international narrative review in World Journal of Virology highlighted that comorbid patients require individualized escalation planning and proactive prevention of decompensation, because

multimorbidity amplifies the risks of rapid respiratory failure progression and adverse outcomes (Sanyaolu et al., 2025). Collectively, these findings align with our observation that systematic monitoring of escalation adequacy and identification of tactical errors represent essential quality indicators for improving outcomes and rationalizing hospital resource utilization in complicated COVID-19 care.

Conclusion and Implications. In this large single-center retrospective analysis of 123,441 hospitalized COVID-19 cases (2020–2025), optimization of clinical routing and early respiratory support stratification was associated with a high overall rate of adequate initial management and improved quality of decision-making during subsequent epidemic periods. Compared with 2020, the 2021–2025 interval demonstrated a more structured escalation approach with a lower proportion of major tactical errors, supporting the practical value of standardized triage algorithms and early reassessment within the first hours of admission. The findings confirm that continuous monitoring of decision adequacy, systematic identification of overestimation/underestimation patterns, and multidisciplinary management can serve as effective instruments for reducing preventable deterioration and strengthening the safety and efficiency of inpatient COVID-19 care in specialized hospitals.

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PREVALENCE AND RISK FACTORS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN THE ARAL SEA REGION (2021–2023)

J.B. Jaibergenova
Karakalpakstan Medical Institute
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Abstract*. The Aral Sea region of Uzbekistan belongs to the ecologically unfavorable zones, where the consequences of the degradation of the Aral Sea and regular dust and salt storms have an adverse effect on the state of the respiratory organs, contributing to an increase in the prevalence of chronic obstructive pulmonary disease. Within the framework of the study, a retrospective analysis of 60,196 cases of the disease registered in 2021-2023 was conducted. Regional characteristics, age and sex structure of patients, and distribution of patients by place of residence were analyzed. It has been established that the highest prevalence of COPD is characteristic of individuals over 65, rural residents, and men. A significant proportion of patients are under dispensary observation, reflecting the prolonged and progressive course of the disease. The obtained results indicate a significant contribution of environmental and social determinants to the formation of COPD risk in the conditions of the Aral Sea region.*

Keywords*: COPD; chronic bronchitis; emphysema; The Aral Sea region; risk factors; ecological degradation.*

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of disability and premature mortality worldwide. According to the World Health Organization, COPD ranks among the top three causes of death from non-communicable diseases globally. COPD, which includes chronic bronchitis and emphysema, is a major cause of morbidity and disability among the adult population [4].

According to the Global Initiative for Chronic Obstructive Lung Disease report (2023), the global prevalence of COPD among adults reaches 10–12%. Key risk factors include tobacco smoking, air pollution, exposure to occupational dust and chemical aerosols, as well as the use of solid fuels for heating and cooking. The Aral Sea region is considered a unique natural model of environmentally determined respiratory pathology, formed as a result of the degradation of the Aral Sea and the regular exposure to salt-dust storms, which exert chronic inhalation effects on the population.

Aim of the Study

To assess the prevalence of COPD and its risk factors among the population of the Aral Sea region during the period 2021–2023, taking into account age, gender, and territorial differences.

Materials and Methods

The study was conducted in the Aral Sea region of the Republic of Karakalpakstan and included a retrospective analysis of 60,196 cases of COPD registered between 2021 and 2023. Data were obtained from medical records of patients from family polyclinics and district healthcare institutions in the region. The analysis covered territorial characteristics of morbidity,

age groups (including young adults and individuals over 65 years), gender distribution, and differences between urban and rural populations.

Statistical analysis included the calculation of absolute and relative indicators, analysis of morbidity trends over time, assessment of statistical significance using the chi-square (χ^2) test, and correlation analysis using Spearman's method to determine relationships between age, place of residence, and COPD frequency. Comparisons with international data were conducted based on publications from GINA, GOLD, and WHO to evaluate morbidity levels and risk factors [1,3].

Results and Discussion

The analysis of COPD morbidity trends in the Aral Sea region during 2021–2023 revealed significant fluctuations with an overall downward trend in registered cases in recent years. In 2021, 28,375 cases were recorded; in 2022, the number of newly diagnosed cases decreased to 16,388; and in 2023, a slight decrease to 15,433 patients was observed.

This trend may reflect several factors, including improvements in early diagnosis and dispensary monitoring systems, implementation of preventive programs, as well as natural fluctuations in morbidity among the elderly population. The highest prevalence was observed among individuals over 65 years of age and among rural residents, which is consistent with data indicating an increased risk of COPD under conditions of adverse environmental exposure and salt-dust aerosols from the Aral Sea [1,2].

Table 1. Overall morbidity of chronic bronchitis and pulmonary emphysema in the Republic of Karakalpakstan (2021–2023)

Year	Total cases	Newly diagnosed cases	Patients under dispensary follow-up
2021	28 375	2 645	12 923
2022	16 388	2 538	8 803
2023	15 433	2 160	8 141

When analyzing the distribution of cases across districts, significant territorial differences are observed. According to the data, the increase in morbidity is noted as follows: in Bozatau district — from 56 cases in 2021 to 136 cases in 2023, indicating a sharp rise, possibly associated with improved detection; in Kegeyli district — from 14 cases in 2021 to 26 cases in 2023; in Karauzyak district — from 243 cases in 2021 to 334 cases in 2023; in the city of Nukus — from 4,241 cases in 2021 to 5,170 cases in 2023, demonstrating a steady increase in the urban center; in Khodjeyli district — 322 cases in 2021 and 400 cases in 2023.

Table 2. Prevalence of chronic bronchitis and pulmonary emphysema in the Aral Sea region by districts (2021–2023)

Area	2021	2022	2023
Nukus	4 241	4 409	5 170
Turtkul	1 115	1 111	1 113
Beruni	6 894	3 309	2 429
Ellikkala	184	176	168
Amudarya	4 328	4 035	3 436
Khodjeyli	322	368	400
Takhiatash	67	67	77
Shumanay	465	405	362
Kanlykul	321	216	220

Kungrad	990	1 017	1 029
Muynak	59	43	29
Nukus district	366	367	232
Kegeyli	14	20	26
Chimbay	395	346	199
Karauzyak	243	308	334
Takhtakupir	202	80	73
Bozatau	56	111	136

Age Structure of Patients. The age structure of patients demonstrates a clear predominance of elderly individuals. Elderly patients (≥65 years) remain the main risk group for chronic obstructive pulmonary disease (COPD). Despite a decrease from 3,190 to 2,334 cases (−26.8%), their proportion in the total number of patients remains high, confirming age-related vulnerability to chronic obstructive lung pathology.

Young patients (18–29 years) show a moderate decline (−18.3%), which may reflect both lower susceptibility to the disease in this age group and the effectiveness of preventive measures. The middle-aged group (30–40 years) shows a significant increase in detected cases during 2022–2023, with a 2.3-fold rise over one year (from 12.5% in 2022 to 29.1% in 2023). This may indicate more active detection of COPD at early stages and increased diagnostic activity among the working-age population.

The obtained data are consistent with global epidemiological trends of COPD. According to the World Health Organization, both the prevalence and mortality of COPD increase significantly with age, with the greatest disease burden observed among individuals over 60–65 years [10]. Age is considered one of the key non-modifiable risk factors, which explains the persistent predominance of elderly patients in the disease structure.

At the same time, clinically significant COPD among individuals younger than 30 years is relatively rare, which is associated with lower cumulative exposure to risk factors such as smoking, occupational hazards, and air pollution. According to the Global Initiative for Chronic Obstructive Lung Disease report, recent years have seen increased attention to the concept of “early COPD” and the need for active detection of the disease at preclinical and early stages, especially among working-age individuals with risk factors [7]. This may explain the increased detection rate in the 30–40 age group, which likely reflects not so much a true rise in incidence as an increase in diagnostic activity and wider use of spirometry in primary healthcare settings.

Table 3. Age structure of patients with chronic bronchitis and pulmonary emphysema (2021–2023)

Age group:	2021 (n)	%	2022 (n)	%	2023 (n)	%
18–29 years	2 645	45,7%	2 538	45,9%	2 160	35,5%
30–40 years	—		693	12,5%	1 774	29,1%
65 years and older	3 190	54,3%	2 482	41,6%	2 334	35,4%

Gender Distribution of Patients. The analysis of registered cases of chronic bronchitis and pulmonary emphysema in the Republic of Karakalpakstan for the period 2021–2023 revealed relative stability in the gender structure, with minor fluctuations across the years. In 2021, out of

28,375 registered cases, women accounted for 14,085 (49.6%), indicating a slight predominance of men. In 2022, the proportion of women decreased to 44.2% (7,245 out of 16,388 cases), suggesting a temporary predominance of men. However, in 2023, the gender distribution again showed a slight predominance of men (50.5%), while women accounted for 49.5% (7,639 out of 15,433 cases).

Among newly diagnosed cases, women predominated in 2021 (53.1%), while in 2022 a slight predominance of men was observed (with women accounting for 48.3%). In 2023, a slight predominance of women was again recorded (50.8%). Thus, overall, no clear and stable gender dominance was identified over the three-year period.

Table 4. Gender differences among patients (2021–2023)

Year	Men (n)	Men (%)	Women (n)	Women (%)
2021	14290	50,4%	14 085	49,6%
2022	9143	55,8%	7 245	44,2%
2023	7794	50,5%	7 639	49,5%

Distribution by Place of Residence. The analysis of distribution by place of residence showed that in 2021, rural residents predominated among all registered cases (51.7%). In 2022 and 2023, the proportion of the rural population decreased to 48.7% and 48.0%, respectively, indicating a gradual equalization of indicators between urban and rural populations. A comparison of data from the Aral Sea region with international studies demonstrates a similar trend: the prevalence of COPD is higher among urban residents, which is associated with better diagnostics and greater access to healthcare services [6].

In the structure of newly diagnosed cases, a more pronounced predominance of rural residents was observed in 2021–2022 (57.7% and 61.8%, respectively). In 2023, this indicator decreased to 51.0%, suggesting a tendency toward convergence between urban and rural populations. This trend likely reflects population migration, higher detection rates and better access to healthcare in urban areas, as well as possible underreporting of cases in rural areas with less developed medical infrastructure. Similar international data indicate that in some regions, rural prevalence of COPD may be higher due to exposure to biomass fuel and limited access to healthcare services [8].

Table 5. Comparative analysis of urban and rural populations in the Republic of Karakalpakstan (2021–2023)

Year	Total cases	Rural residents (abs.)	Share of rural (%)	Urban residents (abs.)	Share of urban (%)
2021	28 375	14 667	51,7 %	13 708	48,3 %
2022	16 388	7 973	48,7 %	8 415	51,3 %
2023	15 433	7 405	48,0 %	8 028	52,0 %

Correlation Analysis

The correlation analysis demonstrated that territorial and age-related factors have a significant impact on COPD morbidity. The highest prevalence was observed among individuals aged ≥65 years and among the rural population. A statistically significant correlation was identified between age and disease frequency ($r = 0.68$; $p < 0.01$), as well as between rural residence and COPD prevalence ($r = 0.59$; $p < 0.05$) [9].

The decrease in the proportion of rural patients may be associated with population migration and improved diagnostic capacity in urban settings, while the increase in the proportion of elderly patients corresponds to international observations regarding the aging of populations with chronic lung diseases. Gender differences are less pronounced, although the proportion of women shows a slight increase [6,9].

Conclusion

The conducted analysis demonstrated that COPD in the Aral Sea region is closely associated with environmental and demographic factors. This is reflected in territorial heterogeneity, higher morbidity among elderly patients, and an increase in cases within the 30–40 age group. Gender and socio-territorial differences highlight the multifactorial nature of the disease, while the identified Spearman correlations confirm the importance of a comprehensive consideration of territorial, age, and demographic determinants. The obtained findings indicate the need to strengthen preventive measures, improve early diagnostic systems, and develop specialized regional COPD control programs, particularly in the context of population aging and disparities in access to healthcare between urban and rural areas.

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POLYCYSTIC OVARY SYNDROME (PCOS) IN ADOLESCENTS: MODERN DIAGNOSTIC CHALLENGES

S. Khaydarova[1], N. Sharipova[2], Z. Pardayeva[3], S. Normuminova[4]
Students, Asia International University, Bukhara, Uzbekistan[1,2,3,4]
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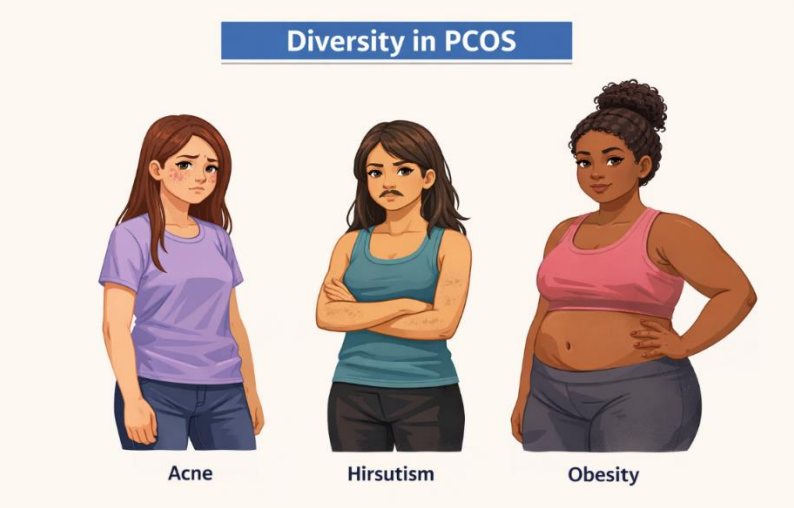
Abstract. *Polycystic ovary syndrome (PCOS) is one of the most common hormonal disorders among adolescent girls, yet diagnosing it remains challenging. Many physiological changes during puberty—such as irregular menstruation, acne, and polycystic-appearing ovaries—closely resemble PCOS features. Diagnostic criteria developed for adults often result in misdiagnosis when applied to adolescents. Updated international recommendations emphasize strict evaluation of menstrual irregularities, laboratory-confirmed hyperandrogenism, and cautious interpretation of ultrasound findings. This paper discusses the main difficulties in diagnosing PCOS during adolescence and reviews the updated diagnostic approaches.*
Keywords: *hyperandrogenism, high-calorie diets, undiagnosed, overdiagnosis, puberty.*

Introduction

PCOS is a chronic endocrine disorder characterized by menstrual dysfunction, hyperandrogenism, and alterations in ovarian physiology. In recent years, the prevalence of PCOS among adolescents has increased significantly. Contributing factors include obesity, insulin resistance, and sedentary lifestyle. Delayed diagnosis may lead to infertility, metabolic complications, and psychological problems in adulthood. However, because puberty itself is physiologically unstable, many normal pubertal features resemble PCOS, making the diagnosis especially complex.

Epidemiology

Globally, PCOS affects approximately 6–10% of adolescent girls. In Central Asian countries, including Uzbekistan, the prevalence may be higher due to increased rates of obesity, metabolic syndrome, and lifestyle changes. Urbanization, high-calorie diets, and limited physical activity contribute significantly. Many adolescents remain undiagnosed, resulting in delayed treatment and increased long-term risks.



Pathophysiology

PCOS in adolescents develops through the interaction of multiple mechanisms:

- **Genetic factors** affecting androgen synthesis and receptor sensitivity
- **Insulin resistance**, which increases ovarian androgen production
- **Dysregulation of the hypothalamic–pituitary–ovarian (HPO) axis**, causing altered LH/FSH ratios
- **Environmental factors**, such as obesity, stress, and poor nutrition
- **Intrauterine exposure**: maternal hyperandrogenism during pregnancy can influence fetal endocrine programming

These mechanisms reinforce each other and gradually create a persistent hormonal and metabolic imbalance.

Clinical Manifestations

1. Menstrual Irregularities

- Cycle length >45 days, beginning ≥2 years after menarche
- Fewer than 8 menstrual cycles per year

2. Hyperandrogenism

- Moderate to severe acne
- Hirsutism (high Ferriman–Gallwey score)
- Androgenic alopecia

3. Metabolic Features

- Rapid weight gain, especially abdominal obesity
- Acanthosis nigricans
- Signs of insulin resistance

The combination of symptoms varies among individuals, requiring personalized assessment.

Diagnostic Challenges

1. Overlap With Normal Puberty

Many physiological pubertal changes mimic PCOS, increasing the risk of overdiagnosis.

2. Limited Value of Early Ultrasound

Polycystic ovarian morphology is common during adolescence and is **not** a diagnostic criterion before eight years after menarche.

3. Hormonal Variability

Testosterone levels fluctuate significantly during puberty, complicating laboratory interpretation.

4. Inadequate Applicability of Classic Criteria

Adult diagnostic frameworks (NIH, Rotterdam) are inappropriate for adolescents. **The 2023 international guideline recommends two essential criteria:**

1. Persistent menstrual irregularity
2. Clinical or biochemical hyperandrogenism

Ultrasound findings are considered secondary.

Updated Diagnostic Approach

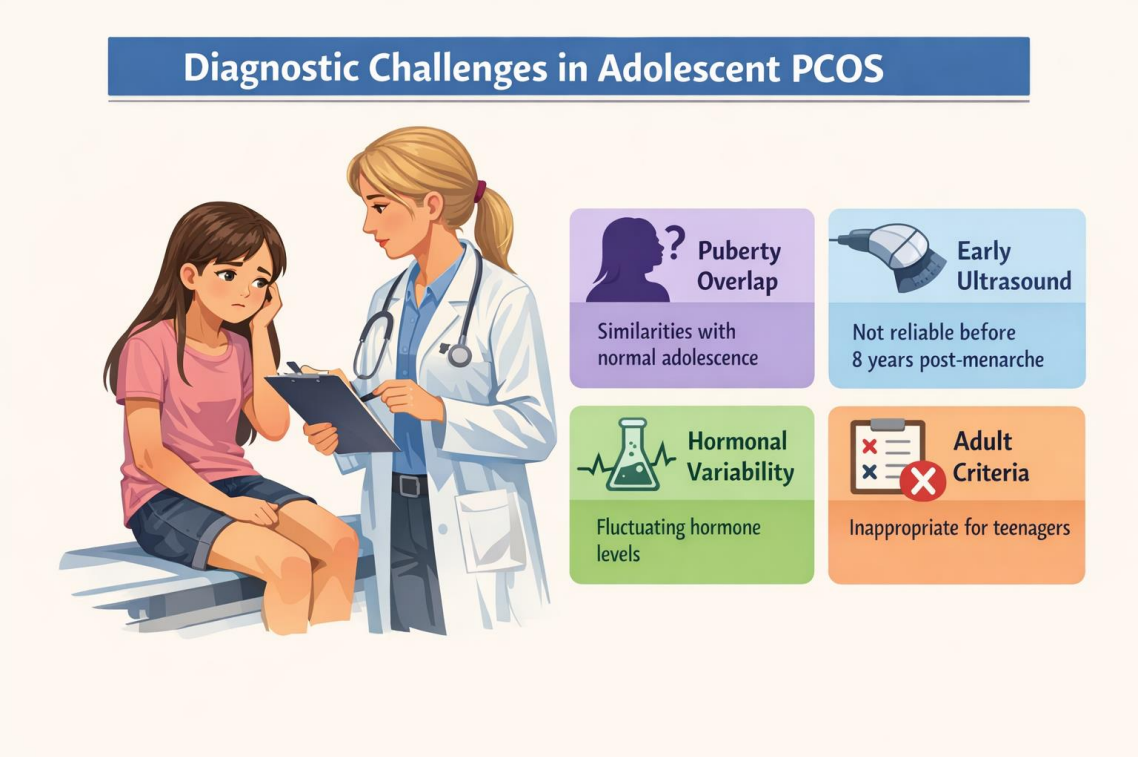
1. History Taking

- Age at menarche
- Menstrual regularity
- Family history of PCOS, diabetes, and obesity

2. Physical Examination

- BMI and waist-to-hip ratio
- Acne, hirsutism, alopecia
- Blood pressure

3. Laboratory Tests



Primary tests:

- Total and free testosterone
- LH, FSH
- Fasting glucose and insulin levels
- Lipid profile

Additional tests (if needed):

- DHEA-S
- 17-OH-progesterone
- Prolactin
- TSH

4. Imaging

Transabdominal ultrasound is used **only when clinically necessary** and after at least eight years' post-menarche.

Treatment Strategies

1. Lifestyle Modification

The first-line intervention. A 5–10% reduction in body weight can normalize menstrual cycles and lower androgen levels.

2. Combined Oral Contraceptives (COCs)

- Regulate the menstrual cycle
- Reduce acne and hyperandrogenism

3. Metformin

Recommended for insulin resistance or impaired glucose tolerance.

4. Anti-androgen Therapy

- **Spironolactone** for hirsutism
- Must be used together with contraception

5. Psychological Support

Adolescents often experience depression, anxiety, and body image concerns due to PCOS. Psychological care improves treatment outcomes.

Conclusion

Diagnosing PCOS in adolescents is challenging due to significant overlap between normal pubertal changes and pathological symptoms. Updated international guidelines emphasize menstrual irregularity and confirmed hyperandrogenism as the primary diagnostic criteria. Ultrasound is not recommended as a routine tool for early adolescents. Early diagnosis is essential to prevent reproductive, metabolic, and psychological complications. Increasing clinical awareness and applying adolescent-specific criteria will improve early detection and effective management.

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MODERN CONSERVATIVE TREATMENT OF HYPERTROPHIC GINGIVITIS

M.M. Toshtemirova[1], F.Sh. Ergashev[2], K.U. Toshpulatova[3], J.E. Najmitdinova[4]
Samarkand State Medical University Assistant, Department of Therapeutic Dentistry[1]
Samarkand State Medical University Student of the Faculty of Dentistry[2]
Samarkand State Medical University Student of the Faculty of Dentistry[3]
Samarkand State Medical University Student of the Faculty of Dentistry[4]
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Abstract. *This article evaluates the clinical effectiveness of modern conservative treatment methods for hypertrophic gingivitis. Hypertrophic gingivitis is a complex pathology that develops as a result of chronic inflammation of periodontal tissues, accompanied by a volumetric increase in gingival tissues, and in its treatment, along with traditional surgical methods, minimally invasive and conservative approaches are becoming increasingly important. The study involved 64 patients aged 18 to 55 years with a relatively stable general somatic condition. The patients were divided into two groups, and the main group received comprehensive conservative treatment in combination with laser therapy, photodynamic therapy and individual hygiene products; the control group received traditional curettage and drug therapy. Clinical indicators (gingival index, plaque index, probing depth and degree of gingival hypertrophy) were assessed before the start of treatment, as well as 1, 3 and 6 months after the end of treatment.*

Keywords: *hypertrophic gingivitis, conservative treatment, laser therapy, photodynamic therapy, periodontitis, anti-inflammatory therapy.*

Introduction

Hypertrophic gingivitis is one of the most common and at the same time resistant pathologies in periodontology. This disease is characterized by a progressive increase in the size, shape and structure of the gingival tissues against the background of chronic inflammation. Clinically, it is manifested not only by an aesthetic defect, but also by functional disorders - traumatization during chewing, difficulties in maintaining oral hygiene, as well as the risk of developing deep inflammatory-destructive changes in periodontal tissues. This condition significantly reduces the quality of life of patients and can cause serious complications, up to tooth loss in the long term.

In modern periodontology, the etiopathogenesis of hypertrophic gingivitis has been fully elucidated, in which local factors (microbial plaque, dental calculus, traumatic occlusion, orthodontic and orthopedic constructions) and general factors (endocrine diseases, especially during pregnancy and puberty, hormonal imbalance, taking certain medications) are involved in a complex combination [1]. It is the combination of these factors that leads to the proliferation of fibroblasts in the gingival tissues, increased collagen synthesis, and chronic activation of inflammatory mediators. Traditional treatment methods are mainly based on mechanical cleaning, subgingival curettage, and surgical excision of hypertrophied tissues. However, surgical interventions have such disadvantages as tissue trauma, a long rehabilitation period, the risk of re-hypertrophy, and psychological discomfort for the patient [2]. In recent years, as in all areas of medicine, interest in minimally invasive technologies has increased sharply in periodontology.

The development of conservative treatment methods, in particular, the introduction of lasers of various spectra into clinical practice, the use of photodynamic therapy, and the development of personalized antibacterial regimens have created new opportunities in the treatment of hypertrophic gingivitis. The main advantages of laser therapy are its pronounced bacteriostatic and bactericidal effect, anti-inflammatory effect, as well as the ability to stimulate regenerative processes through photobiomodulation of tissues [3]. Photodynamic therapy, on the other hand, allows for the selective destruction of pathogenic microflora through reactive oxygen radicals formed as a result of the interaction between a photosensitizer and laser radiation of a certain wavelength [4]. In addition, modern conservative approaches are not limited to hardware treatment, but also include exposure to etiotropic factors. By improving the patient's oral hygiene, choosing individual hygiene products, irrigating periodontal pockets with antibacterial drugs, and adding systemic antibiotic therapy when necessary, it is possible to effectively influence the main cause of inflammation - the microbial factor [5]. However, the clinical effectiveness of this conservative complex approach, especially in the long term, has not yet been sufficiently studied and standardized. The available literature mainly presents short-term observational results, which does not allow optimizing the treatment strategy.

Literature review

Hypertrophic gingivitis is a pathology that occupies a special place in periodontology, and its clinical and morphological features have been studied by many researchers. The mechanisms of the development of the disease, in particular, its association with a violation of the balance between inflammatory mediators (prostaglandins, cytokines, matrix metalloproteinases) and cell proliferation, have been confirmed in a number of fundamental studies [6]. Gingival hypertrophy often occurs against the background of chronic catarrhal gingivitis due to prolonged exposure to local irritants (calculus, improperly placed fillings, orthodontic appliances), but in some cases it can also develop as a result of taking medications (phenytoin, nifedipine, cyclosporine A) [7].

Traditional treatment protocols are primarily based on mechanical debridement, subgingival curettage, and gingivectomy. However, large-scale clinical studies show that the recurrence rate of hypertrophy is 30-40% within 12-24 months after surgical intervention [8]. This is explained not only by the impossibility of complete tissue reconstruction, but also by the difficulty of completely eliminating the main cause of inflammation - microbial biofilms. The complex topography of periodontal pockets, especially the diversity of subgingival microflora under hypertrophied tissues, limits the effectiveness of traditional mechanical cleaning [9]. In the last decade, laser technologies have been widely used in periodontology. Diode laser (810-980 nm), erbium (Er:YAG) and neodymium (Nd:YAG) lasers are characterized by their selective effect on various tissues. The photobiomodulatory, antibacterial and anti-inflammatory effects of diode laser on soft tissues are described in detail in the literature. In a number of randomized clinical trials, a reduction of up to 99% in the number of periodontopathic bacteria such as Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis in periodontal pockets treated with a diode laser has been reported [10]. Another important aspect of laser irradiation is its ability to improve tissue microcirculation and accelerate reparative processes by stimulating the activity of fibroblasts and osteoblasts [3]. Photodynamic therapy (PDT), as a form of laser therapy, has gained a special place in periodontology in recent years. The mechanism of PDT is based on the selective absorption of a photosensitizer by pathogenic bacteria and the formation of singlet oxygen and other reactive oxygen species under the influence of laser radiation of a certain wavelength [4]. As a result of this process, oxidative damage to the cell membrane of

microorganisms and cell death occur. An important advantage of PDT is that it is effective even against antibiotic-resistant strains and has no systemic side effects. A study by Petelin et al. [11] showed that PDT is synergistic with conventional curettage in improving gingival index, plaque index, and probe depth.

Also, the local application of antibacterial and anti-inflammatory agents as an integral part of conservative treatment is important. Solutions, gels, and varnishes based on chlorhexidine bigluconate, povidone-iodine, triclosan, and antibacterial peptides are widely used for periodontal pocket irrigation [5]. However, prolonged use of these agents can disrupt the balance of microflora and cause dysbiotic changes, so the duration and frequency of their use require an individual approach.

Although the effectiveness of conservative methods in the existing literature is mainly assessed based on short-term (up to 3 months) observation results, there is insufficient information on the long-term (12 months or more) remission rate. Most researchers limit the success of conservative treatment to the improvement of clinical indicators, not paying enough attention to objective assessment of morphological restoration of tissues and stability of functional state [12]. This situation creates the need for studies aimed at assessing the long-term effectiveness of modern conservative methods.

Methodology

This study was conducted at the clinical base of the Department of Periodontology of the Tashkent State Dental Institute from September 2023 to December 2024. The study design is planned as a prospective, randomized, controlled clinical trial. Inclusion criteria for the study were: individuals aged 18 to 55 years, clinically and radiologically diagnosed with moderate and severe hypertrophic gingivitis (hypertrophy index 2 and 3 degrees), with compensated general somatic condition, and who voluntarily agreed to participate in the study. Exclusion criteria for the study were: decompensated general diseases (diabetes mellitus, thyroid pathologies, autoimmune diseases), taking medications (anticonvulsants, calcium channel blockers, immunosuppressants), pregnancy and lactation, smoking, as well as periodontal surgical interventions in the last 6 months.

As a result of the initial screening, 78 patients were evaluated, of which 64 fully met the inclusion criteria for the study. Patients were divided into two groups using a computer random number generator: the main group (n = 32) and the control group (n = 32). The groups were matched for age, gender, degree of hypertrophy and periodontal indices and did not differ statistically ($p > 0.05$).

Analysis and results

During the study, no statistically significant difference was found between the initial clinical indicators of patients in both groups ($p > 0.05$), which confirmed the comparability of the groups. At the initial examination, the gingival index (GI) in the main group was on average 2.38 ± 0.31, and in the control group 2.41 ± 0.33 ($p = 0.721$). Plaque index (PI) was 1.85±0.41 and 1.88±0.39 ($p=0.684$), respectively, and probing depth (PPD) was 3.62±0.45 mm in the main group and 3.65±0.48 mm in the control group ($p=0.793$). Gingival hypertrophy index (GIg) was 2.15±0.36 in the main group and 2.18±0.34 in the control group ($p=0.702$). At 1 month after the end of treatment (T1), significant improvements in all clinical parameters were noted in both groups. However, the decrease in parameters was significantly greater in the main group than in the control group. GI in the main group was 1.12±0.22 (52.9% decrease from baseline), and in the control group it was 1.64±0.28 (31.9% decrease) ($p<0.001$). PI decreased to 0.78±0.24 in the main

group and 1.14±0.31 in the control group (p=0.003). Probe depth was 2.35±0.33 mm in the main group and 2.89±0.41 mm in the control group (p=0.007). Hypertrophy index decreased to 0.95±0.31 (55.8% decrease) in the main group and 1.42±0.38 (34.9% decrease) in the control group (p<0.001).

The difference between the groups was even more pronounced at the 3rd month (T2) follow-up. While the positive dynamics of clinical indicators in the main group was maintained and even continued to improve, in the control group a tendency to increase in some indicators was observed. In the main group, GI was 0.82±0.19, PI 0.62±0.21, PPD 2.08±0.27 mm, GIg 0.71±0.24. In the control group, GI reached 1.45±0.31, PI 1.08±0.29, PPD 2.71±0.38 mm, GIg 1.21±0.35 (p<0.001 for all indicators).

At the final follow-up at 6 months (T3), all parameters in the main group remained at or near normal values: GI 0.74±0.18, PI 0.58±0.20, PPD 1.96±0.25 mm, GIg 0.64±0.22. In the control group, signs of inflammation and hypertrophy were re-enhanced: GI 1.38±0.33, PI 1.05±0.30, PPD 2.65±0.39 mm, GIg 1.18±0.34. Although the parameters at 6 months were statistically improved compared to the initial values, they were significantly different from the results in the main group (p<0.001). In particular, the hypertrophy index in the control group was 1.18±0.34, indicating a decrease of only 45.9% from the initial level, while in the main group this decrease was 70.2%. Table 1 below summarizes the dynamics of clinical indicators in both groups during the pre-treatment and post-treatment observation periods.

Table 1. Dynamics of clinical indicators by groups (M±SD)

Indicator	**Group**	**T0 (before treatment)**	**T1 (1 month)**	**T2 (3 month)**	**T3 (6 month)**
GI	Main	2.38±0.31	1.12±0.22	0.82±0.19	0.74±0.18
GI	Control	2.41±0.33	1.64±0.28	1.45±0.31	1.38±0.33
PI	Main	1.85±0.41	0.78±0.24	0.62±0.21	0.58±0.20
PI	Control	1.88±0.39	1.14±0.31	1.08±0.29	1.05±0.30
PPD (mm)	Main	3.62±0.45	2.35±0.33	2.08±0.27	1.96±0.25
PPD (mm)	Control	3.65±0.48	2.89±0.41	2.71±0.38	2.65±0.39
GIg	Main	2.15±0.36	0.95±0.31	0.71±0.24	0.64±0.22
GIg	Control	2.18±0.34	1.42±0.38	1.21±0.35	1.18±0.34

Note: the difference between groups in all observation periods is statistically significant at the p<0.05 level.

Table 2 also assesses the long-term stability of treatment efficacy. This takes into account the change in the indicators in the T3 period compared to the T1 period (relapse rate). In the main group, the relapse index according to GI was 0.38 (T1=1.12, T3=0.74, i.e., the improvement continued), and in the control group it was 0.26, which indicates a partial return of inflammatory signs. According to the hypertrophy index, no relapse was observed in the main group (T3 < T1), and in the control group, although GIg changed from 1.42 to 1.18, this indicator was still higher than the initial level.

Table 2. Changes in clinical parameters (relaxation/relapse) from month 1 to month 6

Indicator	**Group**	**T1 (1month)**	**T3 (6 month)**	**Change (%)**
GI	Home	1.12±0.22	0.74±0.18	-33.9% (improvement)

GI	Control	1.64±0.28	1.38±0.33	+15.9% (worsening)
GIg	Home	0.95±0.31	0.64±0.22	-32.6% (improvement)
GIg	Control	1.42±0.38	1.18±0.34	-16.9% (improvement, but less than T1)

During clinical trials, no side effects (pain, swelling, burning, allergic reactions) associated with laser and photodynamic therapy were observed in the main group of patients. In the control group, short-term gingival bleeding and discomfort were noted after curettage in 4 patients. According to the subjective assessments of the patients, the treatment method (laser + PDT) in the main group was rated as more comfortable (without discomfort and fast).

Discussion

The results of this study showed that the combination of modern methods in the complex conservative treatment of hypertrophic gingivitis - a combination of diode laser and photodynamic therapy - has significantly higher clinical efficacy than traditional curettage and local antiseptic therapy. In particular, according to the results of long-term follow-up (6 months), the minimal degree of inflammation and hypertrophy re-development in the main group confirms the pathogenetic basis of this approach.

The obtained results are consistent with previous studies. For example, Romanos et al. [3] studied the effect of diode laser on periodontal tissues, where it was shown that laser irradiation accelerates reparative processes by stimulating the proliferation of gingival fibroblasts and increasing the production of anti-inflammatory cytokines (IL-10, TGF-β). In our study, the rapid and sustained decrease in GI and GIg in the main group can be explained by this mechanism. In addition, the addition of photodynamic therapy has a synergistic effect on pathogenic microflora, effectively eliminating subgingival biofilms remaining after traditional mechanical cleaning [4]. Maintaining a minimal microbial load in the area is a key factor in long-term remission [9].

Conclusion

According to the results of this prospective, randomized clinical study, a complex conservative method based on a combination of diode laser and photodynamic therapy in the treatment of hypertrophic gingivitis has significantly higher efficacy than traditional curettage and local antiseptic therapy. The main conclusions of the study are as follows:

Firstly, in the main group, where modern conservative methods (laser + PDT) were used, the clinical indicators - gingival index, plaque index, probe depth and gingival hypertrophy index - decreased significantly compared to the control group. In particular, at the final 6-month follow-up, the gingival index in the main group was 0.74±0.18, and the hypertrophy index was 0.64±0.22, which represent values close to the physiological norm.

Secondly, the long-term stability of treatment efficacy in the main group was significantly higher compared to the control group. At the 6-month follow-up, signs of inflammation and hypertrophy were observed to re-emerge in the control group (GI 1.38±0.33, GIg 1.18±0.34), while in the main group these indicators not only remained unchanged, but also continued to improve. This is explained by the long-term depressive effect of laser and photodynamic therapy on the subgingival microflora and the properties that stimulate reparative regeneration in tissues.

Conclusion

As a practical recommendation, it is advisable to first use modern conservative methods in the treatment of patients with hypertrophic gingivitis, without resorting to traditional surgical interventions as the first line. This method is especially optimal for patients with contraindications

to surgical intervention (hemorrhagic diathesis, decompensated somatic diseases), as well as for individuals with high aesthetic requirements and who want to avoid invasive interventions. In the future, large-scale, multicenter studies should be conducted to evaluate the long-term effectiveness of this method, determine optimal laser parameters, and study the comparative effectiveness of different photosensitizers.

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EXTREMELY PRETERM BIRTH: COMBATING A GLOBAL PROBLEM (LITERATURE REVIEW)

D.A. Urinbaeva
Republican Perinatal Center
N.A. Urinbaeva
Republican Perinatal Center
F.U. Babadjanova
Tashkent State Medical University

Abstract. Background. *Extremely preterm birth (EPB) represents a serious medical problem associated with a high risk to the health of both mothers and newborns. Modern diagnostic and therapeutic approaches, including preconception care, pregnancy prolongation, and neonatal intensive care, can mitigate some of the consequences of EPB; however, substantial reductions in perinatal mortality and improvements in long-term outcomes among children born at extremely early gestational ages remain challenging.*

Objective. *To review current evidence on the epidemiology, risk factors, pathogenesis, prevention, diagnosis, management, delivery, and neonatal care associated with extremely preterm birth.*

Materials and Methods. *A literature review was performed based on the scientific sources cited in the original article, including studies addressing the limits of viability, perinatal outcomes, infectious and inflammatory mechanisms, cervical insufficiency, assisted reproductive technologies, fetal cell-free DNA, tocolytic therapy, mode of delivery, neonatal resuscitation, and preconception care.*

Results. *Extremely preterm birth is associated with substantial perinatal morbidity and mortality, particularly at gestational ages of 22-26 weeks. Survival increases with each additional week of gestation, although survivors remain at considerable risk of bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, hydrocephalus, cerebral palsy, neurodevelopmental impairment, and long-term health problems. Major risk factors include previous preterm birth, recurrent pregnancy loss, infection, bacterial vaginosis, premature rupture of membranes, cervical insufficiency, assisted reproductive technologies, fetal abnormalities, and placental complications. Prevention requires a comprehensive strategy encompassing preconception care, identification and management of risk factors, timely diagnosis, appropriate treatment of threatened preterm birth, and delivery in specialized level III facilities with neonatal intensive care capabilities.*

Conclusion. *Combating extremely preterm birth requires an integrated approach beginning before conception and continuing through pregnancy, delivery, neonatal intensive care, and long-term follow-up. Prevention, early identification of high-risk pregnancies, appropriate prolongation of pregnancy when clinically feasible, individualized decisions regarding delivery and neonatal resuscitation, and continuity of specialized pediatric care are essential for improving survival and long-term outcomes.*

Keywords: *extremely preterm birth, perinatal mortality, perinatal morbidity, extremely low birth weight, preterm birth, neonatal intensive care, pregnancy prolongation, prevention.*

Introduction. Preterm birth remains one of the most pressing problems in modern obstetrics and perinatology because it is directly associated with perinatal mortality and morbidity [2, 5, 9]. This problem also has important psychosocial, economic, and demographic implications for pregnancy. Despite advances in modern medicine, the incidence of preterm birth has not decreased over the past 20 years and ranges from 25% to 30%; in some low-income countries, it tends to increase.

Preterm birth has a substantial negative impact on statistics of perinatal morbidity and mortality [6]. For example, early neonatal mortality among preterm newborns may reach 60-70%, while morbidity may exceed 50% [9]. Each additional day of pregnancy between 22 and 28 weeks of gestation plays an important role in improving neonatal survival. A comprehensive comparative analysis of perinatal outcomes associated with different approaches to the management of preterm pregnancy makes it possible to identify the most effective treatment and management strategies and to determine factors influencing outcomes. This allows obstetricians and physicians to make more informed decisions when managing such cases.

The determination of prognostic criteria for fetal maturity using modern technologies helps to identify the optimal timing of delivery more accurately, thereby minimizing risks to the newborn.

Development of an optimal management protocol that takes these prognostic criteria into account may significantly improve treatment outcomes, reduce perinatal mortality and morbidity, and decrease the financial costs associated with the treatment and rehabilitation of newborns [5, 6].

Particular attention should be paid to the care of preterm infants, especially those born with extremely low birth weight (ELBW) [8, 9]. These children frequently require specialized medical care and prolonged rehabilitation to achieve optimal development.

The development of the healthcare system and improvement of the accessibility and quality of medical services are important objectives pursued by the Republic of Uzbekistan within the framework of the Action Strategy for Development for 2017–2021. Measures aimed at improving the quality of healthcare services include several priority areas, such as improving specialized medical care, reforming primary healthcare, developing emergency and urgent medical services, and protecting maternal and child health.

Extremely Preterm Birth and the Limits of Viability. Extremely preterm birth (EPB) is characterized by delivery before 28 weeks of gestation or birth weight below 1000 g and is associated with a high risk of complications for both the newborn and the mother. Studies conducted by the World Health Organization (WHO) and other authoritative researchers provide a deeper understanding of the causes and consequences of EPB and contribute to the development of strategies for its prevention and treatment.

According to WHO recommendations, live birth registration should use criteria beginning at 22 weeks of gestation, or at a newborn length of 25 cm or a birth weight of 500 g, provided that at least one sign of life is present [26]. According to Order No. 21 of the Ministry of Health of the Republic of Uzbekistan, the criteria for live birth and stillbirth also begin at 22 weeks of gestation.

These recommendations have served as a basis for extensive randomized studies aimed at reducing perinatal morbidity and mortality among newborns at these gestational ages.

Although fetal viability begins at approximately 22 weeks of gestation, data reported by T.M. Berger and colleagues demonstrate low neonatal survival at this gestational age: 0-5% at 22.0-22.6 weeks, 4-52% at 23.0-23.6 weeks, 30-67% at 24.0-24.6 weeks, and 51-81% at 25.0-25.6 weeks [12].

Considering these unfavorable outcomes, B. Zlatohlávková and colleagues defined the period from 22.0 to 24.6 weeks of gestation as a "gray zone," in which the probability of delivering a healthy infant is low but nevertheless exists [27].

As survival among infants with extremely low birth weight increases, the incidence of various complications also increases, including bronchopulmonary dysplasia, pulmonary hypoplasia, retinopathy of prematurity, intraventricular hemorrhage, hydrocephalus, and cerebral palsy, as well as a number of other disorders [12, 20, 22]. These complications substantially affect the early neonatal course and represent major causes of mortality during the first year of life.

Data presented by T. Moore and colleagues emphasize the importance of both survival and subsequent development among children born at extremely early gestational ages. By three years of age, survival among newborns was directly associated with gestational age and amounted to 7% at 22.0-22.6 weeks, 22% at 23.0-23.6 weeks, 43% at 24.0-24.6 weeks, 66% at 25.0-25.6 weeks, and 77% at 26.0-26.6 weeks [22].

However, beyond survival, children born with extremely low birth weight face substantial developmental challenges during both the early neonatal period and later life. Outcomes among these children remain insufficiently studied. According to T. Moore and colleagues, such children are at high risk of disability, ranging from 38% to 98%, emphasizing the need for further research and the development of comprehensive rehabilitation programs to improve prognosis and quality of life [22].

By six years of age, children born at extremely early gestational ages may experience a number of problems, including a high incidence of cerebral palsy, affecting almost 20% of children, with severe cerebral palsy occurring in 7%. These children may also experience difficulties with social integration, learning difficulties, impaired motor function, problems with memory and concentration, increased anxiety, and symptoms resembling those observed in autism.

An analysis by L.W. Doyle and P.J. Anderson [26] confirmed a number of health problems among children born with extremely low birth weight by approximately 20 years of age, including hypertension, insulin resistance, reduced physical endurance, bronchial asthma, blindness, schizophrenia, and learning difficulties.

Given these data, prevention of EPB is of paramount importance. This emphasizes the importance of understanding risk factors, etiology, and prediction of this condition, as well as the need for appropriate treatment of threatened preterm birth, selection of the optimal mode of delivery, and long-term follow-up of affected patients.

Risk Factors and Etiology. Current studies indicate that the risk factors for preterm birth (PTB) and extremely preterm birth (EPB) are largely similar. They include various maternal and environmental factors, including maternal age, maternal health, external stressors, and infections.

Particularly unfavorable factors include a history of preterm birth and recurrent pregnancy loss [21]. However, the etiology of preterm birth remains complex because of the diversity of contributing factors, including infections, fetal congenital abnormalities, assisted reproductive technologies (ART), cervical insufficiency, and placental abruption [23].

Infection of the amniotic fluid is reported to be the source of 80% of preterm births occurring before 30 weeks of gestation. One possible source of infection is bacterial vaginosis,

which frequently remains undiagnosed during the early stages of pregnancy, as well as extragenital infectious diseases [16, 23].

Bacterial vaginosis is characterized by an increase in anaerobic bacteria, accompanied by a reduction in lactobacilli and an increase in opportunistic microorganisms [4]. Studies indicate that biofilms, or microbial communities, play a role in the development of bacterial vaginosis by promoting bacterial adhesion to the epithelium and creating a barrier to penetration by therapeutic agents [1, 4].

These bacteria may enter the amniotic fluid and stimulate prostaglandin synthesis, leading to activation of uterine contractions and preterm premature rupture of membranes (PPROM) [8]. Recent studies have demonstrated that the use of antibacterial agents to treat asymptomatic bacterial vaginosis does not reduce the risk of preterm birth.

Regardless of the route of dissemination of the inflammatory agent and its underlying cause, the uterus becomes a major site of the inflammatory process. Inflammatory mediators, including cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-1, chemokines such as IL-8, reactive oxygen species (ROS), and matrix metalloproteinases (MMP-8 and MMP-9), accumulate in this environment, resulting in degradation and disruption of the fetal membranes and initiating preterm labor [3, 8, 23].

Congenital disorders of collagen formation, such as Ehlers-Danlos syndrome, may also contribute to rupture of the fetal membranes [6].

Preterm premature rupture of membranes accounts for 24-36% of all deliveries [6]. In newborns, PPROM increases the risk of neonatal sepsis tenfold. This is associated with the possibility of contact between the fetus and vaginal bacteria following rupture of the fetal membranes. In addition, the maternal risk of purulent-septic complications is increased.

When amniotic fluid leakage occurs during pregnancy, there is a high probability of developing chorioamnionitis, which may lead to infection of both the fetus and the mother. Infection-associated chorioamnionitis may initiate amniotic fluid leakage and may also occur as a consequence of membrane rupture.

Intrauterine infection associated with chorioamnionitis increases the risk of intraventricular hemorrhage in the fetus and thereby increases neonatal mortality. Pregnant women experiencing PPROM also have an increased risk of postpartum sepsis, which may be fatal, with reported mortality reaching 14.2% [3].

Genetic Factors and Prenatal Diagnosis. In cases of preterm birth beginning at 22.0 weeks of gestation, genetic abnormalities play an important role [24]. The World Health Organization recommends genetic screening during pregnancy.

Ultrasonography and biochemical screening are performed during early pregnancy to detect fetal genetic abnormalities [18, 26]. Determination of fetal DNA in maternal blood has become an important breakthrough in the prenatal diagnosis of congenital abnormalities.

Assisted Reproductive Technologies. Modern assisted reproductive technologies, particularly in developed countries, are becoming an increasingly common factor associated with extremely preterm birth.

The incidence of EPB following in vitro fertilization (IVF) remains uncertain in the available literature. However, according to G.M. Savelieva and colleagues [7], the high frequency of preterm birth associated with reproductive technologies is related to multiple pregnancy.

Single-embryo transfer during IVF programs may reduce the risk of EPB to some extent. Data reported by S. Sunderam and colleagues indicate that before 32 weeks of gestation, the

frequency of preterm birth in multiple pregnancies following IVF is significantly higher than in singleton pregnancies [25].

Cervical Insufficiency. Cervical insufficiency is also an important component of the problem of EPB [23]. Timely detection and correction of this condition before 24 weeks of pregnancy are important.

According to A. Conde-Agudelo and colleagues, the risk of preterm birth before 28 weeks is reduced 1.5-fold among women undergoing cervical cerclage for cervical insufficiency [13]. According to R.I. Shalina and colleagues [10], the effectiveness of this procedure is 82.3%.

It is known that iatrogenic cervical shortening caused by procedures such as loop excision and cervical conization for dysplasia also increases the risk of preterm birth.

When vaginal cerclage is not feasible, a transabdominal approach through mini-laparotomy or laparoscopy may be used.

The use of cerclage in multiple pregnancy currently requires further investigation because its efficacy has not been confirmed. Multicenter studies are being conducted to determine optimal methods for preventing preterm birth in such cases.

An alternative to cervical cerclage in women with cervical insufficiency is the use of an obstetric pessary. Its efficacy has been demonstrated in cases of cervical shortening below 25 mm and a history of preterm birth in singleton pregnancies beginning at 20 weeks of gestation.

According to R.I. Shalina and colleagues [10], cervical cerclage is recommended at 20-22 weeks of pregnancy, whereas an obstetric pessary may be placed from 20-22 weeks onward, with simultaneous administration of progestogens.

Cell-Free Fetal DNA. The determination of cell-free fetal DNA has received considerable attention in the diagnosis of EPB. The level of embryonic-origin DNA increases because of enhanced trophoblast cell apoptosis, resulting in increased concentrations both in maternal peripheral blood and in cervical canal secretions.

A. Farina and colleagues found that patients with recurrent miscarriage and normal progression of the first half of pregnancy had significantly higher levels of cell-free fetal DNA at 12.0-14.0 weeks than healthy pregnant women [15].

R. Romero and colleagues, in turn, reported a high probability that fetal DNA participates in mechanisms initiating labor both under physiological conditions and in pathological states [23].

Tocolytic Therapy and Pregnancy Prolongation. For a long period, tocolytic agents, particularly β-mimetics, were considered the most effective treatment for threatened extremely preterm birth. However, these drugs did not always achieve the desired results.

Currently, preference is given to nifedipine, a calcium-channel blocker, and atosiban, an oxytocin-receptor antagonist, as more preferable agents. Among other approaches aimed at prolonging pregnancy and preventing EPB, the administration of progestogens is one of the most widely used and economically justified strategies [23].

Mode of Delivery. Selection of the optimal mode of delivery in extremely preterm birth, particularly in cases complicated by PPROM, remains a difficult issue requiring an individualized approach and consideration of multiple factors.

In the past, cesarean section was often considered the preferred method for improving perinatal outcomes in infants born following EPB because it was believed to reduce the frequency of intraventricular hemorrhage. However, recent studies have not confirmed an advantage of cesarean delivery over vaginal delivery [13].

Currently, the decision regarding the mode of delivery is based on parental preferences and clinical indications. Cesarean delivery may be recommended in critical conditions such as bleeding caused by placenta previa or placental abruption, severe preeclampsia/eclampsia, and other life-threatening conditions.

Nevertheless, observations indicate that under certain circumstances cesarean delivery may reduce mortality and the frequency of adverse outcomes in infants, particularly in cases of PPROM and an unprepared birth canal.

During vaginal delivery, epidural anesthesia is considered necessary to ensure maternal comfort and facilitate labor. It is also important to handle the newborn as gently as possible, particularly during delivery of the head, and to initiate intensive care immediately after birth.

Neonatal Resuscitation at the Limit of Viability. The appropriateness of neonatal resuscitation at different gestational ages remains a subject of considerable debate. Approaches differ between countries and healthcare systems.

In some countries, including the Czech Republic, Sweden, and Germany, the decision to provide full resuscitation to newborns at 22.0-23.6 weeks is individualized and may depend on parental preferences. Parents are provided with information regarding possible outcomes following extremely preterm birth, including long-term outcomes.

In other countries, including Finland, Italy, and Portugal, resuscitation is also individualized; however, full resuscitation and intensive care, including intubation, mechanical ventilation, and infusion therapy, are more frequently initiated from 24.0-24.6 weeks of gestation.

In most European countries, from 25.0 weeks of gestation onward, full resuscitation is provided to the majority of newborns. In Canada, decisions concerning resuscitation are generally discussed between physicians and parents for newborns with a gestational age of 22.0-25.6 weeks [12, 17, 19].

This approach is important for ensuring maximum care and support for these children.

Prevention of Extremely Preterm Birth. Prevention of extremely preterm birth and its associated complications plays a key role in protecting maternal and neonatal health.

Preconception care is an important component of prevention and is aimed at optimizing a woman's health before conception [10].

Preconception care includes a range of measures, including correction of concomitant diseases, elimination of risk factors, education regarding a healthy lifestyle during pregnancy, and regular medical visits to monitor pregnancy.

Effective preconception care may reduce the risk of pregnancy complications, including preterm birth, and improve outcomes for both mother and child. Therefore, preconception care is an important component of obstetric practice and should be provided to all women at high risk of pregnancy complications.

Conclusion. The evidence presented demonstrates that effective prevention of extremely preterm birth is a key objective of modern obstetric practice.

Serious perinatal complications, including cerebral palsy, blindness, and hearing impairment, may affect children throughout their lives, emphasizing the importance of preventing extremely early delivery.

Further reductions in perinatal mortality and improvements in child health require a comprehensive approach. First, obstetricians should identify high-risk groups and provide preconception care, followed by prevention of preterm birth, timely diagnosis, and appropriate treatment of threatened extremely preterm birth.

When indicated, delivery should take place in specialized level III facilities equipped with neonatal intensive care units. It is also essential to ensure continuity of highly qualified pediatric care for children following extremely preterm birth, which may substantially improve their long-term outcomes and survival.

It should not be forgotten that every child surviving extremely preterm birth represents not only a success of medicine and technologies that make it possible to save lives under the most challenging circumstances. At the same time, such cases present substantial economic and ethical challenges for society.

Preserving the lives of and caring for children born with extremely low birth weight requires considerable resources for medical care, rehabilitation, and special education. These costs may place a substantial burden on healthcare and social systems, particularly in resource-limited countries.

Moreover, such situations may create ethical dilemmas for parents and society as a whole, raising questions regarding quality of life, the ethical dimensions of treatment, and the allocation of healthcare resources.

Therefore, it is important not only to develop medical technologies but also to focus on prevention and reduction of the risk of extremely low birth weight. Such efforts may reduce the number of cases of this severe complication and decrease the social and economic burden on society.

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www.scientists.uz, info@scientists.uz, +998901259654