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SYNTHESIS AND BIOLOGICAL ACTIVITY OF β -O-(2,3,4,6-TETRA-O-ACETYL-D-GALACTOPYRANOSYL)-2-METHYL-4-BROMO PENTANOATE

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ABSTRACT

Reaction reactions of monosaccharides, namely galactose allyl derivatives, with ethyl ether of 2-bromo propionic acid have been studied. The study of the alleged biological activity of the synthesized substances was carried out using the PASS Online computer program. Evaluation of the structure-bioactivity revealed the synthesized β -O-(2,3,4,6-tetra-O-acetyl-D-galactopyranosyl)-2-methyl-4-bromo pentanoate in the biological activity spectrum of bromo ethylvalerate [-CH₂-CH(Br)-CH₂-CH(CH₃)-COOC₂H₅] the influence of the group.

Keywords: Bromo propionic acid ether, D-galactopyranosyl, β -Acetylated products, Bromo pentanoate, PASS Online, bromo glycosides.

აბსტრაქტი

შესწავლილია მონოსაქარიდების, კერძოდ გალაქტოზას ალილის წარმოებულების რეაქციის რეაქციები 2-ბრომპროპიონმჟავას ეთილის ეთერთან. სინთეზირებული ნივთიერებების სავარაუდო ბიოლოგიური აქტივობის შესწავლა განხორციელდა PASS Online კომპიუტერული პროგრამის გამოყენებით. სტრუქტურა-ბიოაქტიურობის შეფასებით გამოვლინდა სინთეზირებული β -O-(2,3,4,6-ტეტრა-O-აცეტილ-D-გალაქტოპირანოზილ)-2-მეთილ-4-ბრომპენტონატის ბიოლოგიურ აქტივობის სპექტრში ბრომოეთილის ვალერატი [-CH₂-CH(Br)-CH₂-CH(CH₃)-COOC₂H₅] ჯგუფის გავლენა.

საკვანძო სიტყვები: ბრომპროპიონის მჟავას ეთერი, D-გალაქტოპირანოზილი, β -აცეტილირებული პროდუქტი, ბრომპენტონატი, PASS Online, ბრომგლიკოზიდები.

Introduction: Carbohydrate derivatives are widely used in medicine and agriculture. Carbohydrate-based synthesized substances, with their ability to permeate membrane tissue and activate reserve mechanisms, enhance the resistance of living cells to outside factors and diseases, enabling the production of environmentally friendly products. By "inserting" carbohydrate molecules, insoluble drugs are dissolved in water and easily absorbed by the body, significantly reducing their toxicity, which significantly increases the effectiveness of drugs.

Analysis of the scientific literature in recent years shows that the interest of chemical researchers in the synthesis of products containing bromides, has increased dramatically [1-2]. Studies in this area are expected to lead to the development of new, less toxic, biologically and physiologically active drugs.

The therapeutic effect of glycosides on tissue cells is mainly due to aglycones. The presence of sugar residues helps to improve their solubility, reduce toxicity, permeability to biological membranes, thus creating favorable conditions for reducing the active concentration of some potent pharmacological agents and increasing the range of therapeutic action. The project will synthesize physiologically and biologically active derivatives of bromine [3-4].

Brominated compounds have a special place among pharmaceutical preparations to their resemblance to bromine ethylvalerate. They are Widely used in the production of medicinal (antidepressant, anti-inflammatory, antisclerotic action) drugs [5]. They are tranquilizers, used in bronchial asthma, pneumonia.

It can be assumed that the ability of nucleophilic substitution of bromine atoms makes possible the presence of bromine containing glycosides: β -O-(2,3,4,6-tetra-O-acetyl-D-galactopyranosyl)-2-methyl-4-bromo pentanoate (3), which have a wide range of biological activity (antitumor, antibacterial) and are reagents suitable for organic synthesis.

Experimental Part: The allyl derivative of galactose was reacted with ethyl 2-bromo propionic acid. Initially, in the presence of acetic anhydride and sodium acetate on galactose, a β -acetylated product was obtained: 1,2,3,4,6-penta-O-acetyl- β -D-galactopyranose (1). Allyl-2,3,4,6-tetra-O-acetyl- β -D-galactopyranose (2) was synthesized on the β -acetylated product by the action of allyl alcohol in dichloroethane in the presence of the $\text{BF}_3[(\text{C}_2\text{H}_5)_2\text{O}]$ catalyst. By dissolving allylated monosaccharides in 2-bromo propionic acid in ethyl ether and adding dropwise a solution of benzoyl peroxide (dissolved in 2-bromo propionic acid in ethyl ether) with constant stirring in a nitrogen atmosphere, a new substance was synthesized: β -O-(2,3,4)-O-acetyl-D-galactopyranosyl)-2-methyl-4-bromo pentanoate in a yield of 0.7 g (50%) (3):

The synthesized compounds are white, very soluble in chloroform. The composition of the derivative was determined by physico-chemical research methods [6].

Composition of compounds, physical and chemical characteristics will be determined by instrumental research methods (elemental, polarimetric, chromatographic analyzes, the so-called BMR ^{13}C and BMR ^1H spectroscopy. The definition of optical rotation using elemental analysis, IR and ^{13}C Spectroscopy. The purity of the substance as checked using thinlayer chromatography using "silufol" plate in the following solvent system by volume: chloroform-ethanol 1:1. Optical rotation was measured on a SU-3 universal saccharimeter at 20°C . IR spectra of the samples were taken on a UR-20 spectrometer in KBr tablets. ^{13}C NMR was recorded on a Bruker AM-300, 75.5 MHz spectrometer in deuteriochloroform:

In the infrared spectrum of the synthesized products, no absorption band characteristic for the allyl group is observed in the $1643\text{--}1660\text{ cm}^{-1}$ area and the following absorption bands are formed: 1041.4 ; A characteristic stripe (C-O-C) for the bond is observed in the area of 1241.9 cm^{-1} ; $516.8\text{--}601.7\text{ cm}^{-1}$ (C-Br); 3463.7 cm^{-1} (C-CH₃); 2923.7 cm^{-1} CH₂; 3471 cm^{-1} CH₃

BMR ^{13}C (δ , M.N.); 100.8 (C-1); 61.8 (C-6); $168.7\text{--}170.4$ (RO-CO-CH₃); 72.6 (RO-CH₂-CHBr-); 39.4 (RO-CH₂-CHBr-); 41.8 (RO-CH₂-CHBr-CH₂); 54.8 ((RO-CH₂-CHBr-CH₂-CH-CH₃); 27.2 (-C₂H₅); 38.3 (-CH₃); $20.5\text{--}20.6$ (RO-CO-CH₃).

This substance has a wide range of predicted biological activities. Prediction of the biological activity of the synthesized carbohydrate product: β -O-(2, 3, 4)-O-acetyl-D-galactopyranosyl)-2-methyl-4-bromo pentanoate and free hydroxyl-containing β -D-galactopyranosyl-2-methyl-4-bromo pentanoate was performed using the PASS (Prediction of Activity Spectra for Substance) ONLAIN computer program [8].

The Biological Activity Spectrum of a chemical compound is the set of different types of biological activity that reflect the results of the compound's interaction with various biological entities. Biological activity is defined qualitatively ("yes"/"none") suggesting that the biological activity spectrum represents the "intrinsic" property of a substance depending only on its structure and physical-chemical characteristics. Though this may be a generalization, it provides the possibility for combining information from many different sources in the same training set, which is necessary because no one particular publication comprehensively covers all the various facets of the biological action of a compound.

The specified computer program evaluated the biological activity of β -O-(2, 3, 4)-O-acetyl-D-galactopyranosyl)-2-methyl-4-bromo pentanoate (3) (tab. 1) and his deacetylated product β -D-galactopyranosyl-2-methyl-4-bromo pentanoate (4) (tab. 2).

β -O-(2, 3, 4)-O-acetyl-D-galactopyranosyl)-2-methyl -4-bromo pentanoate (3)

Tab.1

All	Pa*>Pi**	Pa>0,3	Pa>0,7
0,887	0,006	Benzoate-CoA ligase inhibitor	
0,792	0,005	Immunosuppressant	
0,763	0,007	Antifungal	
0,665	0,032	Antineoplastic	
0,637	0,012	Antiprotozoal (Leishmania)	
0,632	0,015	Cholesterol antagonist	
0,602	0,004	Sclerosant	
0,542	0,013	Antibacterial	
0,525	0,033	Immunostimulant	
0,503	0,036	Hypolipemic	
0,454	0,013	Antiprotozoal	
0,485	0,046	Antipruritic, allergic	
0,458	0,051	Antihypoxic	
0,412	0,030	Antiviral (Herpes)	
0,398	0,031	Anticarcinogenic	
0,393	0,026	Antileukemic	
0,402	0,038	Mediator release inhibitor	
0,377	0,014	Antioxidant	
0,393	0,041	Antimycobacterial	
0,337	0,012	Antimycoplasmal	
0,363	0,043	Macrophage stimulant	
0,408	0,089	Lipid metabolism regulator	
0,315	0,027	Free radical scavenger	
0,363	0,076	Vasodilator, coronary	
0,349	0,063	Antimetastatic	
0,310	0,029	Antidote	
0,308	0,029	Alpha-amylase inhibitor	
0,303	0,024	ATPase stimulant	
0,292	0,020	Ganglioside galactosyltransferase inhibitor	
0,299	0,028	Ethanolaminephosphotransferase inhibitor	
0,279	0,016	Antibiotic	
0,281	0,024	Paraoxonase substrate	
0,346	0,089	Respiratory analeptic	
0,271	0,017	Endoglycosylceramidase inhibitor	
0,297	0,050	Hepatic disorders treatment	

0,327	0,082	Antiinfective
0,382	0,148	Membrane integrity agonist
0,257	0,031	1,4-Alpha-glucan branching enzyme inhibitor
0,294	0,074	Immunomodulator
0,243	0,027	Microtubule formation inhibitor
0,219	0,017	Thromboxane synthase stimulant
0,207	0,006	Reductase inhibitor
0,229	0,050	Mucorpepsin inhibitor
0,299	0,130	Beta-adrenergic receptor kinase inhibitor

Biological activity of deacetylated product β -D-galactopyranosyl-2-methyl-4-bromo pentanoate (4)

Tab.2.

☐ All ☐ Pa*>Pi** ☐ Pa>0,3 ☐ Pa>0,7

0,948	0,003	Benzoate-CoA ligase inhibitor	
0,836	0,004	Cholesterol antagonist	
0,835	0,010	Beta-adrenergic receptor kinase inhibitor	
0,812	0,004	Antihypoxic	
0,794	0,002	Sclerosant	
0,759	0,010	Immunosuppressant	
0,744	0,008	Antifungal	
0,701	0,002	1,4-Alpha-glucan branching enzyme inhibitor	
0,692	0,002	Alpha-amylase inhibitor	
0,684	0,016	Immunostimulant	
0,646	0,010	Antiinfective	
0,634	0,002	Ganglioside galactosyltransferase inhibitor	
0,627	0,004	Ethanolaminephosphotransferase inhibitor

0,604	0,014	Vasodilator, coronary	
0,580	0,016	Antiprotozoal (Leishmania)	
0,519	0,015	Antibacterial	
0,531	0,032	Hypolipemic	
0,513	0,035	Respiratory analeptic	
0,488	0,020	Anticarcinogenic	
0,500	0,046	Lipid metabolism regulator	
0,457	0,016	Immunomodulator	
0,453	0,016	Antiprotozoal (Amoeba)	
0,446	0,019	Antiviral (Herpes)	
0,430	0,004	Antineoplastic, alkylator	
0,473	0,052	Antipruritic, allergic	
0,426	0,010	Antioxidant	
0,427	0,015	Free radical scavenger	
0,425	0,033	Antimycobacterial	
0,482	0,108	Membrane integrity agonist	
0,373	0,013	Antidote	
0,366	0,008	ATPase stimulant	
0,370	0,051	Mediator release inhibitor	
0,307	0,018	Antimycoplasmal	
0,297	0,045	Antileukemic	
0,268	0,018	Antibiotic	
0,260	0,022	Microtubule formation inhibitor	
0,200	0,032	Endoglycosylceramidase inhibitor	
0,182	0,028	Thromboxane synthase stimulant	
0,156	0,059	Acylglycerone-phosphate reductase inhibitor	
0,147	0,095	Paraoxonase substrate	

A comparison of the PASS predictions data showed, that similar biological activities: Benzoate-CoA ligase inhibitor, Beta-adrenergic receptor kinase inhibitor, Antihypoxic, Sclerosant, Immunosuppressant, 1,4-Alpha-glucan branching enzyme inhibitor, Alpha-amylase inhibitor, Ganglioside galactosyltransferase inhibitor, Vasodilator, coronary, Respiratory analeptic, Immunostimulant - compound-4 has with higher Pa value than substance-3 and biological activity: Antifungal, Thromboxane synthase stimulant, Antileukemic, Antibiotic, relatively low Pa.

Based on a generalization of a vast literary material, biologically active compounds are characterized by a certain specificity of composition and structure. Structural modification of compounds by introducing various molecules or atomic groups in a molecule can determine the effect of molecular separation of fragments on bioactivity.

*Pa (probability "to be active") estimates the chance that the studied compound is belonging to the sub-class of active compounds.

**Pi (probability "to be inactive") estimates the chance that the studied compound is belonging to the sub-class of inactive compounds.

Conclusion: A biologically active compound was synthesized on the basis of carbohydrates. For the synthesis of bromine containing sugars, the reactions of allyl derivatives of monosaccharides with ethyl ester of 2-bromo propionic acid were studied.

By inserting a virtual molecule of test compounds into the PASS program, Online has identified a broad spectrum of biological activity. By assessment of structure-bioactivity relationships biological activity spectrum of synthesized glycosides have been revealed. The results of the study will enable us providing selection of the most prospective compounds from the set of synthesized samples.

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KARABAKH'S TOURISM PROSPECTS AS A KEY FACTOR IN THE DEVELOPMENT OF THE NATIONAL ECONOMY

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ABSTRACT

In the modern world, tourism is perceived as a socio-economic event that directly and indirectly affects the development of all related infrastructure. Modern tourism is based on a high level of development of transport, social and service sectors, which ultimately makes it a highly profitable sector of the economy. According to the World Tourism Organization (WTO), tourism is one of the most profitable and dynamic sectors of the world economy today. It is the second most profitable after oil production and refining. Tourism accounts for about 6% of the world's gross domestic product, 7% of global investment, every 16th job, 11% of global consumption spending and 5% of all tax revenues. In this regard, the tourism sector is actively developing in many countries with state support. The main purpose of the study is to analyze the prospects for the development of tourism in Karabakh.

Nagorno-Karabakh has great tourism potential, and the restoration of lost infrastructure communications in the liberated territories is expected to create favorable conditions for business, including the development of tourism. The article discusses the features of tourism in Karabakh, the concept of tourism development prospects, as well as its problems.

Keyword: Karabakh, tourism, development, economy, prospects

Introduction: There are great opportunities for the development of many types of tourism in Karabakh - eco, mountain, winter, hunting, health tourism. This region of Azerbaijan with an ancient history, unique flora and fauna, cuisine, historical, cultural and religious monuments, ancient castles, bridges, forests, springs, etc. will attract tourists with its sights. It is possible to organize various types of extreme tourism, agrotourism, green tourism in Karabakh, which has rich natural resources. All this creates great prospects for the development of tourism. It is important to build tourism infrastructure in the form of interaction in our liberated territories. Shusha will be one of the symbolic cities of Azerbaijani tourism. The historical monuments and unique architecture of Shusha, the pearl of Azerbaijani culture, will allow the creation of new tourist routes. The climate of Shusha is temperate, and mineral waters have healing properties. These are also very useful places for tourism. Well-known composers, mugam masters and artists grew up here.

Infrastructure construction has already begun in our liberated lands: At the same time, the article discusses the work to raise awareness of Karabakh's tourism potential to the world and preliminary research to take advantage of the region's tourism opportunities, the positive impact of the development of the tourism sector in Karabakh on the region's rapid economic recovery.

At the end of the Patriotic War, which ended with the complete victory of Azerbaijan on November 10, the future prospects of economic and cultural development in Karabakh remain on

the agenda. The Republic of Azerbaijan intends to restore Karabakh and surrounding areas, build modern infrastructure, increase tourism opportunities in the region, etc. targeted.

The victory of Azerbaijan also showed the creative determination of our people. Restoration of important state structures in the liberated regions, involvement of tourism and hydropower in Sugovushan, road infrastructure works in these areas, use of Khudafer reservoirs for hydropower and land reclamation are on the agenda as purely economic measures. The revival of the region's economy after the complete withdrawal of the enemy from Karabakh suggests that in the near future this country will once again become a thriving cultural center of the entire South Caucasus, a popular tourist destination.

Karabakh and seven other regions liberated from Armenian occupation have historically had integrative relations with other regions of the country in terms of economic development within the independent Republic of Azerbaijan. Thirty years ago, the region's geographical location, natural resources and human resources played an important role in the development of the Karabakh economy. Along with the transport and infrastructure conditions created during that period, the existing natural resources allowed the implementation of important projects in the fields of energy, mining, and agriculture, processing industry, forestry, fisheries and tourism. Until 1988, the collapse of the USSR, the Nagorno-Karabakh economic region achieved significant development due to these resources, and these economic results were directly reflected in the living standards and employment of the population living in the region. If we look at the statistics of that period, we can see that the republic has achieved serious results in the production of a number of products. Thus, if we look only at agriculture, we can see that along with grain, vegetables, fruit, viticulture, cotton and tobacco, important indicators have been achieved in the production of meat and dairy products. Historically, the types of occupations and experience gained by the Karabakh people have played a key role here. Also, the name of Karabakh has become a world brand in the processing industry and crafts, especially in the world-famous carpet weaving. Along with all these and other areas, Karabakh has been in the spotlight of tourists with its unique tourism resources and resorts, protected nature and recreation areas.

Karabakh, with its breathtaking views, magnificent mountains, lakes, valleys and plains, has an ancient history and cultural heritage, as well as a rich tourism potential. The city of Shusha is the cultural capital and cradle of culture of the region, located on a picturesque hill. Travelers visiting Azerbaijan in ancient and especially the Middle Ages spoke about the beauty of this land, its unique natural, historical and cultural riches. Starting from the second half of the 19th century, foreign capitalists who came to Azerbaijan for oil visited Karabakh, one of the most beautiful places in the South Caucasus - Shusha and Kalbajar. Later, during the Soviet era, Karabakh was very popular with both foreign and local tourists. Since the 30s of the XX century, resorts, boarding houses, sanatoriums in Shusha, Turshsu pastures, Sakili spring, Isa spring, the legendary Cidir plain have become a favorite place of visitors. At the same time, the tourism and recreation potential of the region's Khankendi, Agdam and Kalbajar regions is internationally recognized, and a significant part of the hundreds of thousands of tourists visiting our country fell to Karabakh. In particular, since the 1970s, hundreds of thousands of local and foreign tourists use the services of tourism and recreation facilities established here every year. However, as a result of the Armenian military aggression since 1988, the placement of refugees not only in Karabakh, but also in the country's resorts and sanatoriums has seriously damaged domestic and inbound tourism, looted tourism resources, especially Azerbaijan's rich historical and cultural heritage. There is an ecological crisis in the region, all the infrastructure has been destroyed. [1]

The visits of Karabakh people, their close relatives, representatives of international organizations carrying out various humanitarian missions, the media army from all over the world and investors coming to Azerbaijan to invest in the region will be accompanied by other activities. As for the types of tourism, November 8 - the liberation of Shusha from occupation will be of special importance in terms of historical tourism. On this historic day, people of all ages and social groups participating in the tours will travel the path of victory of the Azerbaijani Army as tourists this time. For those making their first visit to Shusha, especially for foreign media, such visits will be a special opportunity to show the true nature of Armenian vandalism. The main motive of such tours will be to show to all mankind the primitive Armenian way of life, reminiscent of the human settlements destroyed during the 30-year occupation of Karabakh, damaged ecosystems, destroyed graves, as well as the Stone Age. These routes will have a very rich information resource from Sugovushan to Khankendi, from Jabrayil to Kalbajar, which was liberated from the first occupation. When foreign journalists, as well as all foreign tourists, see the cities and villages inherited from the occupation, they will get the most realistic picture of the real lifestyle of Armenians. Then the whole world will know that these fascists are ready to leave such traces at any time in Los Angeles, Marseille, Beirut and Rostov.

The development of tourism in post-occupation Karabakh will be one of the most important factors for the revival of the region's economy and the return of the local population to other parts of the country. The very serious socio-humanitarian functions of tourism allow us to do this. This will lead to an influx of labor into the region, as the services offered to tourists will be completed faster than in other areas. Due to the wide range of opportunities for medical tourism and ecotourism in Karabakh, the range and content of services offered to tourists will be wide. Watching the Shusha orchid plant, which is very popular in the world in terms of tourist interest, live in Shusha, especially increases the tourist attractiveness of Karabakh. Unlike many parts of Azerbaijan, the Karabakh region is rich in greenery and has mild winters and summers. After the Armenian occupation, the rapid renewal of rural infrastructure and the creation of all conditions for normal life will make the villages of the region a favorite place for urban tourists. [2]

Along with the multiplier effect on the economy, the future development of tourism in Karabakh is of great political importance. All this means that the image of a risky region created by Armenians for 30 years, not only for this region, but for the entire South Caucasus, is being destroyed. The concept of a risky region in connection with the occupation of Karabakh has seriously damaged not only our country, but also the entire region, both inbound and outbound tourism. Today, the defeated Armenian society, which does not give up its crazy dreams and is greedy for a piece of dry wood, should know that we also had very valuable tourism resources, such as Azerbaijani gold, forest resources, looted construction materials. in occupied Karabakh. Therefore, the positive results that Azerbaijan will get from Karabakh tourism in the short term will be a more convincing argument for the material compensation that Armenia must pay for the damage to our country's tourism resources, tourism industry and our economy in general. According to the results of 2019, about 2.5 million foreign tourists visiting Azerbaijan bring about \$ 3 billion to the country's economy, which is the level of income we lost as a result of the occupation of Karabakh.

Tourism is not only the fruit of peace and stability, but also an important factor in a comfortable life. Therefore, if the liberation of Karabakh goes down in history as the first important event of the XXI century, the development of tourism in this country will be an important contribution to the humanitarian development that everyone wants in this region. [5]

One of the other natural resources of Karabakh is the Istisu mineral water spring and the Istisu resort built on this spring. The Kalbajar region, home to the Georgian resort of Istisu, which left the Shaltuba River behind, was occupied by Armenia in April 1993. Occupying the Istisu resort, Armenia changed the name of the famous medicinal mineral water of the same name and began to sell it to foreign countries under the name "Cermux".

If we look at the history, we can see that although the main tourism potential of Karabakh was concentrated in Shusha and Agdam, all regions of the region were suitable for treatment and recreation. During the Soviet period, tourism potential was developed in Shusha and Agdam in the 1980s. The first rest house in Shusha was put into operation in 1936. Shusha Sanatorium and Resort Association for 1316 seats in Shusha, "Shafa" tourist base for 130 seats and 100-seat treatment and recreation centers in Gulabli village of Agdam region, 50-medical shelters in Shelli village and 40-seat medical recreation centers in Shahbulag. Shusha sanatorium-resort association included 17 buildings with 2 and 3 floors.

In addition, the construction of another sanatorium for 200 beds in Shusha and 255 beds in Agdam in the 1980s was not commissioned due to the conflict. The Shusha sanatorium-resort association also had a 28-bed residential complex for employees. In addition, there were summer camps for schoolchildren in the city. Two of them served at the national level for 500 and 300 seats, and the other served the students of the region.

Earlier, 14 cottages and 4 Kyrgyz tents were built in the area. The sanatorium, which is planned to operate throughout the year, also had a treatment building. The establishment of auxiliary farms in the sanatorium has provided visitors with high-quality food products and additional income. One of the interesting facts is that tourists are taken for a walk on the Karabakh horse presented to the enterprise. By the way, it should be noted that tourists were offered to ride horses at the Shahbulag tourist base. Shahbulag tourist base, which receives 40 tourists, was put into operation in 1988. Gulabli sanatorium is currently on the balance of the Union of Collective Farms of Azerbaijan.

Conclusion: It is clear that the occupation of Karabakh and surrounding areas by the Armenian armed forces, among other things, has seriously damaged the region's tourism economy. Measures have already been taken for the reconstruction and sustainable development of Karabakh. According to the State Tourism Agency, work has already begun to study the tourism potential of the Karabakh region. Currently, demining works are underway. Infrastructure work must be done. Today, it is too early to talk about organizing any tour to the region. This work must be done first. Most importantly, the condition of historical and architectural monuments should be studied. They need to be reconsidered. Although a number of scientists have studied the historical monuments in Karabakh, 30 years have passed. Of course, they need to be reconsidered. Which monuments should be taken under state protection? They need to be restored. It is necessary to build sidewalks, draw and mark sidewalks. Preparation of tourist maps and other work should be done. We will be able to cope with this in the coming years. This work should be carried out by a number of departments, ministries and agencies. There are issues that need to be addressed by various institutions and institutions.

In general, Karabakh will become a new tourist destination for us. Not only a few regions, but the entire territory of Karabakh will become a new tourist destination. It is necessary to ensure the security of these areas. Travel there must be safe for tourists. I hope that all scientists will jointly analyze the territory of Karabakh, create new tourist routes and tourism products. After the crisis

in the tourism sector is over, we will attract more tourists by selling these products. Special new types of tourism will appear. I am confident that Karabakh will become an ecological tourism area and will be recognized as a regional area for ecological tourism. The time will come when we will create more beautiful places in Karabakh and adjacent regions than the resorts in the Swiss Alps, resorts in France, Italy and Germany.

The development of tourism in the Karabakh region will be of great benefit to our country.

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ISSUES OF INTEGRATION INTO THE GREEN ECONOMY IN THE REPUBLIC OF AZERBAIJAN

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ABSTRACT

In recent years, the developed countries of the world are building their policies to ensure more sustainable development. The main goal of sustainable development, which is a model of economic development, is to ensure that available resources are used for human needs while protecting the environment. Thus, when using these resources, not only the current situation, but also the potential needs of future generations must be considered. Given the demand for energy and energy resources in modern times, we can see how important a sustainable energy policy is.

Keywords: green economy, sustainable development, green policy.

Introduction: The idea of green economy has emerged recently and is soaring into greater prominence through the conference known as Rio+20. To understand it a little better, we must seek the origin of the concept, which is found in the idea of sustainable economic development, also known as sustainable development.

The rapid development of the oil sector since Azerbaijan gained independence has led to an environmental crisis. The end of the oil era and the spread of environmental problems in the country are forcing Azerbaijan to join the phenomenon of "green economy" in the world.

Analysis: According to the classic definition provided in the so-called Brundtland Report, sustainable development is development that "meets the needs of the present without compromising the ability of future generations to meet their own needs" (World Commission ..., 1987).

Behind this concept was the need to rethink economic development under a new perspective, considering the inter-generational equity. Until then, economic development was seen from a slightly narrower perspective that usually considered the fundamental determinants of economic growth, without regard for the environment. These fundamental determinants have ultimately produced changes in the accumulation of factors of production and in productivity (encompassing technological progress and changes in the efficiency with which the factors are used), besides influencing the country's growth rate. Less orthodox currents also have studied problems of income distribution, among others, using a less rigorous formalization. Currently, less orthodox ideas are incorporated into economic models, largely due to the dissemination of more sophisticated mathematical methods in Economics (Krugman, 1995). The empirical analysis of economic growth models has also gained new momentum since the interest in economic growth models was renewed in the mid-1980s.

The relationship between economic development and environment has become more explicit since 1970s, when researchers began to examine what the limits to growth would be in a context where natural resources are finite. At the time, several disturbing forecasts emerged (Meadows et al., 1972), which later were put into perspective, when the analysis began to incorporate a more

sophisticated modeling method that considered technological progress, the discovery of new reserves of natural resources and the use of reserves that previously had not been economically viable.

The current environmental changes in the world and the geometric series of population growth are leading to a further reduction of limited resources. Therefore, businesses engaged in the supply of basic consumer goods are moving towards new green economy standards, reducing the "carbon footprint" and developing new strategies and mechanisms to increase adaptability, considering the growing consumption and demand of the population. must implement policies.

The government of Azerbaijan is now looking to implement a policy that will bring about the country's transition to a low-carbon, resource efficient and socially inclusive economy.

Two Strategic Road Maps of Azerbaijan approved in late 2016 - on the production and processing of agricultural products and on the production of consumer goods at the level of small and medium enterprises - also reflect the issue of a gradual transition to a 'Green Economy'.

In 2018, Azerbaijan will study the possibility of introducing the principles of the "Green Economy" in agriculture, and after 2025 will begin developing a legal framework for the transition of small and medium-sized businesses to the "green economic model."

Nowadays, Azerbaijan is increasingly proposing to introduce a "green tax" on the utilization of old household appliances and electronics, as well as toughen penalties for environmental pollution.

At the national level, Azerbaijan is in the process of redefining its medium-term development strategy by supporting private sector development and improving the enabling environment. In December 2016, it launched a strategic roadmap for development of the national economy and 11 key sectors, with medium and long-term goals for reforms and sustainable development. There is also a focus on regional connectivity, transit and trade (e.g. Baku-Tbilisi-Kars and the Trans-Anatolian Natural Gas Pipeline (TANAP) and Trans-Adriatic Pipeline (TAP).

The government of Azerbaijan has prepared several policy documents setting ambitious targets and creating a framework to encourage investment in low-carbon, climate-resilient development.

- Azerbaijan 2020 highlights the possible impact of climate change on the country's society and economy, and the importance of preparing necessary policy measures. It also states that the amounts of energy and CO₂ used to produce one unit of gross domestic product (GDP) should be in line with the appropriate OECD member country benchmarks by 2020.
- Azerbaijan's Intended Nationally Determined Contribution (INDC) outlines some of the priority sectors in mitigation. These priorities include residential and commercial buildings, fugitive gas from the oil and gas sector, and the transport sector.
- The Strategy of Development of Renewable and Alternative Energy Sources in 2012-2020 aims to increase the share of electricity consumed to 20% by 2020, with a total of 9.7% of total energy consumption to be met by renewable energy sources.

To meet these commitments and ambitious policy targets, Azerbaijan needs policies founded on a good understanding of what determines green growth. This will require appropriate indicators to monitor progress.

Talking about numbers, we can mention that renewable energy accounted for 7% of total electricity generation in 2015, compared to 6% in 2013. Wind and solar power generation are relatively new forms of electricity production for Azerbaijan and are on the list of the Government's priorities.

Since 2000, total investment in this sector by the State Agency for Renewable and Alternative Energy has reached AZN 800 million (AZN 64 million in 2014).⁶ The rate of development is promising, even though, by comparison to traditional hydropower generation, the numbers are modest.

Figure 1: Renewable energy rates in Azerbaijan

Source: State Committee of Statistics of Azerbaijan, 2016.

Azerbaijan is already making efforts to reduce the negative impact on the environment and the development of "green technologies", including alternative energy sources and related technologies. Spokesman of Minister of Ecology and Natural Resources said that the republic plans to reduce greenhouse gas emissions to the atmosphere by 35 percent and to receive 30 percent of energy from renewable sources until 2030.

Figure 2: Capital investment for environment protection, thousand USD

Source: State Committee of Statistics of Azerbaijan, 2017.

Methods: The main methods to be used in the research process will be correlation-regression, consent-statistical and forecast methods. Thus, research will be carried out in the economy of the Republic of Azerbaijan using methods such as studying the main characteristics of the green economy, studying the source of problems, the causes, and difficulties of solving them.

The main source of research will be public and private structures that include the concept of green economy in Azerbaijan and the world. The main direction in the public sector will be the study of environmental and green policy projects put forward by the Ministry of Agriculture and the Ministry of Ecology and Natural Resources, as well as the return methods of the new "Smart Village" projects in Karabakh and East Zangezur.

In the private sector, companies and enterprises with environmentally friendly projects and "green" business policies in the country and around the world will be investigated.

In addition, SWOT, BCG Matrix analysis and mathematical-statistical methods will be used in the study. At the global and Azerbaijani levels, the term green economy will be researched, evaluated and future forecasts and risk prevention activities will be developed.

Conclusion and Results: Green economy is considered as a future of mankind. Since the crisis of the real economy in 2008, an intense discussion about the need for changes in the economy, supported by several declarations on the global scale, has been developed. The analysis of the causes and effects of the economic downturn and the challenges of the future have had a huge impact on this situation. As a result, some states have taken action to remedy the situation. Many of them were aimed at structural changes in production, consumption, and environmentally friendly investment. At the same time, the concept of "low carbon economy" and "green economy" gained importance. The aim of this research is to present the role of the state in the economy in terms of creating conditions for a green economy.

In Azerbaijan, green economy has a good chance to thrive and develop intensively. The main factors are there is strong political will. It determines that there is wide recognition across the government and among different stakeholders.

Another factor is inter-ministerial co-ordination. Due to strategic vision by state ministries and government organizations work together to hit thresholds.

Also, State policy of Azerbaijan is very vital on this issue. It aims to serve as background and as a starting point for follow-up development of green growth policies in Azerbaijan. It provides a basis for policy makers to assess their decisions.

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DETERMINING THE EFFECT AND EFFICIENCY OF INVESTING IN HUMAN CAPITAL

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ABSTRACT

In the concept "Azerbaijan 2021-2030: National Priorities for Socio-Economic Development" approved by the Decree of the President of Azerbaijan dated February 02. 2021 the following five National Priorities for socio-economic development of the country should be implemented in the next decade:

1. Steadily growing competitive economy;
2. A society based on dynamic, inclusive and social justice;
3. Competitive human capital and space for modern innovations;
4. Great return to the liberated territories;
5. Clean environment and "green growth" country.

It is clear that sustainable development is also a process of economic and social change in which harmonious development, balanced development, natural resources, investment, scientific and technological development, personal development and institutional change are linked and strengthen the current situation.

In our opinion, there are currently two concepts in the field of sustainable development: 1. Models based on the concept of slow and moderate sustainable development (USA, England, France, Italy, Canada, and so on).

2. Models based on the concept of leaps and bounds (China, Japan, South Korea, Germany, Estonia, Malaysia, Singapore, and so on).

These models were formed in the early 50 and 60 of the twentieth century on the basis of the theory of human capital as an independent branch of economic analysis, thanks to the research of famous American economists, Nobel laureates T. Schultz and G. Becker. Thus, the term "human capital" was first used by T. Schultz, which meant a set of investments that increase a person's ability to work. The scientist argued that the well-being of the poor depended not on land, technology or their efforts, but on the knowledge and skills that constitute human capital. T. Schultz wrote: "All human resources and abilities are innate or acquired. Each human being is born with an individual gene complex that determines his or her innate human potential. We call human capital valuable qualities that a person acquires throughout his life and can be strengthened with appropriate investments. T. Schultz considered that the main result of investing in people is the accumulation of people's working capacity, their effective creative activity in society, the protection of their health. He proved that human beings have the necessary characteristics and properties that are productive because they are able to accumulate and reproduce capital [1,2].

G. Becker, the successor of T. Schultz, developed his idea by substantiating the efficiency of investments in human capital and forming an economic approach to human behavior. In the book "Human Capital", which is the basis for future research in this field, G. Becker defines human

capital as a set of innate abilities, acquired skills, knowledge and motivations embodied in man, which he uses to produce. G. Becker calculated the economic efficiency of investing in education by comparing the benefits and costs of education. To calculate the additional income from higher education, the scientist deducted the lifetime earnings of people with secondary general education from the lifetime income of people with higher education. Education costs include both direct costs of acquisition and opportunity costs or lost profits - money lost by a person during the study period. The return on investment in education is calculated as the ratio of income from education to the cost of obtaining it.

Keywords: intellectual, innovation, human capital, model, scheme, cost, education, health.

Structure and characteristics of human capital in sustainable development: The following generalized model of sustainable development is applied in modern developed countries (Figure 1.).

As can be seen from the figure, the model consists of several systems. Along with other structural elements, innovation is important for sustainable development. Because innovation is an intellectual property, it is created on the basis of human capital and ensures the construction of industries on the basis of high innovative technologies.

There are many different approaches to the classification of human capital in the economic literature, which is explained by the complexity of the economic category. We propose to classify human capital according to the following criteria:

- components or components of human capital;
- forms of ownership operating in the country;
- levels of development of the country's economy;
- main directions of investments aimed at increasing human capital and sources of their formation;
- economic efficiency of investment in human capital development.

Figure 1. Generalized model of sustainable development

Source: The model was developed by the authors. If we analyze the structure of human capital, we can distinguish two main components [3,4,5]:

- educational capital;
- health capital.

The explanation of the distribution of human capital by type of property is as follows:

1. Educational capital is formed during the period of education and consists of the necessary knowledge and skills acquired by a person, which he uses to produce goods and services and is a source of income. Investments in educational capital are necessary to transform human instincts into natural qualities required in the labor market.
2. Health capital is an investment in a person needed to protect and improve a person's health, as well as to increase his activity. Health is the most important element of human capital, because its level directly depends on how well and fully a person can work and bring income to himself and his family, employer and the state.
3. National human capital or national capital includes labor resources, competitive industries, innovative technologies that ensure the country's competitiveness in the world market in the context of globalization.
4. Individual human capital is a fund of accumulated knowledge, skills and professional qualities that allow a person to earn extra income.
5. Corporate human capital (human capital of the enterprise) is expressed by the presence of highly qualified personnel, computer and information technology, know-how, which increases the efficiency of the enterprise.

Figure 2. Scheme of distribution of human capital

Source: The scheme was created by the authors.

It should be noted that until recently, the most active research was conducted on education capital, but now more attention is paid to health capital as a component and main part of human capital. Some scholars, in addition to educational and health capital, include biological or natural capital, family capital, and cultural capital in human capital [9,11].

Human natural capital includes the mental and intellectual abilities of a person, as well as the biological inherited abilities that are passed on to him at birth, which include the health he received from his parents.

Family capital includes upbringing, motivation, and moral values passed down from generation to generation.

Assessment levels of human capital: Here we offer the following levels (Figure 3):

- macro level: characteristics of total human capital on the scale of the national economy;
- meso-level: assessment of human capital of large organizations and regions;
- micro level: characterization of human capital at the individual and enterprise level.

At each level, investments are required for the formation and accumulation of human capital, and depending on the direction of their investment, the types of costs are differentiated and the level of assessment is characterized by a set of relevant indicators.

Figure 3. Levels of investment in human capital development

Source: The model was developed by the authors.

It is clear from the figure that the main cost elements include:

- education costs: first of all, the costs of higher education, professional development, retraining and training;
- health protection and maintenance costs: the sum of costs that affect life expectancy, health level (health care, health insurance, disease prevention, housing improvement costs);
- Mobility costs associated with the migration of people looking for a better job.

As a result of our analysis, it is possible to say that the specific features of investments in human capital that distinguish them from other types of investments can be distinguished:

- Investment in human capital is long-term: the period of investment in education is about 15-20 years, and investment in health is carried out throughout life;
- Return on investment in human capital depends directly on the length of human life, especially the length of working age, and better and longer-term investments have a higher and longer-term effect in the future;
- human capital accumulates during human life, but is also subject to physical and moral erosion: physical erosion is determined by the aging of the human body, moral erosion is characterized by the obsolescence of knowledge and the reduction of the value of education.

Analysis of methods for assessing investment in human capital development

Methods used in the valuation of human capital in foreign countries: At present, the balance sheets of foreign firms do not reflect investments in human capital development, only intellectual capital in the form of intangible assets. As a result, the real market value of the enterprise is distorted and various methods are used to estimate the value of human capital and funds invested in it. The methods used for this purpose are [6,7,8]:

* Expert method or quality assessment method. This method assesses the quality characteristics of individual employees, as well as the workforce of the enterprise as a whole. Qualitative characteristics of the employee are represented by indicators such as level of education, work experience, specialty category, creativity, non-standard thinking.

* The method of estimating the value of human capital based on the determination of costs is one of the most common methods in practice. It is implemented in two ways:

- live ;
- indirectly.

The indirect method involves comparing the market value of an enterprise with the cost of replacing it. Nobel laureate in economics D. Tobin proposed a coefficient q calculated as the ratio of the market value of the assessed object to the value of its replacement. This includes the cost of setting up the business. If $q < 1$ and the value of the assessed object is lower than the cost of its replacement, then the investment in this object should not be made due to low human potential. If $q > 1$, then the object being valued has high human capital and the investment is attractive.

On the basis of the direct method, the total costs necessary for the formation of human capital in the enterprise are determined:

- cost of employees' salaries;
- improvement of working conditions and protection of life;
- training costs of employees;
- Improving the health of employees.

The formula proposed by us for calculating the nominal (potential) annual value of human capital in the enterprise is as follows:

$$\dot{I}_k = S_{in} \times \frac{(V_{sh} + M_m + K_{mhx} + X_{tu})}{H_{ios}}, \quad (1)$$

where $\dot{I}_k$ - value of human capital in the enterprise, man; S_{in} - total number of staff, people; V_{sh} - actual annual salary of general employees, man .; M_m - annual financial incentive fund for employees of the enterprise, man .; K_{mhx} - annual expenses related to rewarding and motivating employees of the enterprise from additional financial sources, man .; X_{tu} - costs associated with the education and training of employees, man .; H_{ios} - the average annual number of employees in the enterprise, people.

* Eric Flamholz's model of determining the initial and replacement costs of personnel. This model takes into account the company's costs of acquisition and replacement, rather than staffing.

* The method of finding the individual value of the employee. This method uses conventional value concepts developed by scientists at the University of Michigan. The individual value of an employee is determined taking into account the probability that he will work in the organization for a certain period of time. The expected selling price is represented by two elements:

-expected conditional value;

- continuation of the employee's work in the organization.

* The method of capitalization of future income is the most common method, where the value of human capital is determined based on its use, ie the economic effect of gross income. In other words, measuring the value of human capital involves determining the value of future income flows for the present and present.

Of course, the methods discussed above do not provide a complete list of all available methods for assessing the effectiveness of human capital investments. However, it can be understood that the difficulty in determining the value of human capital and the effectiveness of investments in it is often due to the lack of statistical data required for analysis [7,12].

Impact of human capital on the economic growth of the enterprise: Today, the innovative development of the enterprise cannot be ensured due to previous experience in the field of human resource management based on traditional methods of personnel management. It is inevitable that a significant part of the innovation activity of enterprises will move in the direction of accumulation of human capital, adequate to the innovation-type tasks of the economy.

The accumulation of human capital is conditioned by the constant increase in knowledge, skills, production experience and skills of employees throughout their lives. Higher vocational education plays a special role in this process, which will form the professional, special and innovative skills of employees. Achieving a competitive advantage of the enterprise is mainly due to knowledge and innovation. Increasing labor productivity in an enterprise is not possible without investing in fixed capital and especially human capital, because the level of the latter determines the success rate of innovation, as well as the efficiency of the use of fixed capital [11,13].

The main effect of investing in human capital is the highly productive work of each employee, which confirms the positive correlation between the level of development of human capital and the employee's salary. It follows that the greater the amount of human capital, the higher the rate of labor productivity and economic growth (Figure 4).

The experience of developed countries shows that the main condition for economic growth is the accumulation and maintenance of human capital, as well as its development and growth.

Following a survey of 192 countries, World Bank experts concluded that 16% of economic growth in countries is due to investment in fixed capital or physical capital, 20% - to natural capital, and 64% - to the level of development and quality of human capital.

Figure 4. The impact of investment costs on the economic growth of the enterprise

Source: The model was developed by the authors.

In countries such as Germany, Switzerland and Japan, the share of human capital reaches 80%. In Germany and France, the share of funds allocated for social protection is almost half of the state budget - 43.3% and 43.1%, respectively. Economic development in these countries is measured by comparing GDP per capita in comparative estimates for the period under study.

The share of expenditures on the development of science from the budget of Azerbaijan in the state budget in 2018 is only 0.01% (117.8: 22731.6), which is higher than in Estonia, Israel, South Korea, Germany, Japan, Singapore and other developed countries. at a very low level (Table 1).

Table 1. Dynamics of expenditures allocated from the state budget for the development of human capital in Azerbaijan

Years	State budget (million manat)	Educational expenses (million manat)	Health care costs (million manat)	Science costs (million manat)	Spending on Culture, Media and sports (million manat)	Total costs (million manat)	Share in the state budget (%-lə)
2009	10503.9	1147.9	402.4	83.3	158.3	1791.8	17%
2010	11765.9	1180.8	429.2	92.8	168.4	1871.2	16%

2011	15397.5	1268.5	493.4	106.1	189.9	2057.9	13%
2012	17416.5	1453.2	609.4	116.7	240.8	2420.1	14%
2013	19143.5	1437.7	618.9	117.0	274.9	2448.5	13%
2014	18709.0	1553.9	665.3	124.2	294.0	2637.4	14%
2015	17784.5	1605.1	708.2	113.2	272.4	2698.9	15%
2016	17751.3	1754.4	702.5	110.2	687.4	3254.5	18%
2017	17594.5	1742.7	704.7	109.8	253.3	2810.5	16%
2018	22731.6	1966.6	709.9	117.8	299.5	3093.8	14%

Source: Compiled by the authors on the basis of the State Statistics Committee of the Republic of Azerbaijan.

Unlike our country, developed countries, in addition to achieving a high level of economic development and quality of life of the population in the distribution of budget funds, prefer to invest in human resources rather than fixed capital. From this point of view, the most obvious manifestations of the crisis in the impact of the components of human capital on the economic growth of the country are as follows:

- devaluation of human capital in the economically active population;
- creation of intellectual unemployment;
- higher education workers are forced to change their profession and seek additional income;
- "brain drain" (migration of scientific personnel from Azerbaijan abroad);
- lack of experienced and modern teaching staff capable of training qualified personnel.

The result: 1. As a result of the study of human capital, its structure, formation factors, distinctive features and properties, it can be said that human capital is a complex economic category, its logical study and analysis is an important factor from a scientific point of view.

2. There are many interrelated problems in the classification of human capital, as a result of which the study of human capital becomes much more complicated. Therefore, in the future it is necessary to develop a unified system of classification of human capital, which will eliminate the difficulties in its assessment.

3. Due to the increase in the level of education of the population in the country, the work of each person will be more productive if the creation of innovative technologies and the continuation of their application in the economic sphere will create conditions for sustainable economic development.

4. Simultaneous solution of three main problems: innovative development, technological modernization of industry and development of human capital is an important condition for the success of the innovative leap in our country.

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PROGNOSTIC MEANING OF SERUM NSE AS THE FACTOR OF BAD OUTCOME IN SECONDARY BRAIN DAMAGE

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This research is dedicated to the study of brain neuronspecific markers and indicators of brain damage outcome.

Purpose of the study: To examine the prognostic role of serum NSE as the predictor of unfavorable outcome in traumatic and vascular brain damages.

Methods: Prospective cohort study with 219 patients. Blood serum neuronspecific markers (NSE,S100B),acid-base state, blood gas were derived during the period of observation: upon enrolment, on the 3-rd, 5-th and 7-th days spent in the hospital in the intensive care unit.

Results: The most significant risk factor of unfavorable outcome is the marker NSE with the cut point 12,5 ng/ml. The results of the analysis indicate the presence of a statistically significant direct relationship between NSE> 12.5 ng / ml and LDH, compared to other variables, 3.7 times more often; with an increase in blood lactate more than 4,1 mmol/l almost 3,8 times; with GCS 13 points below by 1,7 times; S100≥0,2 by 2,8 times; with an increase of PCO2 <38,5 it was documented more than 3 times often. The measure of certainty the resulting model by the pseudo R2 Nagelkerke criterion-250.6; logLikelihood - 154.04 which corresponds to the excellent predictive ability of the mathematical model. The best predictive value of the model is a cut-off point of 88.89%, AuROC-0.809; Se-51.59%; Sp-95.06%; NPV-55.80%; PPV-94.20%.

This model can be used to predict the outcome in patients with acute cerebral pathology.

Keywords: strokes, brain traumatic damages, neuronspecific markers, diagnostic and prognostic criterias, stroke outcomes.

Traumatic and vascular lesions of the brain cause abnormal brain functioning due to disturbances in the vascular system. Millions of people are admitted to emergency departments every year for brain damage, of which 1.5 million die [1, 2]. Many deaths occur before the patient arrives at the hospital or during treatment [3]. However, ongoing inflammatory processes in secondary brain damage cause damage to molecular cells, changes in metabolism and cerebral blood flow, axonal disruption and apoptosis, which can influence the development of long-term mortality in the separated period of cerebral damage [4,5]. According to the authors, these patients have a reduced

points with GCS in assessing the severity, dynamics and prediction of outcomes of neurological status [6,7]. Also, in computed tomography of the brain, the diagnostic value is low, due to low sensitivity and insufficient specificity [8,9]. Magnetic resonance imaging allows us to assess the severity of neuroaxonal injuries, but its inaccessibility to some hospitals, long study time, often severe patients requiring continued mechanical ventilation significantly limit its use [8, 10]. In daily clinical practice, due to invasiveness and the presence of certain indications, the control of intracranial pressure is also limited [10]. Therefore, more and more clinical and experimental studies are aimed at studying the role of neurospecific blood proteins in the diagnosis and prognosis of outcomes of acute cerebral neuropathology [7,11]. In diseases associated with the direct involvement of nervous tissue in the pathological process, qualitative and quantitative determinations of the NSE protein in cerebrospinal fluid or blood serum provide valuable information on the severity of neuronal damage and violations of the overall integrity of the blood-brain barrier [12].

NSE also characterizes the degree of post-ischemic brain damage. NSE has a long half-life compared to S100B. Unlike S100B, which is present in high concentrations in glial cells and Schwann cells, NSE originates predominantly from neurons and neuroendocrine cells [13, 14]. It is possible that S100B simply reflects the inflammatory response of glial cells, while NSE may serve as a marker of neuronal damage [15,16].

The assessment of the significance of markers in the prediction of the dominance of injuries was carried out by us using the Wald method. The ability of NSE as a predictor of mortality has been shown in several studies [17]. However, a number of studies refute these results [18]. Different results may be associated with methodological differences, sample size, out-of-the-box tests, and different demographics. To further deepen the usefulness of NSE as a predictor of poor outcome, this article will present its predictive value in vascular and traumatic brain injury.

Methods: The study was carried out in accordance with the standards of good clinical practice (Good Clinical Practice), the principles of the Declaration of Helsinki and in accordance with the principles of the ethical commission of the West Kazakhstan Medical University named after Marat Ospanov No. 12 dated January 30, 2018 [11]. The content of NSE protein in blood serum upon admission and in dynamics was determined in 219 patients with vascular and traumatic brain diseases who were treated in the intensive care units and intensive care units of stroke centers in Aktobe (Republic of Kazakhstan) for the period from 2018 to 2020. The study included patients with hemorrhagic strokes (HI) - 146 patients (66.6%), ischemic stroke 43 (19.6%) and with acute closed craniocerebral injuries of mild and moderate severity - 30 (13.60%). Criteria for inclusion in the study of patients with hemorrhagic stroke were cases of intracerebral hemorrhage with a hematoma volume of more than 30 cm³ (mainly hemispheric hemorrhages); patients with ischemic stroke - with the presence of cerebral infarction, confirmed by clinical and CT data; patients with severe craniocerebral trauma - moderate and severe cerebral contusions. Patients with: intracerebral hemorrhages with a hematoma volume of more than 80 cm³, with severe decompensated somatic diseases, with benign and malignant tumors of the brain, lungs and skin were excluded from the main group. According to the outcome of the disease, regardless of the diagnosis, the patients were divided into groups: survivors - 59.3% (n = 130) and deaths - 40.6% (n = 89). Laboratory studies of the NSE were carried out upon admission and in dynamics. The supernatant was removed and stored at -80 ° C until analysis. For NSE determination, all samples were analyzed in duplicate using immunoluminometric assay using a human ELISA kit. To

measure blood gases, lactate and glucose, samples were analyzed using an ABL 735 analyzer (Radiometer; Denmark). The neurological grading scales GCS (Glasgow Coma Scale) were used to assess the severity of brain damage and to predict the outcome of the clinical course of the disease in patients. The study was approved by the hospital ethics committee and informed consent.

The distribution of patients in groups by sex ($\chi^2 = 0.0184$, $p = 0.8922$) and age ($\chi^2 = 0.0183$, $p = 0.4288$), where all predictors were examined were comparable. To determine the possibility of using the NSE protein in predicting the outcome of secondary brain injuries in vascular and traumatic brain injury, an analysis of variance was carried out. Maximum, minimum, and mean protein levels were assessed for each outcome group.

Statistics: The study of the statistical relationship between a qualitative trait and clinical outcome was carried out using the analysis of contingency tables, with the calculation of the Pearson χ^2 criterion. If the condition of applicability of the χ^2 criterion is not met (more than 25% of cells in the contingency table have an expected frequency of less than 5), the analysis was carried out in pairs according to the two-sided Fisher's exact test (2p (F)). In the case of insufficient statistical significance of the relationship between two nominal features in a multi-field contingency table, several similar gradations of a feature were combined into one, followed by calculation of the Pearson χ^2 criterion with the achieved level of statistical significance (p) and the odds ratio (OR) with a 95% confidence interval (95% CI). The study of the relationship between the quantitative and qualitative trait was carried out using one-way logistic regression analysis with the calculation of Wald's χ^2 statistics with the achieved level of statistical significance and OR with 95% CI. Multiple linear regression analysis was performed to identify variables independently associated with serum NSE levels. NSE was used as a dependent variable. A step-by-step forward technique was used. Data are presented as mean $\pm$ SD or median and percentile, p -values less than 0.05 were considered significant.

The construction of mathematical models for predicting the risk of an unfavorable outcome was carried out using the method of multivariate binary logistic regression analysis with step-by-step inclusion of independent variables. The effect of the independent variable on the probability of outcome was determined using OR and 95% CI. To assess the quality of the mathematical model, we calculated the Nigekirk coefficient of determination (R^2), which shows the share of the influence of all variables included in the model on the variance of the dependent variable, as well as the Hosmer-Lemeshov goodness test, which makes it possible to establish how the model agrees with the initial data. The discriminatory ability of the mathematical model was assessed based on the analysis of the classification table. Evaluation of the predictive efficiency of the model was carried out using the analysis of ROC curves, with the calculation of the area under the ROC curve, called AUC (Area Under Curve). In the statistical analysis procedures, the achieved level of statistical significance (p) and the number of degrees of freedom (df) were calculated. The critical value of the level of statistical significance in the study was $p < 0.05$.

The results of the study were subjected to statistical analysis and mathematical data processing using the Statistics (SPSS25) software package.

Results: Neurospecific enolase (NSE) performs an enzymatic function by participating in glycolysis processes and is one of the specific markers of nerve tissue damage. A very rapid increase in blood concentration was noted during hypoxia, brain injury and other pathological

conditions accompanied by massive destruction of neurons. When comparing the groups of survivors and deceased, it was found that the concentration of the NSE protein on the first day after injury increased by 2 and 3 times, respectively. In the surviving patients, on the third day after the incident, the NSE level returned to the control figures, and in the deceased - it remains high relative to the control indicators. Figure 1 shows the distribution of the mean NSE protein for each outcome group.

Figure 1. Diagram of NSE range in disease outcome groups.

As shown by the studies, when comparing the dynamics of the content of neuron-specific proteins in the groups of surviving and deceased patients, statistically significant differences were determined. So, if in both groups of patients there was a 1.4-fold increase in NSE on day 1 14.76 95% CI (12.98; 16.54) versus 20.75 95% CI (16.10-25.39) ng / ml, respectively for the groups), then a significant increase in its concentration was observed in the group of patients who died on the 3rd day by 1.39 times 19.75 95% CI (14.52-24.97) $p = 0.0260$) by the background of the treatment, which suggested an early occurrence of an unfavorable course of the disease.

In all other fatalities, the NSE concentration increased over time, reaching a maximum at the time of death. Analysis of variance was performed to determine the statistically significant difference. Maximum, minimum, and mean NSE protein levels were assessed for each outcome group.

The revealed differences in the nature of the body's response to brain damage gave us the basis for the subsequent development of a differential diagnostic algorithm. Variables showing a statistically significant relationship with (predictors of) an increase in target $\text{NSE} > 12.5 \text{ ng / ml}$ by factors of secondary brain injury in univariate analysis were introduced into multiple LRA step by step. In the first step, clinical and laboratory parameters were included (simple model) The results of the analysis are presented in Table 1.

Table 1. Predicting the risk of increasing $\text{NSE} > 12.5 \text{ ng / ml}$.

Factor	AuRO C	Stand errors	OR	95%CI OR lower upper	Coeff.regr ession	χ^2	Level P
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Const		-1,9577				-1,9576	19,4029	<0,0001
LDH ¹ ≥218	0,728	0,3376	3,74	1,93	7,25	1,3195	15,279	<0,0001
GCS ² <13	0,766	0,3447	1,68	0,85	3,29	0,5168	2,2485	0,1337
Age<53	0,783	0,3901	2,95	1,37	6,34	1,0829	7,7076	0,0055
S100B≥0,2	0,790	0,3868	2,79	1,31	5,95	1,0256	7,0288	0,0080
PCO2 ³ ≥38,5	0,804	0,3741	3,08	1,48	6,41	1,1242	9,0311	0,0027
Lactate	0,809	0,6625	3,29	0,90	12,07	1,1922	3,2392	0,0719

Notes:

1 LDH- lactate dehydrogenase

2 GCS- The Glasgow Com Scale

3 S100B – calcium binding protein

4 PCO2- partial pressure of carbon dioxide

The measure of certainty of the resulting model according to the pseudo R2 criterion is 250.6%. Independent factors associated with NSE were: LDH ≥218, GCS <13, Age<53, S100B≥0.2, PCO2≥38.5, Lactate≥4. The results of the analysis indicate the presence of a statistically significant direct relationship between NSE>12.5 ng / ml and LDH, compared to other variables, 3.7 times more often; with an increase in blood lactate above 4.1 mmol / l, almost 3.8 times; with a Glasgow scale below 13 points by 1.7 times; S100B 0.2 by 2.8 times; with an increase in PCO2 <38.5 were documented more than 3 times more often. The measure of certainty of the resulting model by the criterion of pseudo R2 Nagelkerke-250.6; logLikelihood 154.04.

The logistic regression equation of the model is as follows:

Risk = 1/(1 + Exp(-(-1,958 + 1,319*LDH ≥218 + 0,517*GCS <13 + 1,083*Age <53 + 1,026*S100B ≥0 + 1,124*PCO2 ≥38 + 1,192*Lactate ≥4)))

Where P is the probability of risk of increasing NSE> 12.5 ng / m, e-base of natural logarithm (e = 2.72), -1.9577 is a constant;

The best predictive value of the model had a cut-off point of 88.89%, AuROC-0.809; Se-51.59%; Sp-95.06%; NPV-55.80%; PPV-94.20%.

When forming multivariate analysis of variance, when predicting the risk NSE> 12.5 ng / ml, we obtained regressions from several factors, which are indicated in Table 11.

Table 11. Regressions

Factor	Cut off	Relative risk (95% CI)	Se	Sp	χ ²	AuROC	P-level (df=1)
4 factor ≥ 1,0	1,0	4,54 (2,01; 10,24)	96,24%	32,56%	33,8465	0,80	<0,0001
3 factor ≥ 1,0	1,0	3,66 (1,86; 7,18)	94,74%	34,88%	32,6368	0,79	<0,0001
5 factor ≥ 2,0	2,0	2,45 (1,56; 3,86)	89,47%	40,70%	27,3740	0,82	<0,0001

Regression consisting of 4 factors relative risk of poor outcome 4.54 (95% CI 2.01; 10.24); Se-96.24%, Sp-32.56%, χ²-33.8465, AuROC-0.80.

We calculate: if LDH> 218 then score = 35; GCS <13 then score = 15; Age <53 then score = 24; S100≥0.2 then score = 26. Total = 100bb. If on admission the patient gains 100 bb in the patient during the study, the risk of NSE is> 12.5 ng / ml and the mortality rate exceeds 4.54 times. To

predict the NSE score, we used multiple regression analysis with the NSE dependent variable and the independent variables LDH, Lactate, S100, Glucose. All variables listed in the table predicted the quantitative value of this marker. Below are the extended results of the regression analysis in Table 2.

Table 2. Advanced regression results

factor	R-square(correcte d)	R-square changes	Correl. With target	B-coef	Stand. erroe	p
constant					3,1990	0,2439
LDH ¹	18,2%	41,87%	0,43	0,008	0,0085	<0,0001
lactate	22,4%	23,62%	0,28	17,748	0,6259	0,0105
S100B ²	41,4%	19,43%	0,55	52,207	0,5757	<0,0001
glucose	42,1%	0,50%	0,05	-3,529	0,3241	0,0598

Notes:

1.LDH-lactatdehydrogenaze

2. S100- calcium binding protein

Model quality

R-square	42,9%
R-square corrected.	42,1%
Standard error Y	12,46
F-statistic	40,22
number of degrees of freedom	214
Level P	<0,0001

Figure 14. The graph of the dependence of the observed values on the predicted values and the quality of the model $NSE = 3,17 + 0,05 \cdot LDH + 1,7 \cdot \text{lactate} + 4,9 \cdot S100B - 0,63 \cdot \text{glucose}$

Where:

3,166 - constant

0,052 - regression coefficient of LDH;

1,699 - regression coefficient of lactate;

4,900 - regression coefficient of S100B;

-0,632 - regression coefficient of glucose

The results of the regression analysis showed that the variables independently statistically associated with NSE were LDH, lactate, S100B, and blood glucose. In this part of the study, we

have focused on those variables that are strongly associated with the dependent variable. Differences in the mean value of NSE protein in serum with different outcomes. The group with a favorable outcome (GOS 4,5,3) and the group with a poor outcome (GOS 1,2) with a lethal outcome significantly differ in the mean and maximum values of the level of NSE protein in blood serum ($p = 0.05$). Next, we plotted Kaplan-Meier survival curves for NSE <12.5 ng / ml

Figure 15. Kaplan-Meier survival curves for NSE <12.5 ng / ml and NSE > 12.5 ng / ml

As can be seen from the figure, the cumulative indicator of cases of poor outcome in the group with a level and NSE > 12.5 ng / ml began to diverge already in the first days of observation. The achieved level of significance according to the log Rank criterion (Mantel Cox) = 0.0062, the differences in the study groups are significant. Thus, the NSE protein level > 12.5 ng / ml can serve as a predictor of death in the early stages of the disease.

It was found that the levels of neuron-specific proteins, blood gases and predictors of impaired brain metabolism differentiated among themselves depending on the outcome of the disease. The revealed differences were explained by the biochemical characteristics of cerebral injuries, which, in turn, were determined by their morpho-functional characteristics. The essence of the dominant brain damage is the development of a pathological process in the direction of an increase in cytotoxic edema (edema-swelling) of the brain, an increase in intracranial pressure with possible dislocation and wedging of the brain. In general, the results of the comparison of blood serum indices gave a positive result. They showed that the magnitude of individual neuromarkers can serve as a criterion for the dominance of secondary brain injury.

Discussion: Death rates from traumatic and vascular injury differ in several studies. Some studies also use different temporal methods and parameters to analyze this mortality. Mortality ranges from 13 to 22% [20]. It has been established that after the primary injury, from the first minutes, secondary brain damage develops, which can continue in subsequent periods for several years due to excessive metabolic, cellular and molecular activity of inflammation [20]. The research results

indicate that the immunoenzyme screening of neuron-specific proteins (NSE) makes it possible to assess the degree of damage to the blood-brain barrier and the depth of pathological changes occurring in the nervous system [21]. During the infectious process, immunopathological reactions are triggered in the central nervous system, leading to the activation of T-lymphocytes and an increase in the BBB permeability [22,23]. The penetration of the virus into the central nervous system is largely determined by the state of the BBB. Violation of the BBB permeability is accompanied by the release of NSE into the blood.

Determination of NSE and S100 protein in serum and cerebrospinal fluid in the acute period of traumatic and vascular brain damage can serve as an additional criterion for early diagnosis of impaired blood-brain barrier permeability in the acute period of the disease and as a criterion for the restoration of its permeability in the long-term period [24, 25].

The researchers also found that this biomarker reflects the severity of injury based on GCS [26]. Based on this study, it was shown that high NSE levels were significantly different in surviving or deceased subjects with head injuries. The brain damage that causes high levels of NSE can be strongly associated with impaired BBB and ischemia. So, for example, according to [27], postischemic vasospasm usually develops within 3 days after traumatic and vascular lesions. The strength of short-term predictors of mortality is also better than predictors of long-term mortality risks, both in significance of mean differences and in diagnostic power. Another study argued against the results that NSE level could not be a predictor of mortality. The differences were associated with variations in the time of NSE collection in each study, from the time of injury to 84 hours after injury. These studies were carried out heterogeneously in terms of time and methodology, so the results of the study also differ [28]. In this article, we describe the development of a predictive model of increasing complexity based on predictors to predict poor patient outcomes. The model adequately differentiated between patients with poor and good outcomes. The largest amount of prognostic information was contained in the main set of predictors: S100B, GCS, pCO₂, glucose and LDH at admission. These characteristics have already been taken into account in many predictive models [29,30]. Further validation of this estimate is needed, but the required data were insufficiently available in most of the IMPACT studies. Glucose and hemoglobin have been shown to contribute to predicting outcome, although their influence is less than that of other predictors such as age [31]. In intensive care units, intensive treatment of hyperglycemia has been shown to reduce mortality [32]. Early prediction of outcome allows a baseline risk profile to be established for individual patients, thereby providing a reference for assessing the quality of care. Predictive models are especially important for better planning and analysis of RCTs. For example, we can exclude patients with a very good or very poor prognosis [33], perform a covariate adjustment for treatment effect [34,35], and consider other analyzes that lead to increased statistical power [36].

The proposed scales can also assist physicians in their initial assessment of the severity and prognosis of patients with brain damage. However, we note that models can only complement and not replace clinical judgment, although it is unlikely that any clinician has equivalent systematic experience with the thousands of patients that underlie our models. The prognosis should be treated with caution and not used directly to make decisions about limiting treatment [37].

These models can be useful for providing relatives with realistic information about expected outcomes, for quantifying and categorizing the severity of brain injury, for stratifying and correcting covariance in clinical trials, and as a reference for assessing the quality of care.

Thus, early detection and control of the S100B level, as well as simultaneous studies of S100 and NSE, make it possible to identify and confirm the presence of brain damage at an early stage, it is possible to successfully predict secondary brain damage.

Limitations and further study: This study had limitations. The study with a small number of patients was single-center, which limits its validity. Secondly, there were certain difficulties in the process of work associated with the refusal of patients or their relatives from further participation in this study; there was no dynamic long-term follow-up of the studied patients.

This study provides the basis on which further multicenter studies should be built in order to establish generalizability and improve the validity of the results obtained.

Conclusion: 1. The levels of the dependent variable (NSE) and independent variables (S100B, blood glucose, GCS and HB) can be used as multimodal predictors of predicting neurological outcome in patients with acute cerebral pathology. In this study, we were able to predict the quantitative indicator of the NSE $y = 0.4292x + 9.58$. $R^2 = 0.4292$

2. The proposed mathematical model, which includes the dependent variable (NSE) and independent variables (S100B, blood glucose, GCS and HB) as predictors of poor outcomes, had a cut-off point. The best predictive value of the model had a cut-off point of 88.89%, AuROC-0.809; Se-51.59%; Sp-95.06%; NPV-55.80%; PPV-94.20%, which corresponds to the excellent quality of the predictive ability of the mathematical model. The model can be used in everyday practice to identify and reduce the likelihood of a high risk of adverse clinical outcome in patients with acute cerebral pathology.

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IMMUNOHISTOCHEMICAL FEATURES IN SOFT TISSUE SARCOMAS

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ABSTRACT

Sarcomas are relatively rare, accounting for only 1% of all adult malignancies and 15% of childhood malignancies [2]. According to the World Health Organization (WHO), the group of soft tissue sarcomas includes more than 100 different histological subtypes [3]. According to the recommendations of the WHO to improve the accuracy of diagnosis in soft tissue sarcoma, the traditional histopathological examination should be supplemented with immunohistochemical and molecular methods [1]. It was carried out immunohistochemical research of CD31 receptor of Vascular Endothelial Growth Factor (VEGF) in 129 patients with STS.

The age range of patients is on average 14-77 years with a peak in the age of 50-59 years. The most common reason for initial visit to a medical institution was palpable tumor (100%). It was studied the following correlative interdependences:

It was determined that histodifferentiation of tumour is in inverse correlation with expression CD31 receptor. Distinctions of expression level of CD31 are shown, depending on the degree of tumor differentiation, presence or absence of its spontaneous necrotization, lymphoid infiltration of pathological nidus and amount of vessels in tumor tissue. That is as high the degree of histological differentiation of tumour as low the level of expression CD31 receptor ($\chi^2=35,4$; $p<0,001$; $p=-0,322$). In FHTof ST is exposed inverse dependence between expression CD31 endotelial cells with spontaneous necrosis and lymphoid infiltration. As more the size and foci of spontaneous necrosis ($\chi^2=67,1$; $p<0,001$; $p=-0,473$) and lymphoid infiltration ($\chi^2=46,1$; $p<0,001$; $p=-0,346$), as low the level of expression CD31 receptor. It was found that the high level of expression CD31 receptor is in direct correlation with metastasis ($\chi^2=18,6$; $p=0,42$; $p<0,001$) and recurrence ($\chi^2=9,43$; $p=0,30$; $p<0,01$) of the process. Studied modern approaches to the diagnostics and treatment of malignancies. One such approach is "Oncology Control", which means minimizing the risk of recurrence at the local and systemic level. Following treatment, follow-up should include history and physical examination accompanied by imaging (Ultrasound or MRI) every 3 to 6 month for 2 to 3 years, and then every 6 to 12 months thereafter to asses for recurrence. So in high positivity of CD31 receptor is exposed unfavourable prognosis in patients with STS.

Summarizing before said we have come to the conclusion that immune-histo-chemical investigation of CD31 receptor of VEGF has important prognostical meaning in patients STS.

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THE LEVEL OF S100 IN BLOOD SERUM AS A PROGNOSTIC FACTOR OF OUTCOME IN SECONDARY BRAIN LESIONS

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ABSTRACT

This study is devoted to the study of the prognostic value of neuron-specific markers of the brain and indicators of the outcome of brain damage.

The purpose of the study. To study the prognostic role of serum S100 as a predictor of mortality in vascular and traumatic brain injuries.

Materials and methods. A prospective cohort study involving 219 patients. In the blood serum, neuron-specific markers (S100, NSE) and glucose, acid-base state and gas composition of arterial blood were obtained during follow-up periods: at admission, on the 3rd, 5th and 7th days of patients' stay in the intensive care unit.

Results. The most significant risk factor for an unfavorable outcome is the marker S100 with a cut-off point of 0.2 mcg/l. The results of the analysis indicate the presence of a statistically significant direct relationship between $S100 > 0.2$ mcg/l and $NSE \geq 18.9$ ng/ml compared to other variables, while the chance ratio (OR) is 11.9 (95%CI:3.2927-1.6693;). With an increase in blood sugar above 7.4 mmol/l, the OR is 3.82 (95% CI: 2.1289- 0.5539;); with a Glasgow scale below 13 points, the OR is 3.69 (95% CI: 2.1316-0.4819;); with an increase in $pCO_2 < 43.5$ mm Hg, the OR was 3.15 (95% CI: 1.8916- 0.4062;). The measure of certainty of the obtained model according to the criterion of pseudo R^2 Nagelkerke is 263.5, which corresponds to the excellent quality of the predictive ability of the mathematical model. The developed prognostic model, including the dependent variable S100 and independent variables as predictors of a poor outcome of NSE, pCO_2 , GCS and Hb, reached a cut-off point of 84.51%, AUC - 0.88 with high levels of sensitivity and specificity: 91.89% and 64.14%, respectively. This model can be used to predict the outcome in patients with acute cerebral pathology.

Keywords: strokes, traumatic brain injuries, neuron-specific markers, diagnostic and prognostic criteria, stroke outcome.

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