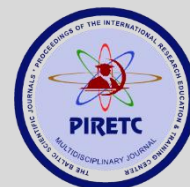


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MODERN FINANCIAL MARKETS AND “GREEN” ASPECTS OF THEIR FUNCTIONING

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ABSTRACT

At the global level, ensuring sustainable development and improving climatic conditions is an inevitable process that has a great impact on the financial sector and the world economy. That is why the question of developing new development strategies, which involves changes at the state and corporate level, the introduction of innovative "green" financial instruments, and a different approach to the functioning of financial markets for developed and developing countries, has arisen with all urgency.

Various methods have been used to achieve the main goal of the research, including dialectical, comparative analysis, and descriptive analysis methods.

It is emphasized that green bonds, as a tool for raising loans and financing "green projects", are quite popular and widespread in international practice, but "green" bonds are a fairly new term and have been established relatively late in Georgian practice.

Finally, our research provides evidence as to why the share of green bonds, their popularity, and investment attractiveness in international financial markets is increasing.

Keywords: Sustainable development, financial markets, green finance, green bonds.

Introduction

In the modern, global world, society faces many problems and challenges, the most important of which is achieving sustainable development and ensuring environmental security. Recently, issues and ideas about "sustainable development", "green economy", and "green finance" have been voiced more and more at international events, scientific conferences, and international forums.

The uniqueness of green finance is manifested in the effective and targeted use of financial resources in the process of developing and implementing measures necessary for the implementation of "green projects". The field of green finance includes various financial instruments, such as green bonds, green loans, and green insurance. The central place in our research is devoted to the analysis of issues related to new financial instruments - green bonds.

It is important to note that the criteria for "green projects" are defined by the relevant taxonomy. In international practice, the standards of such projects and the issuance of green financial instruments are mainly determined by the taxonomy of climate bonds developed by the international organization Climate Bonds Initiative (CBI) and the principles of green bonds developed by the International Capital Markets International Association (ICMA).

Many scientists and researchers have already touched on the issue of green finance and related "green products". For example, according to the research of Peterson K. Ozili (2022), [1] some important concepts [1] that have dominated the green finance literature in recent years are given, such as the importance of green finance; definitions of green finance; green finance products and instruments; Strategies for promoting green financing and investment, etc.

As noted by Doronzo, Siracusa, and Antonelli (2021) Even if funds raised by green bonds are used for specific green projects, their returns are tied to the issuer, not the success of the projects. This means that the risk of the project remains with the issuer and not the investor. This feature is attractive due to the higher risk of green projects.

The purpose of the research is to reveal and determine: green aspects of the functioning of modern financial markets; Similarities and differences in the process of issuance and circulation of conventional and green bonds, to determine the specific share of green bonds compared to other instruments of the financial market and to evaluate its impact on the capitalization of the financial market.

Materials and Methods

In the research part, we used the following materials:

1. Overview analysis and periodical studies of various international organizations such as the Climate Bonds Initiative, The European Environment Agency, the International Capital Market Association and others.
2. Official websites of stock exchanges, where information about green bonds is posted.
3. Studies of foreign and Georgian scientists about the trends and problems of green bond market development.
4. Specific share of green bonds about other market bonds.
5. Scientific publications on the impact of investor sentiment on the price of green bonds, etc.

To achieve the main goal of the research, the following methods of economic analysis were used: The dialectical method, the inevitable requirement of which is to consider economic events in strict cause-and-effect relationships. Our research includes a discussion of the reasons and prerequisites why the introduction and circulation of "green" financial instruments became necessary at the modern stage of human development, and what resulted from the spread of these financial instruments. It is interesting to see what changes are observed in the behaviour of the relevant official agencies, issuers, and investors with the spread of these financial instruments on the financial market. In addition, the cause-and-effect relationship related to the mentioned issues is discussed in the dynamics (2007 - 2024 years).

In the research process, the method of comparative analysis is used, which allows to reveal the similarity of different events. Today, there are many types of bonds circulating in the international financial markets, whether they are government bonds or corporate bonds. There are some similarities as well as differences between corporate bonds themselves, and green bonds among them.

In addition, the method of descriptive analysis was used to determine the factors influencing the growth of the specific share and popularity of "green bonds" in the modern financial market.

Results and Discussion

Modern financial markets have significantly expanded the boundaries of their activity and today are not limited to their classical function, which involves the flow of cash flows directly or indirectly (through intermediaries) from money lenders to borrowers.

The modern financial market is a rather complex and multidimensional economic category, where the economic processes that are carried out at the international level are reflected.

The transition to a green economy model is impossible without the development of a green financing mechanism. The development of the green financial market has become an integral component of the formation of the green economy, which has contributed to the spread of innovative financial instruments at the international level. The main green financial instruments include: "green" bonds; "Green" promotions"; "green" loans; and "Green Insurance".

Definition and Criteria of Green Bonds

At the modern stage of development of financial and economic relations, green financial instruments are gradually gaining popularity, but green bonds remain the leading financial instrument of the green market, due to the scale of its issue and accessibility to a wide range of investors.

As for the definition of "green finance" itself, we find different definitions in various official materials and scientific studies.

As defined on The Global Environment Facility page: Green finance includes climate finance, but is not limited to it. It also refers to a wider range of other environmental objectives, such as industrial pollution control, water sanitation, or biodiversity protection.

We see a different approach to green finance on the website of Lloyds Bankin Ggroup, according to which, What exactly is green financing? Simply, green financing is a loan or investment that supports environmentally friendly activity, such as purchasing environmentally friendly goods and services or building environmentally friendly infrastructure.

The following interpretation of green finance and its purpose can be found on the official website of the European Parliament, according to which green finance and green financing are driving the green transformation of the financial system. Greening finance aims to mainstream climate and environmental factors into the financial system and to improve the identification and management of financial risks related to the climate and the environment.

It can be considered that the formation of the green bond market started in 2007, a year after the European Investment Bank issued climate bonds. The main impetus for the development of the green bond market was the publication of the Green Bond Principles (hereinafter referred to as GBP/Green Bond Principles). The Green Bond Principles (GBP) are voluntary process guidelines that recommend transparency and disclosure and promote integrity in the development of the Green Bond market by clarifying the approach to issuance of a Green Bond. (Official site of the International Capital Market Association). On the website of the mentioned association, we find the following classification of green bonds: 1. Standard Green Use of Proceeds Bond; 2. Green Revenue Bond; 3. Green Project Bond; 4. Secured Green Bond.

Green bonds are one type of ESG bond. They must meet the special standards of the International Capital Markets Association (ICMA) - the Green Bond Principles (GBP). ICMA has also developed separate criteria for social bonds, sustainability bonds, and sustainability-related bonds. The origin of such bonds is related to the spread of the principles of sustainable business development - ESG (environmental, social, and corporate governance).

What is the difference between green finance and sustainable finance? "Sustainable finance integrates environmental, social, and governance (ESG) factors into investment decisions to promote long-term economic growth, social outcomes, and environmental sustainability" Long-term economic growth, social outcomes and environmental sustainability However, green finance and sustainable finance aim to drive positive change by mobilizing capital in projects that promote sustainability and are understood as green projects.

The publication of the first climate bond standard (in the field of wind energy production) and scheme by the international organization Climate Bond Initiative (CBI) at the end of 2011 can be considered the beginning of the standardization of "green" bonds.

However, after a short period, four sectoral (industry) standards were developed and approved in 2012–2015 – for solar energy projects, low carbon, public transport (bus rapid transit), and energy-efficient buildings.

It is important to note that these documents are advisory in nature, however, if a green bond issuer wants to certify it, it is required to undergo an audit by the CBI - Climate Bond Initiative to ensure that the bonds it issues meet predetermined sustainability criteria.

The most popular instrument for financing green projects is green bonds. Bonds are loans to a company at a fixed interest rate. When you buy a bond, you are buying a promise that the company will pay you a coupon rate over the life of the bond until it matures. The main difference between green bonds is the purpose of their issuance and their purpose is to finance green projects. The Green Financing Fund was created to finance green projects. As indicated on its official page - The Green Climate Fund was established by 194 countries party to the UN Framework Convention on Climate Change in 2010. The Green Climate Fund's (GCF) aim is to expand collective human action to respond to climate change. The Fund aims to mobilize funding at scale to invest in low-emission and climate-resilient development on our home planet.

It is interesting how the "green" bonds themselves differ from each other. According to the International Capital Markets Association, there are 4 types of green bonds: 1. Standard Green Use of Proceeds, which is mainly used to finance green projects. 2. Green Revenue Bond, this type of securities can finance or refinance green projects, but the obligations are covered by the revenue streams raised by the issuer, such as taxes or fees. 3. A Green Project Bond is similarly used to finance green projects and its redemption depends on the cash flows of one or more green projects. 4. Green Securitized Bond, this category of bonds usually has more than one asset related to Green Projects that are used as collateral and redeemed using cash flows from these assets.

According to our research, the advantages of green bonds for issuers and investors are as follows:

- Expanding the financing base for issuers by establishing relationships with new investors who value investment directions that contribute to the financing of green projects and sustainable development in general.
- Increasing the awareness of the issuer and its image, to get access to the capital markets, for the issuers to adapt their business to the needs of the market and to operate the business with more social responsibility.
- In the practice of some countries, the issuers of "green" bonds have a greater guarantee of receiving benefits, in which the support and financial benefits provided to them by the state play a big role (it means the tax benefit imposed on the coupon income received from holding the bond).

As for the important advantages for investors:

- the ability to finance environmental projects with transparent and targeted use of funds and to achieve generally established ESG goals;
- By investing in green bonds, investors can support the realization of environmental benefits, which contributes to the creation of a sustainable and ecologically safe environment and guarantees more benefits from holding bonds;

- The main buyers of green bonds are institutional investors - pension and insurance funds, as well as various investment funds. Investors who diversify their financial portfolio, and at the same time prefer financing in long-term and lower-risk bonds.
- For individual investors - the motive for purchasing ESG bonds is the growth of social responsibility and environmental awareness, as well as the expectation that the funds received from the sale of green bonds will be used to improve the environmental condition and social infrastructure that they and future generations will use.

One of the characteristics of "green" bonds is their exceptionally high rating, which issuers see as a competitive advantage. High ratings are typical of both labeled and unlabeled climate bonds, which are linked to

With broad state support for this issue. More generally, the growing diffusion of 'sustainable' and 'socially responsible' investment strategies has led investors to integrate ESG factors into their investment strategies" Doronzo, Siracusa, and Antonelli [2]

International Standards of Green Financing

In general, the green bond system is quite diverse and includes various types of bonds, including corporate and sovereign, secured and direct issue bonds, etc. Sh. There is a division of bonds based on the direction of the use of funds, proposed by the Association of International Capital Markets in the "Principles of Green Bonds".

Initially, the task was much more complex than simply developing tools for environmental impact. Given the current situation, the need to issue and circulate a new class of securities that would be reliable, scalable, and attractive to investors and environmental organizations was on the agenda.

The World Bank Green Bonds is an example of the kind of innovation the World Bank is trying to encourage within this framework. Since 2008, the World Bank has issued approximately USD 19 billion equivalent in Green Bonds through over 220 bonds in 28 currencies. [13]

The first green municipal bond was issued by the state of Massachusetts in June 2013. In October 2013, Gothenburg issued the city's first green bond. It should be noted that the main issuers of municipal green bonds are American states. Local government green bonds continue to grow.

Sometimes climate or environmental projects are financed through the sale of a bond. A decade ago the EIB started issuing special Climate Awareness Bonds, which have come to be called green bonds. It's now a EUR 200 billion market. Sometimes climate or environmental projects are financed by selling bonds. Ten years ago, the EIB began issuing special climate awareness bonds, which became known as green bonds. Now it is a 200-billion-euro market. [Lots of climate questions, one podcast, all the answers. <https://www.eib.org/en/stories/green-finance>]

The European Union is a world leader in this field. In the 2018 Action Plan on Financing Sustainable Growth, the European Commission set out an EU strategy to link sustainability with finance.

Commitment of many countries to the goals of the 2016 Paris Agreement on Climate Change (Paris Agreement on Climate Change). The changes put forward new policy priorities, including increased investment in a green, low-carbon economy and a major shift in resource allocation. At the same time, the European Environment Agency (The European Environment

Agency - EEA), in its 2020 State of the Environment report, recommends increasing investment and overhauling the financial sector to support sustainable projects and businesses. "The OECD

estimates that €6.35 trillion a year will be required globally to meet Paris Agreement goals by 2030. [7]

The Green Climate Fund was established in 2010 by 194 countries participating in the United Nations Framework Convention on Climate Change. The goal of the Green Climate Fund (GCF) is to scale up collective human action to respond to climate change. The fund aims to mobilize large-scale financing to invest in low-emission and climate-resilient development for our planet.

International Methods of Green Financing.

For the development of the green bond market, both at the national and global level, international cooperation plays an especially important role.

For the issuers of "green" bonds, the existence of generally accepted standards means a reduction in the costs of preparing the issue and placing the bonds, in particular, to prove their "green" character. In addition, compliance with generally accepted standards allows issuers to expect higher credit ratings and cheaper borrowing.

For investors, compliance with international green bond standards significantly reduces the risk of default. It should be noted that institutional investors (large insurance and pension funds, various investment companies) have shown great activity in establishing international cooperation for the development of green bond standards.

In 2016, the G20 established the Green Finance Study Group GFSG, which focused on five main areas: greening bond markets; greening of the banking system; greening of institutional investments; Risk analysis, and progress measurement. The group developed the use of Environmental Risk Analysis (ERA) and publicly available data to inform financial risk analysis and decision-making.

"Green financing" stands for "financing the green economy" or "financing the green transition", and corresponds to the aim of increasing the level of financial flows towards green investment. "Green finance" means "green economy finance" or "green transition finance" and corresponds to the objective of increasing the level of financial flows towards green investments. [4]

It is important to note that green financing projects cannot be implemented at the global level without the help and efforts of various international organizations in developed or developing countries.

Green, social, sustainability, and sustainability-linked (GSSS) bonds are key to ensuring capital is channeled from international investors to developing countries where it is needed most. [14]

In Georgia, the issues of green financing have acquired more relevance in the recent period. Accelerating Georgia's energy efficiency efforts, the EBRD has established a new Green Economy Financing Facility (GEFF) for the country. The bank also awards the best energy efficiency and renewable energy projects financed in the field of energy credit. It is co-financed by the Green Climate Fund (GCF) and supported by the Austrian Federal Ministry of Finance.

"The EBRD is a leading institutional investor in Georgia. Since the start of its operations in the country, the Bank has invested over €3.5 billion in 237 projects in the financial, corporate, infrastructure and energy sectors, with 89 percent of these investments in the private sector. [1]

EU4Environment has launched a new green bond project. Green bonds can raise additional resources for the transition to a sustainable low-carbon economy and can become an important source of financing for green investments. Green climate bonds are similar to conventional bonds, but the proceeds are specifically earmarked for green investments: clean/renewable energy,

energy efficiency, reduction of air, water and soil pollution, waste recycling and recycling, environmentally friendly transportation.

"There are several potential benefits from tapping sovereign climate bond financing, but also limitations and challenges. First, the growing popularity of green bonds may allow governments to issue bonds with longer maturities (given the longer horizon of green projects) and at a lower borrowing cost relative to plain vanilla bonds (the "geranium"). [3]

For more than 50 years, ICMA - International Capital Market Association - and its members have worked together to develop international capital and securities markets, developing rules, principles, and guidelines that have laid the foundation for their successful operation.

According to ICMA's recommendation, the issuance of green bonds should be related to the issuer's capital investment in the following areas:

energy efficiency, renewable energy, green buildings, biodiversity, water management, climate adaptation, and more.

"It is recommended that issuers communicate clearly to investors the rationale and process according to which the KPI(s) have been selected and how the KPI(s) fit into their sustainability strategy, or, sovereign issuers, their sustainable development policy" [9]

Evolution of green bond issuance (USD bn)

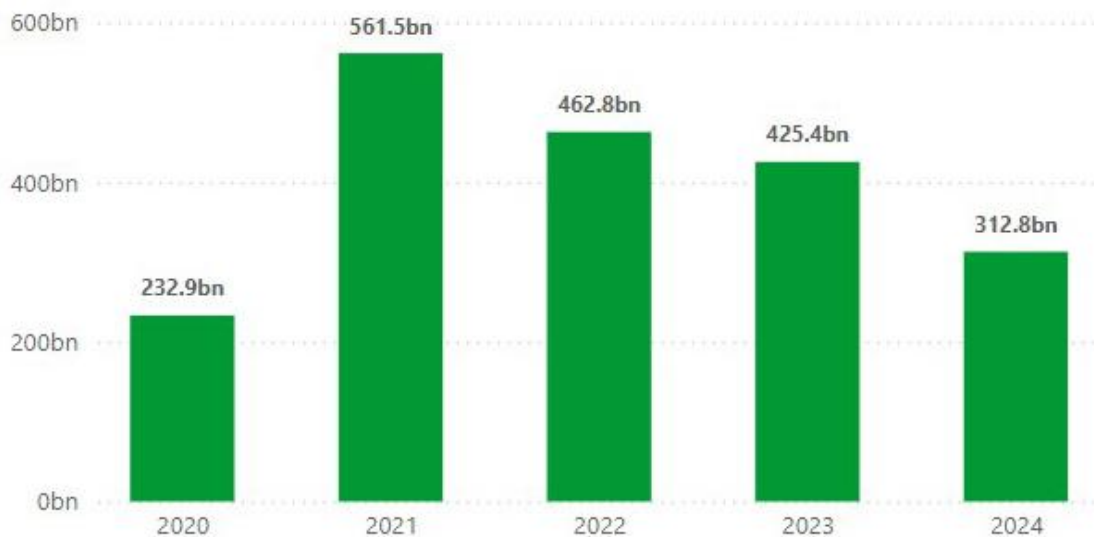


Figure 1. Sustainable Bond Market Date

Source: <https://www.icmagroup.org/sustainable-finance/sustainable-bonds-database/>

As can be seen from the presented diagram, the volume of issuance of green bonds reached the highest level in 2021, and already today its volume has decreased by almost 45%.

Green bond issuance per region (USD bn)

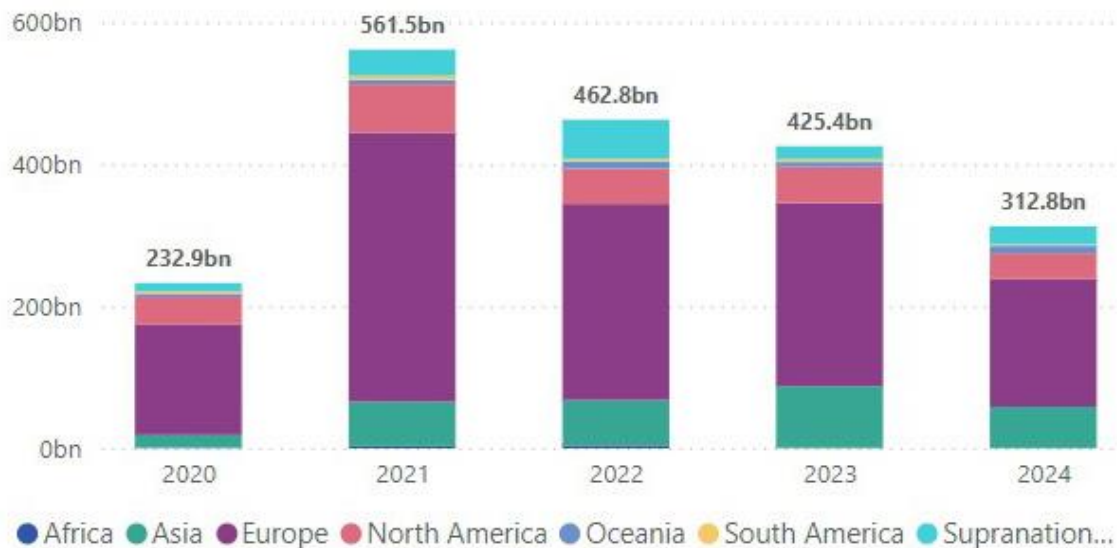


Figure 2. Sustainable Bond Market Data

Source: <https://www.icmagroup.org/sustainable-finance/sustainable-bonds-database/>

As can be seen from the Figure 2, European countries and North America play the role of leaders in issuing green bonds.

As it is known, any financial instrument carries a certain risk, as for green bonds, we have formulated the classification of related risks as follows:

- Climate-related risks are increasing as global warming continues on the planet. According to the potential global warming scenarios, there will be a significant difference in the future in different geographical points and sectors of the world.
- low degree of liquidity, which is related to the long period of circulation of green bonds;
- low value of the profit from owning green bonds, which is related to their changing demand from investors in the capital market;
- Non-uniform approach to the definition of a green bond, the existence of green bond issuers on the market with an unscrupulous reputation for money laundering.

However, the GBP recommends that investors, underwriters, and market agents have full information regarding the characteristics of bonds.

"The GBP recommends a clear process and disclosure for issuers, which investors, banks, underwriters, arrangers, placement agents, and others may use to understand the characteristics of any given Green Bond". The GBP recommends that issuers have a clear disclosure process that investors, banks, underwriters, arrangers, placement agents, and others can use to understand the characteristics of any given green bond [15]

Conclusions

The future of the financial sector at the global level is unimaginable without green financing. Green finance refers to investments that promote environmental security and environmental

improvement. It involves the joint actions of public and private entities, including financial institutions, governments, companies, non-profit organizations and others. This funding covers all kinds of activities and initiatives, such as the development, implementation, and promotion of projects that can have an impact on sustainable development.

The specificity of green bonds is manifested not only in obtaining the expected benefit (coupon income) from its ownership but also in achieving the goals of improving the environment and solving global problems. However, if such goals are relevant for states and international institutions, the amount of income obtained as a result of issuing green bonds is more important for issuers.

Green bonds have grown in popularity largely due to investors seeking socially responsible investments rather than the better risk and return potential of conventional bonds. As we mentioned, green bonds operate in the same way as conventional bonds.

However, green bonds may offer tax benefits (depending on the issuer and jurisdiction) such as tax exemptions and tax credits. This is done to attract investors to finance projects that benefit the environment and/or climate.

The transition to a green economy is quite a difficult and at the same time feasible process. Institutional transformation, as a way of economic paradigm reform, as well as joint efforts of developed and developing countries and effective use of green finance to finance green projects, is the cornerstone of ensuring sustainable development.

Conclusions should fully and specifically reflect the research results, correspond to the purpose and title of the article, while verbatim duplication of the text in the abstract is unacceptable. It is important to indicate the prospects for further research on the selected topic.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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AN EVALUATION OF THE EFFICIENCY OF THE USE OF PRODUCTION POTENTIAL IN MODERN ECONOMIC CONDITIONS

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ABSTRACT

Production potential is the maximum production capacity of the factory. enterprises must be aware of this potential and take advantage of it by incorporating it into their labor and capital decisions to meet demand growth. This information helps to make the right management and internal decisions and increase the efficiency of production. In the conditions of the market economy, the main indicator of productivity is the increase of profit and costs per resource unit. Technical and organizational measures increase the volume of output, reduce costs and increase labor productivity. Economic efficiency is determined by the ratio of the product received to the labor used for production. Evaluation of economic efficiency is carried out on three groups of indicators: volume indicators (quantity of production), final results (quality of production) and social results (living standard of the population and impact on the environment). The quality of production capacity and the application of innovations serve the enterprise's goals and improve economic performance by creating new products.

Keywords: Efficiency of production capacity, economic efficiency, types of efficiency, market economy, quality of production, volume indicators, final indicators, indicators of social results, measurement of efficiency.

Introduction

In the most general terms, by the sector's potential, we understand the set of strategic resources at its disposal to be able to function normally under any circumstances.[1]

Not all resources available to a business can be considered "strategic". Resources classified as "strategic" are resources whose quantity and composition can be changed by the company through strategic choices. Therefore, "potential" refers to the possibilities that must be achieved to achieve this or that goal.[6]

These capabilities can be in the form of money, information, raw materials, technology, methods or human resources. Production capacity is the maximum output that a factory or manufacturing facility can produce. In addition to knowing how much capacity a factory has, it is also important to know how much of that capacity is being used and how much is remaining at any given time. For example, if a manufacturing plant wants to fulfill larger orders in larger quantities, decision makers need to know whether the operation can adequately meet the increased demand.[4]

In addition, manufacturers use production capacity to inform capital decisions, including the use of machinery, equipment, and facilities, as well as labor. Therefore, it is important for manufacturers to know the production potential of their operations, as it informs both administrative and business decisions and allows the business to maximize production efficiency. In the conditions of the market economy, the nature and characteristics, criteria, level and requirements of production efficiency in enterprises are characterized by changes. In other words,

since profitability is the basis of market economy and entrepreneurship, from this point of view, as the main criterion of economic efficiency, the element of increasing the profit obtained per unit of funds and expenses is improved under the condition of improving the quality of products and services. comes to the fore. On the other hand, one of the most important conditions of this system is to ensure the competitiveness of manufactured products and services in domestic and foreign markets.[3]

Aim

The aim of this study is to assess the efficiency of production potential in modern economic conditions and the factors that play an important role in this process, paying attention to the correct assessment of production potential, its efficient use, and the measurement of various factors, including various aspects. productivity indicators, product quality, social outcomes and environmental impact. These studies support the importance of evaluating productivity based on different indicators.

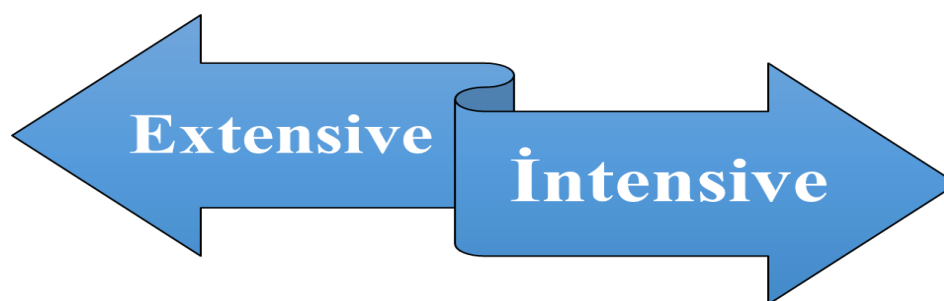
Method

Economic growth and efficiency, which indicates the level of satisfaction of needs at the expense of the produced product, if on the one hand it raises the standard of living of the population, on the other hand, it directly depends on the content and conditions of the standard of living of the population. labour. Efficiency - indicates the economic result in absolute measure obtained in various sectors of the economy or in each enterprise separately due to the implementation of measures aimed at increasing the efficiency of public production. Therefore, the result can only have an economic content, because the improvement of production from a technical organizational point of view leads to the improvement of economic indicators such as increasing the product, lowering its cost, increasing labor productivity. The economic efficiency of the implementation of any organizational-technical measure is defined as the ratio of the economic benefit received during a certain time unit (year) to the amount of living and materialized labor involved in its production. In other words, efficiency is relative; where the effect is compared to the costs that led to its creation. Without efficiency, of course, there can be no question of efficiency.[3]

The transition of the country's economy to market relations requires a new approach to economic efficiency, new rules and methods of its calculation. Thus, the market mechanism requires the distribution of the limited production resources at the disposal of the society in such a way that it is possible to ensure the maximum satisfaction of the demand.[5]

Effective use of limited production resources requires the fulfillment of 2 conditions - the correct distribution of resources and increasing the economic efficiency of production by using them economically. In order to correctly evaluate the efficiency of production, its criteria and indicators should be based on precise scientific-theoretical and methodological grounds. It should be noted that the efficiency of production, on the one hand, implies the intensification of the effective use of production resources, on the other hand, it requires a full accounting of incurred costs - with the aim of constantly reducing them; objective assessment of production efficiency, in other words, correct determination of the ratio between the effect of an economic measure and the costs incurred for its implementation, ultimately ensures the management of the reproduction process.

It is appropriate to reflect the classification of factors affecting the efficiency of production and economic activity as follows.

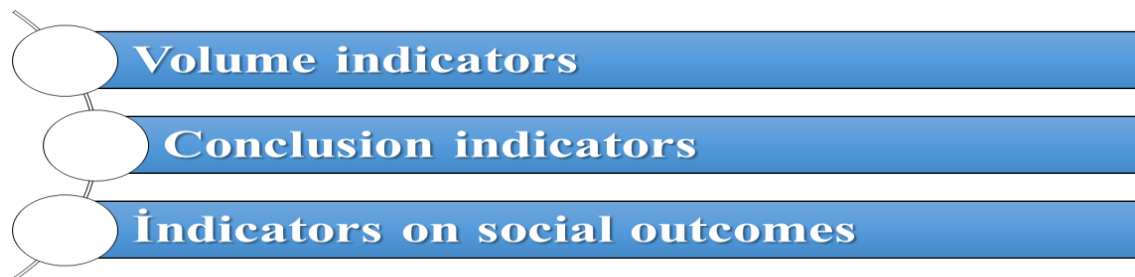


Picture 1. Classification of factors affecting the efficiency of the economic entity.[3]

Extensive factors are factors aimed at increasing the number of resources to expand the activity of the economic entity. The purpose of these factors is to increase production and productivity, but this increase is not achieved by more efficient use of resources, but only by increasing their number. For example, increasing labor resources is increasing productivity by hiring more labor. This method is especially widespread in agriculture and industry. Attracting additional workers leads to an increase in production capacity. For example, a factory can increase production by hiring more workers. However, the effectiveness of this method can be limited by the decrease in productivity of each additional worker. Land expansion is the increase in production through the use or acquisition of additional land. This method is widely used in agriculture, animal husbandry and farming. For example, farmers can increase crop production by planting more land. However, land expansion requires additional resources and labor. Increasing capital resources increases production by obtaining more financing or buying more equipment. This method is widely used in industrial and manufacturing sectors. For example, an enterprise can increase production capacity by purchasing additional equipment and technology. However, raising capital resources may require high financing and may not always be cost-effective. Increasing production by using more energy and raw material resources. This method is widely used in industrial enterprises and factories. For example, a factory can increase production by providing more raw materials and using more energy. However, the use of additional resources may incur additional costs, and resource constraints may limit the effectiveness of this method. Increase productivity by using more machines, equipment and technologies. This method is widely used in industrial and manufacturing fields. For example, a factory can increase production capacity by purchasing more technological equipment. However, if additional equipment is not used effectively, it may require high investment costs and reduce efficiency. The use of extensive factors can lead to an increase in production and productivity in a short period of time. But for long-term efficiency, it is important to support these methods with intensive factors. Intensive factors include technological innovations, increased labor productivity, improved quality, and more efficient use of resources. Intensive impact factors are mainly possible because of increased efforts of employees and subjects related to the improvement of the activity of the economic entity, and these factors are reflected in the system of various efficiency indicators. Intensive factors characterize the production activity of the economic entity either by its nature or by its evaluation characteristics. Quantitative indicators in terms of nature and value also play an important role. Relative, percentage and ratio indicators can also be used in their determination. Intensive impact factors demonstrate the level of efficiency of the economic entity's activity, and in many cases, they are also taken as the basis of qualitative factors and indicators of the entity's activity. A balanced use of extensive and intensive factors will ensure the long-term success of the economic entity.[3]

The coefficient of efficiency is distinguished as general (absolute) and comparative (relative). Calculation of total efficiency is necessary in terms of analysis and assessment of efficiency and general economic results at different levels of the economy in a specific period to compare the level of efficiency within economic entities and regions. Comparative efficiency is determined to justify the adoption of production, economic, technical and organizational decisions, as well as to choose the most optimal and alternative options in this area. Such a choice is made because of the quality of efficiency, the efficiency coefficient of additional capital investment or the calculation of the repayment period, as well as the comparison of various options of the system of technical and economic indicators.[3]

Real information about the level of efficiency is closely related to its expression form and classification. As a rule, three groups of indicators are used in the evaluation of economic efficiency:



Picture 1. Indicators in the assessment of economic efficiency.[3].

Basic indicators expressing the natural or value indicators of production and provided services are applied to the volume indicators of economic efficiency. The natural form of the volume indicators is the volume of the manufactured product, the total commodity product, the volume of construction and installation works, and the natural normative value of the processed product, etc. As a rule, the final productivity indicators reflect the state of the quality structure of production, the satisfaction of market demand and the final results of economic activity at different levels of management. Relevant indicators include national and net income, the level of national output, economic profit, the amount of cost savings, the volume of product sales at current prices, the utilization of productive capacities, and the quality of products and services. In many cases, volume indicators are also characterized as quantitative indicators of production activity. This factor is often used when calculating productivity indicators that are differentiated from related indicators.

Social consequences are of particular importance in the assessment of production efficiency. Thus, the priority of the human factor in economic development, the expression of the results of production and economic activity in accordance with the social goals of the society and the labor collective is reflected in the social indicators of productivity. The interests of the economic subject are closely related to social results, so when production results increase, it has a positive effect on social results, on the contrary, when production results decrease, this factor has a negative effect on social results. Social outcomes include the following indicators:

- Raising the standard of living of the population (increase of wages, real incomes, minimum living wage, social and communal needs of the population and standard of living);

- The efficiency of using leisure time and working conditions (reducing accidents in production, preventing the flow of specialized personnel, increasing the employment level of the population, etc.)

- Improvement of the ecological environment, impact of the production process on the environment. [3]

It should be noted that the following types of advantages are distinguished from the development of scientific and technical progress and the application of innovations to production in enterprises:

Types of efficiency	Factors, indicators
1. Economic	Taking into account all types of costs in the indicators of the result and value declaration determined by the application of the innovation
2. Scientific and technical	Innovation, simplicity, utility, aesthetics, compactness
3. Finance	Indicators reflecting financial results
4. Resource	Innovation on the volume of production or other indicators that reflect the impact of the type of resource on consumption
5. Social	Indicators that take into account the social consequences of the introduction of innovations
6. Ecological	Considering the impact of innovation on environmental indicators: Noise, electromagnetic field, lighting (view comfort), vibration.

Table 1. Types of productivity received in production.[3].

In today's era, it is important to measure the efficiency of the production potential to determine its efficiency. These are some fundamental methods for calculating production efficiency as well as basic production efficiency calculations.

1. Overall Equipment Effectiveness (OEE)

Equipment utilization efficiency is evaluated using a comprehensive metric called Overall Equipment Effectiveness (OEE), which considers performance, availability, and quality. It measures the difference between actual production speed and the typical pace at which products are released, which helps pinpoint areas that could be improved, such as cycle time optimization and downtime reduction. It is calculated as follows:

$$OEE = \text{Performance} \times \text{Availability} \times \text{Quality}$$

2. Cycle time

Cycle time is a measure of how long it takes for a manufacturing process to go through a cycle from start to finish. It demonstrates how productive the production process is and allows you to see areas that need more productivity as well as bottlenecks.[9]

The cycle time is calculated as follows:

$\text{Cycle Time} = \text{Real Run Time} / \text{Number of Units Produced}$

3. Yield

The quantity of high-quality units produced relative to the total number of units produced is known as productivity.[7]

It helps identify wasteful areas such as scrap or rework and draws attention to areas where quality control procedures can be strengthened.

This is calculated as follows:

$\text{Yield} = (\text{Number of Good Units Produced} / \text{Total Number of Units Produced}) \times 100\%$

4. Unit cost

A basic statistic known as unit cost is used to determine the average total cost per unit of production. Unit cost monitoring helps you find cost-saving strategies, provides information on how resources are allocated over time, and allows you to change the pricing strategies used by the business.[9]

The unit cost is calculated as follows:

$\text{Unit Cost} = \text{Total Manufacturing Cost} / \text{Number of Units Produced}$

Direct material costs, direct labor, and manufacturing overhead make up the three components of the manufacturing accounting statistic known as total manufacturing costs.[9]

The quality and perfection of the enterprise's production potential is determined by the creation of new products, and its elements must be adapted to the requirements of the manufactured product from a technical and economic point of view. The production potential can fulfill its purpose when the composition and characteristics of its elements correspond to and are determined by the technical parameters of the manufactured product. Only in this case, can all elements of the production potential serve the common goal facing the enterprise.

Conclusion

In conclusion, companies seeking to maximize their output and maintain their competitiveness must assess the efficiency of their production capacity in the current economic environment. This study highlights how important it is to understand the broad and intensive aspects that affect production efficiency. While increasing resource quantities are a broad example of a factor that can temporarily increase production, sustained long-term success requires strengthening intensive variables such as technical innovation and better resource utilization.[8]

The analysis of various indicators is necessary to evaluate economic efficiency, such as volume indicators (quantity of production), final results (quality of production) and social results (impact on the environment and living standards). By focusing on these factors, businesses can make well-informed decisions that improve economic outcomes and productivity. In addition, increasing production capacity depends mainly on applied innovations. By developing new ingredients and simplifying current procedures, innovation not only improves the quality of the final product, but also improves economic and social performance. Enterprises are ensured to be able to develop with the support of continuous innovation by using the wide and intensive variables in a balanced manner in competitive market conditions.

In conclusion, companies must effectively evaluate and use production capabilities to achieve optimal economic performance and sustainability in the current economic environment. This can be achieved by having a thorough knowledge of many efficient variables and indicators.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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CORRELATION OF ROUTINE INFLAMMATORY MARKERS WITH IL-6, STREM-1, AND APACHE-II: A STUDY ON SEPSIS AND SEPTIC SHOCK

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ABSTRACT

Sepsis and septic shock due to gram-positive microorganisms are major concerns in intensive care units, as they significantly contribute to patient mortality. Traditional diagnostic markers like C-reactive protein (CRP) and procalcitonin (PCT) often fail to provide the necessary sensitivity and specificity required for effective early diagnosis and prognosis. Consequently, there is an ongoing search for more reliable biomarkers. Recent research has focused on interleukin-6 (IL-6) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) as potential indicators that could enhance the diagnostic and prognostic capabilities in the management of sepsis and septic shock.

The retrospective cohort study included 236 patients hospitalized for sepsis between October 2022 and August 2023. Bacteriological examination of blood revealed Gram-positive bacteria in 24 patients. Serum concentrations of IL-6 and lactate were determined using the electrochemiluminescence immunoassay (ECLIA) method, while The enzyme-linked immunosorbent assay (ELISA) technique was used to determine the amounts of the sTREM-1 biomarker.

Study results showed that the probability of lethality is accurately predicted by logarithm of sTREM-1 and can serve as a clinical marker. After applying the logarithmic transformation, the correlation coefficient of procalcitonin and CRP with Log10(sTREM-1) decreased, indicating that they are regulated by different mechanisms. No association was observed between leukocytes and sTREM-1.

In conclusion, Log10(sTREM-1), Log10(Lactate), and Log10(Interleukin) levels significantly differed between APACHE-II < 50% and APACHE-II ≥ 50% groups, indicating that these characteristics are strong predictors of lethality. Conversely, CRP and PCT are more direct markers of disease severity.

Introduction

Sepsis and the systemic inflammatory response syndrome (SIRS) are two of the leading causes of mortality in intensive care patients. Early diagnosis and immediate initiation of appropriate treatment significantly impact disease outcomes. In 1992, the Society for Critical Care Medicine (SCCM) introduced the diagnosis of SIRS and established definitions for sepsis, severe sepsis,

and septic shock [1]. It has been found that SIRS criteria do not provide enough specificity in clinical practice [2]. The third worldwide consensus definition of sepsis and septic shock is represented by the current guidelines, which were released in 2016. The prior definitions' limitations included an overemphasis on inflammation, a misleading model that suggested sepsis progresses from mild septic shock to severe septic shock, and insufficient SIRS criteria specificity and sensitivity. [3].

Additionally, procalcitonin (PCT) and C-reactive protein (CRP), two markers frequently used in diagnosis, are insufficiently sensitive and specific. [4]. To give patients with suspected SIRS and sepsis more helpful diagnostic and prognostic tools, novel indicators of acute inflammation are being studied. Among these are interleukin-6 (IL-6) and sTREM-1 (soluble triggering receptor expressed on myeloid cells-1).

The study aimed to assess IL-6 and sTREM-1's diagnostic and prognostic value in correlation with routinely used markers such as CRP, lactate, and PCT in sepsis and septic shock induced by gram-positive microorganisms. Additionally, we aimed to identify markers that are directly and causally related to CRP, PCT, and APACHE-II scores, with the goal of finding a high probability predictor of lethality in septic shock.

Materials & Methods

The study was conducted on 24 patients hospitalized with sepsis in the intensive care unit of the First University Clinic of TSU, who were bacteriologically tested for gram-positive bacteria, from October 2022 to August 2023. Exclusion criteria included patients under 18 years of age, those with a history of current chemotherapy, those on current corticosteroid therapy, or those with HIV, hepatitis B (HBV), or hepatitis C (HCV).

SIRS was diagnosed when, in addition to fever (body temperature greater than 38.5°C), at least one of the following three criteria was met: 1. tachycardia, 2. tachypnea, 3. White blood cell count above or below normal for age, or neutrophils <10% more than normal.

An arterial blood sample was drawn and centrifuged for 15 minutes at 3,000 rpm for separation of serum at the time of initial laboratory evaluation for sepsis. The sera were stored at -70°C until analysis. Measurements of IL-6, sTREM-1, PCT, CRP, and lactate were performed on all patients on days 0, 1, 2, 3, and 5. Serum Lactate and IL-6 levels were measured in duplicate in each sample using the electrochemiluminescence method on a fully automated analyzer (Cobas e411, Elecsys IL). The concentration of sTREM-1 was determined using the enzyme-linked immunosorbent assay (ELISA) method (Quantikine ELISA, Human sTREM-1 ELISA Kit, Fine Test, Wuhan Fine Biotech; lower detection limit 3.88 and 0.7 pg/ml, respectively), according to the manufacturer's instructions. The PCT level (upper reference range 0.05 ng/ml in healthy subjects) was analyzed via an enzyme-linked fluorescent immunoassay for the quantitative measurement of PCT. The minimum detection thresholds were 18.75 pg/ml for sTREM-1 and 1.5 pg/ml for IL-6.

Blood samples for blood culture were aspirated after thorough disinfection of the aspiration site and added directly to the culture medium (10 mL whole blood in 84 mL brain-heart infusion broth). Blood samples were collected from different veins at the peak of fever, placed into two blood signal bottles (OXOID Signal, Thermo Fisher), and incubated at 37°C for 10 days. One blood culture bottle was incubated anaerobically. The organisms isolated were identified down to the species level using the API identification system (biomerieux, France) according to the manufacturer's instructions. Presence of infection was defined according to the clinical and

microbiological criteria of the CDC. Blood culture-positive bacteremia was defined as the growth of bacteria with recognized pathogenic capacity in one blood culture or the growth of common skin pathogens (i.e., coagulase-negative *Staphylococcus* spp., diphtheroids, *Bacillus* spp., *Propionibacterium* spp., or micrococci) in two blood cultures.

For statistical analysis and data visualization, Pearson's correlation coefficient (Pearson r) and linear regression methods were used to explore possible causal relationships between the characteristics. Statistical confidence was assessed using the p -value. Analysis of variance (ANOVA, Fisher F test) was employed to determine the statistical significance of differences between study groups. Calculations and visualizations were performed using the statistical software SPSS-19.

The study was approved by the Institutional Review Board (IRB) of TSMU Biomedical Research Ethics Committee with IRB number N8-2021/92. Informed written consent was obtained from all patients or first-degree relatives for illiterate patients after oral commitment. The study complied with the Declaration of Helsinki.

Results

The APACHE-II / sTREM-1 scattergram was analyzed to reveal the functional nature of the possible causal relationship between APACHE-II and sTREM-1. Figure 1 clearly shows a logarithmic relationship between APACHE-II and sTREM-1. This was confirmed by the fact that the regression of APACHE-II on $\text{Log}_{10}(\text{sTREM-1})$ is described with high accuracy by a linear function: $\text{APACHE-II} = a + b * \text{Log}_{10}(\text{sTREM-1})$, where $a = 8.325$ (std. Err = 3.310, $p = 0.015$); $b = 26.259$ (std. Err = 1.58, $p < 0.001$). The linear correlation coefficient between APACHE-II and $\text{Log}_{10}(\text{sTREM-1})$ is $r = 0.922$, $p < 0.001$ (Figure 2).

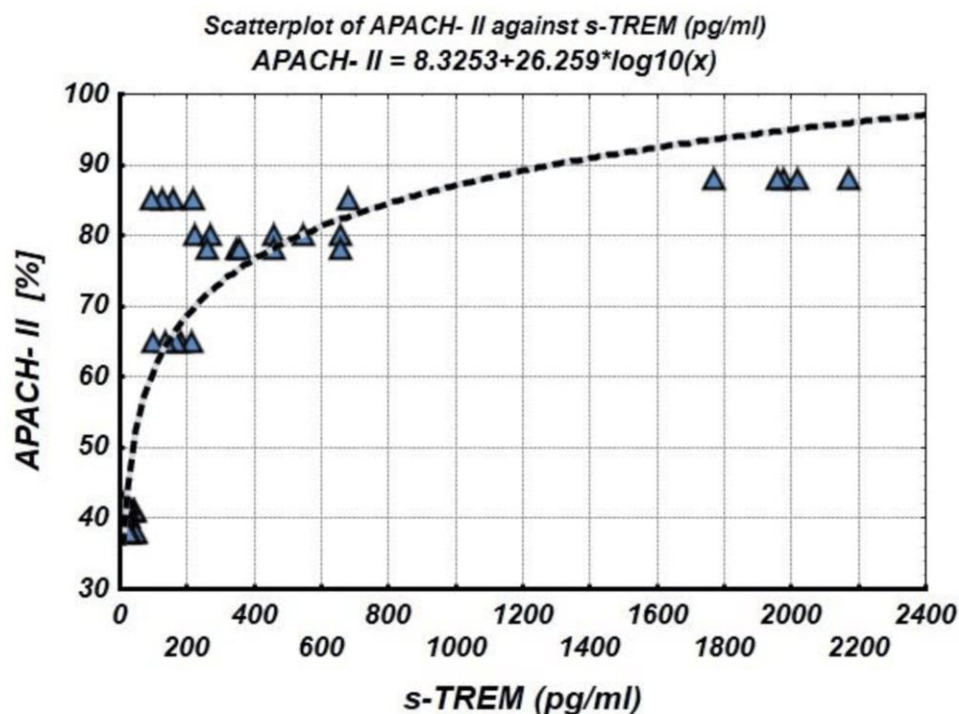


Figure 1: APACHE-II / sTREM-1 Scattergram and logarithmic function interpolation curve.

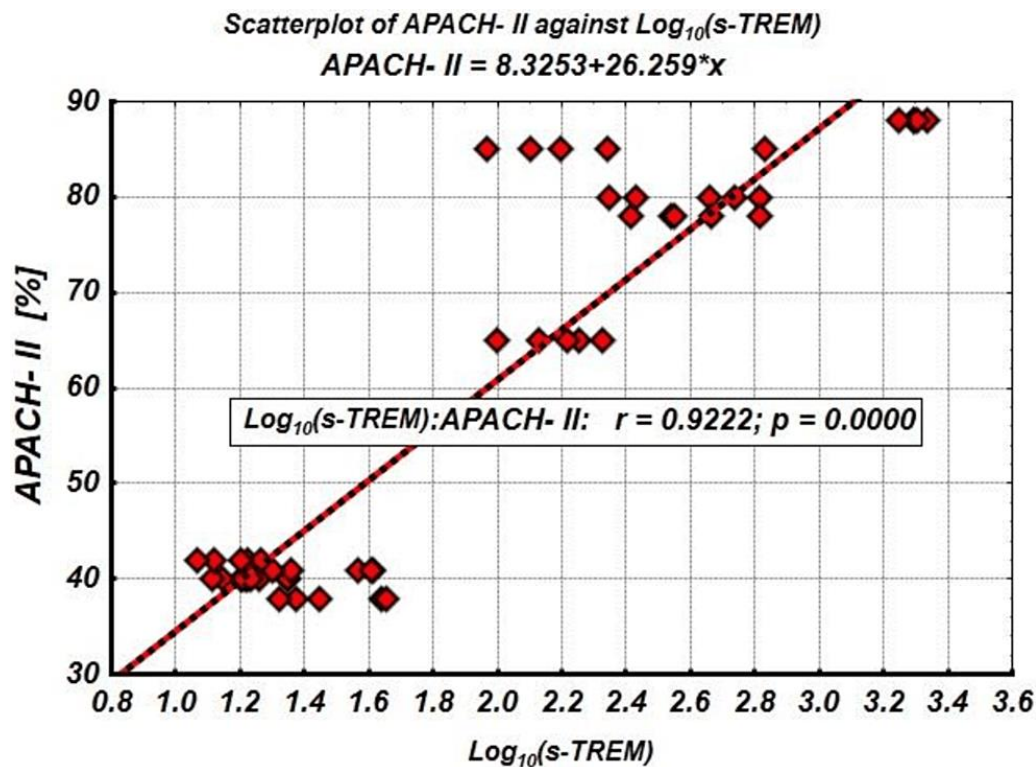


Figure 2: APACHE-II / $\text{Log}_{10}(\text{sTREM-1})$ scattergram and linear regression

The revealed pattern indicates that with the increase of sTREM-1, the value of APACHE-II increases sharply at first, and then a saturation effect becomes somewhat evident. This observation, on the one hand, reflects the potential of sTREM-1 in elucidating the role of this biomarker in the development of sepsis, and on the other hand, highlights $\text{Log}_{10}(\text{sTREM-1})$ as a highly informative predictor of sepsis progression.

Based on the results obtained, we considered it appropriate to analyze the possible causal relationship between $\text{Log}_{10}(\text{sTREM-1})$ and other research parameters. Table 1 presents the correlations between $\text{Log}_{10}(\text{sTREM-1})$ and other research parameters along with their statistical confidence.

As shown in Table 1, all the studied characteristics except leukocytes are reliably correlated with $\text{Log}_{10}(\text{sTREM-1})$. However, two groups of characteristics were identified: 1) Interleukin 6 and Lactate: The degree of correlation with $\text{Log}_{10}(\text{sTREM-1})$ increases after logarithmic transformation (Figure 3A), and 2) sTREM-1 and CRP: The degree of correlation with $\text{Log}_{10}(\text{sTREM-1})$ also increases after logarithmic transformation (Figure 3B).

Variables	Log 10 (s-TREM)	
	Correlation (r)	p-value
$\text{Log}_{10}(\text{s-TREM})$	$r=1.00$	
Leucocyte's	$r=0.152$	$p=0.295$
Procalcitonin	$r=0.722$	$p<0.001$
$\text{Log}_{10}(\text{Procalcitonin})$	$r=0.680$	$p<0.001$

Interleukin	r=0.630	p<0.001
Log10(Interleukin)	r=0.857	p<0.001
CRP [mg/L]	r=0.661	p<0.001
Log10(CRP)	r=0.493	p<0.001
Lactate [mmol/L]	r=0.750	p<0.001
Log10(Lactate)	r=0.851	p<0.001
Lactate [mmol/L]	r=0.750	p<0.001
Log10(Lactate)	r=0.851	p<0.001

Table 1: Correlations Variables / Log10(sTREM-1); Marked correlations are significant at $p < 0.050$.

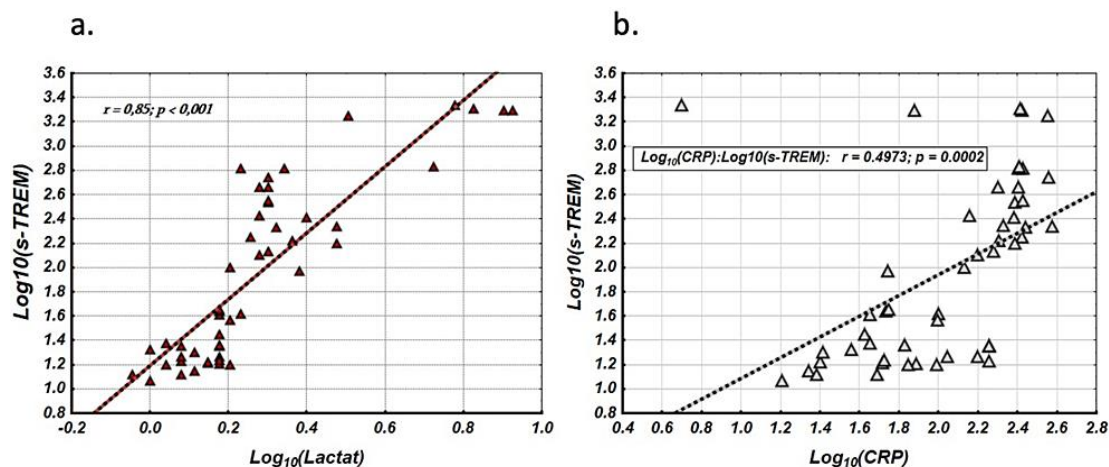


Figure 3: a. Log10(sTREM-1) / Log10(Lactate) scatterplot and linear regression. b. Log10(sTREM-1) / Log10(CRP) scatterplot and linear regression.

The obtained results likely indicate that the regulatory mechanisms of sTREM-1, lactate, and interleukin are more causally related to the risk of developing sepsis than the regulatory mechanisms of PCT and CRP (Table 1).

To further clarify the identified patterns and determine the informative value of the characteristics in predicting the development of sepsis, we analyzed the dynamics of the logarithms of these characteristics on the 0th, 1st, 3rd, and 5th days of observation. This analysis was conducted separately for patients with a favorable APACHE-II prognosis (APACHE-II < 50%) and an unfavorable prognosis (APACHE-II \geq 50%).

As can be seen in Figure 4, the levels of Log10(sTREM-1), Log10(lactate), and Log10(interleukin 6) in the favorable prognosis group (APACHE-II < 50%) from day 0 of observation are significantly higher than those in the unfavorable prognosis group (APACHE-II \geq 50%). Specifically, the differences are as follows: Log10(sTREM-1) with $F = 47.24$, $p < 0.001$; Log10(lactate) with $F = 6.10$, $p = 0.030$; and Log10(interleukin) with $F = 11.35$, $p = 0.009$. At the same time, the dynamics of changes in these characteristics do not reliably differ during the observation period.

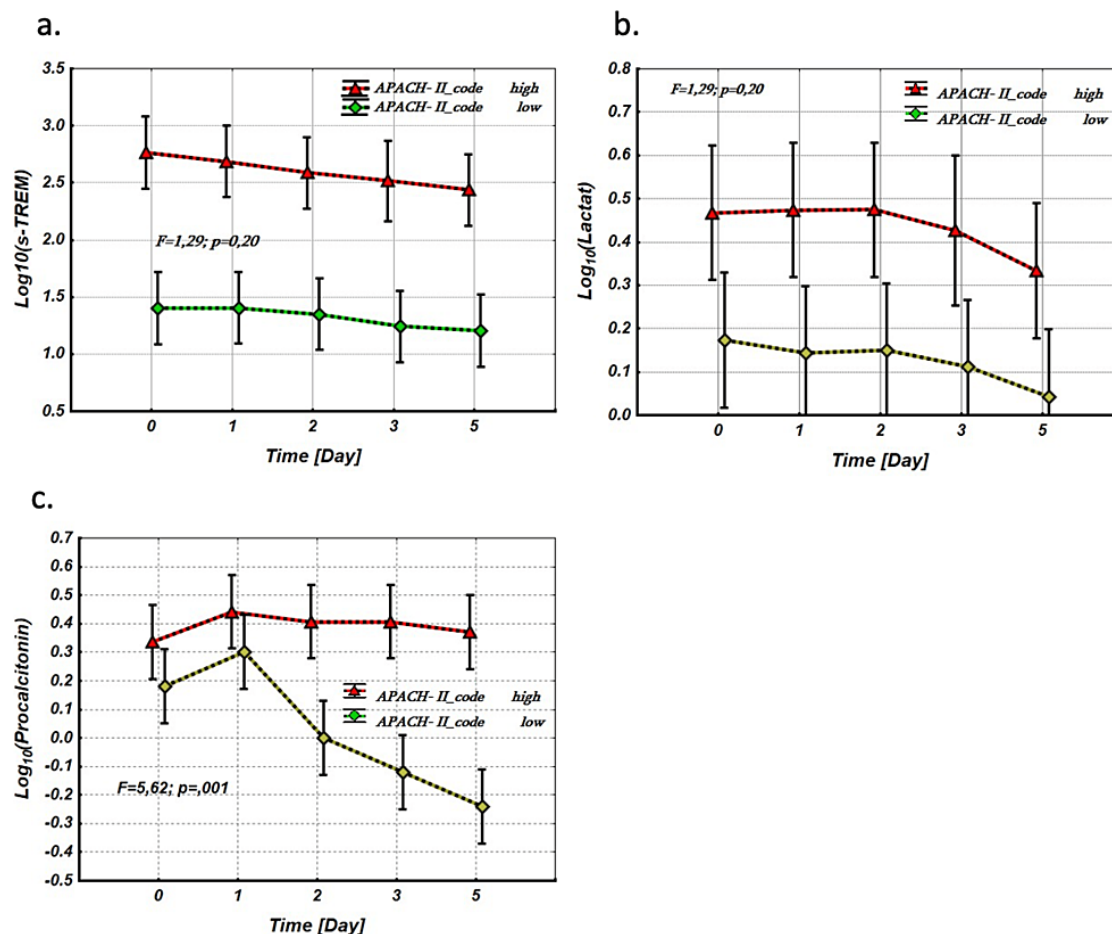


Figure 4: Dynamics of a. Log₁₀(sTREM-1), b. Log₁₀(Lactate), and c. Log₁₀(Interleukin) levels over a period of 5 days in patients grouped by APACHE-II scores, indicating high (APACHE-II $\geq 50\%$) and low (APACHE-II $< 50\%$) risk of lethality.

As for CRP and procalcitonin, the initial levels on day 0 are not significantly different between the groups (CRP: $F = 0.01$, $p = 0.933$; Procalcitonin: $F = 3.627$, $p = 0.093$). However, the dynamics of their level changes are significantly different between the APACHE-II $< 50\%$ and APACHE-II $\geq 50\%$ groups. This indicates that CRP and procalcitonin levels should be considered markers of the severity of the disease (Figure 5).

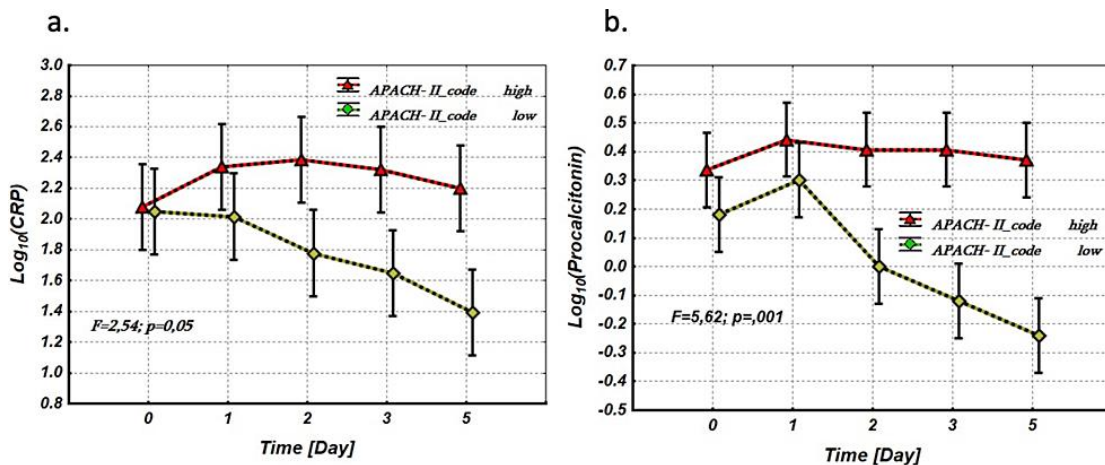


Figure 5: Dynamics of a. Log10(CRP) and b. Log10(Procalcitonin) levels over 5 days in patients grouped by APACHE-II scores, indicating high (APACHE-II $\geq 50\%$) and low (APACHE-II $< 50\%$) risk of lethality.

Discussion

Sepsis is a multifaceted process that includes humoral and cell-mediated reactions, inflammatory and anti-inflammatory processes, and changes to the circulatory system. When evaluating the severity and prognosis of sepsis, clinical findings are not very useful. Biomarkers can be useful for sepsis care due to different reasons, including prognostic assessment, Early detection, to stage and monitor treatment response. [5] Although the most accurate method, microbiological diagnosis of sepsis has low sensitivity and delayed results. [5]

In this study, according to the blood-culture results, we collected data of the patients with gram positive sepsis. Interleukin-6 (IL-6) is a key pro-inflammatory cytokine with a notable impact on innate immune cells. It enhances the cytotoxicity of NK cells and boosts the responsiveness of monocytes and neutrophils, while also influencing the humoral and adaptive immune response. IL-6 is secreted by various immune cells, including monocytes, T and B lymphocytes, neutrophils, and NK cells, as well as non-immune cells, including muscle, endothelium, fibroblast, and keratinocyte cells. [6] In both infectious and non-infectious conditions, such as myocardial infarction, surgery, trauma, stroke, autoimmune and neoplastic diseases, the physiological concentration of IL-6 in serum increases and varies from 1 to 5 pg/ml. [7] Following an inflammatory stimulus, serum IL-6 levels increase within 1 to 3 hours. [8]

CRP in serum has been widely studied as a biomarker for sepsis and is associated with various inflammatory diseases. [5] While there is ongoing debate on the usefulness of CRP as a biomarker for early sepsis diagnosis, most hospitals are able to use CRP analysis for diagnosing and predicting the prognosis of sepsis. [8] It is well recognised that lactate is essential for cellular metabolism and energy production. [9] Numerous illnesses, including sepsis, liver ailments, shock, trauma, strenuous exercise, drug abuse, and malignancy, can result in lactic acidosis [9], Despite this, There have been few studies examining the prognostic value of lactate levels and clearance of lactate in both sepsis and septic shock patients diagnosed in accordance with the most recent Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). [2]

Serum procalcitonin levels change more rapidly than CRP levels during the onset and resolution of bacterial infections. [10] Procalcitonin, a peptide and precursor of calcitonin, is released into

the bloodstream in response to bacterial toxins. This results in a quick increase in serum levels in patients with bacterial infections. Procalcitonin appears to offer slightly better specificity, sensitivity, and predictive values compared to CRP. [10]

TREM-1 (triggering receptor expressed on myeloid cells-1) was identified by researchers in Switzerland in the year 2000. [11] Bacterial and fungal stimuli control its expression and are predominantly seen on monocytes, neutrophils, and macrophages. TREM-1 plays a crucial role in modulating innate immunity by enhancing or attenuating signals induced by Toll-like receptor. It uses the adaptor protein DAP12 in interactions related to signaling and function. TREM-1 activation results in the synthesis of proinflammatory cytokines TNF- α and IL-1 β as well as chemokines like IL-8 [12].

Activated phagocytes secrete a soluble form of TREM-1 (sTREM-1), which is present in pleural fluid, urine, plasma, cerebrospinal fluid, and bronchoalveolar lavage, as well as other biological fluids. Because of this, sTREM-1 may be used as a biomarker for bacterial infections. Serum sTREM-1 has a high specificity as a biomarker for infection, and many studies believe it is not present in non-infectious inflammatory disorders. [13]. But the latest study indicates that TREM-1 also plays a role in the genesis of a number of acute and long-term non-infectious inflammatory illnesses, including cancer, inflammatory bowel disease, atherosclerosis, and tissue damage caused on by ischemia and reperfusion. [14,15].

In our study, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) was identified as a significant prognostic biomarker for predicting mortality risk. This finding aligns with the results reported by Latour-Pérez et al. in their cohort study, which highlighted the prognostic value of sTREM-1 plasma levels in sepsis patients. According to their research, elevated sTREM-1 levels during hospitalization correlate with an increased risk of fatality in septic patients. [16] The ability of sTREM-1 to predict lethality underscores its potential utility in clinical settings for monitoring and managing patients with sepsis. Our data support this, suggesting that regular measurement of sTREM-1 levels could be instrumental in identifying high-risk patients and guiding therapeutic interventions.

Additionally, Zhang and Zhang (2021) found that serum sTREM-1 levels were significantly elevated in patients who died within 28 days, reinforcing its role as a prognostic indicator for assessing death risk in sepsis patients. [17] Our findings corroborate this, showing that sTREM-1, along with lactate and IL-6 levels, serves as reliable markers for determining mortality probability. Lefeng Zhang's study further demonstrated a significant positive correlation between serum sTREM-1 and APACHE II scores, while no such correlation was observed for serum CRP or lactate levels. [17] In contrast, our research revealed that CRP and procalcitonin (PCT) levels exhibited distinctly different dynamics between patients with APACHE II scores below and above 50%. This suggests that CRP and PCT are closely related to the underlying processes leading to septic shock and can thus be considered markers of disease severity. These findings highlight the importance of using a combination of biomarkers to improve the prognostic assessment and management of sepsis.

A notable strength of our research is that it was conducted on ICU patients, with serum biomarkers measured at multiple time points: days 0, 1, 2, 3, and 5 of admission. This study is the first at our facility to measure sTREM-1 and investigate its correlation with other biomarkers such as CRP, PCT, lactate, and interleukin-6. However, the study has limitations, including a small sample size of 24 patients. Further research with larger sample sizes is necessary to thoroughly evaluate the clinical relevance of sTREM-1 as a prognostic marker in sepsis. Such studies could

enhance the use of sTREM-1 alongside traditional laboratory findings, microbiological data, and clinical methods to improve the rapid diagnosis and treatment of sepsis.

The aim of this research was to assess the prognostic and diagnostic value of sTREM-1 and IL-6 in sepsis and septic shock induced by gram-positive microorganisms. Additionally, we aimed to identify markers that are directly and causally related to CRP, PCT, and APACHE-II scores, with the goal of finding a high probability predictor of lethality in septic shock.

Conclusions

Our study confirmed that sTREM-1, PCT, Lactate and IL-6 levels in the APACHE-II < 50% and APACHE-II \geq 50% groups differ with a high degree of confidence throughout the observation period. This indicates that these markers determine the probability of lethality, although they do not reflect the process of septic shock formation. Therefore, they can be considered predictors of the development of septic shock.

Conversely, CRP and PCT levels showed reliably different dynamics of changes between the APACHE-II < 50% and APACHE-II \geq 50% groups. This suggests that these markers are likely closely causally related to the processes involved in the formation of septic shock and can thus be considered markers of the severity of the disease.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

Acknowledgment

The authors would like to express gratitude to the care support the Tbilisi State Medical University departments professionals for the contribution to the data collection and for completing the survey.

Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects were approved by the The First University Clinic of Tbilisi State Medical University.

This study was reviewed and approved by the Medical Ethics Committee of the First University Clinic of Tbilisi State Medical University. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the patient for the publication of this case report.

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ASSESSMENT OF Ki-67 CELL PROLIFERATION MARKER EXPRESSION IN GASTRIC CANCER

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ABSTRACT

Tumor cell proliferation is a key mechanism in the pathogenesis and progression of gastric cancer. The Ki-67 marker, expressed during active phases of cell division, is a critical indicator of tumor proliferative activity. This study performed a quantitative analysis of Ki-67 expression levels in 40 gastric cancer samples from different stages, utilizing ImageJ software for digital morphometric analysis. The findings highlight a significant correlation between the Ki-67 index and the stage of the disease, confirming its value as a prognostic marker. ImageJ's use ensures high accuracy, objectivity, and reproducibility in the analysis.

Keywords: gastric cancer, Ki-67, proliferation, ImageJ, immunohistochemical analysis, digital morphometry.

Relevance

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide. Ki-67 as a marker of cellular proliferation is crucial for diagnosis, predicting disease progression, and guiding therapeutic decisions. However, traditional methods of analyzing immunohistochemical (IHC) specimens are often subjective, which underscores the need for automated approaches. The ImageJ software standardizes the analysis process, making it more reliable and consistent.

Objective

To assess the proliferative activity of gastric cancer cells at various stages using Ki-67 expression and ImageJ software. The study also aims to compare changes in Ki-67 levels across different stages and evaluate the utility of ImageJ in quantifying IHC data.

Materials and methods

- Materials: 40 gastric cancer specimens, representing stages from early to late disease.
- Methods:
 1. Standard IHC analysis was conducted to detect Ki-67 expression in all specimens.
 2. Digital image analysis was performed using ImageJ software:
 - Digital microphotographs were imported into the program.
 - Images were converted to 8-bit format.
 - Threshold segmentation was applied to highlight positively stained nuclei.
 - The total cell count was calculated, and the Ki-67 index (percentage of stained nuclei) was determined.

Results and Discussion

- Early stages: The Ki-67 index was relatively low, ranging from 0-5%, indicating minimal tumor cell proliferation.

- Intermediate stages: The Ki-67 index increased to 5-10%(+), 10-30%(++), reflecting active tumor progression.
- Late stages: The Ki-67 index surpassed 30%, indicating high proliferative activity and aggressiveness of the tumor.

The use of ImageJ significantly improved the accuracy and efficiency of the analysis, eliminating subjectivity and reducing time spent on the analysis.

These results support the use of Ki-67 as a valuable prognostic marker for gastric cancer.

Conclusion

Ki-67 expression levels correlate strongly with gastric cancer progression, making it a crucial biomarker for diagnosis and prognosis. ImageJ software provides high precision and objectivity in analyzing IHC specimens, minimizing subjective influences. The implementation of automated tools like ImageJ standardizes the research process, making it more reliable and essential for both clinical and scientific applications.

Practical Significance

The data obtained from this study has the potential to improve diagnostic accuracy, prognosis, and treatment strategies for gastric cancer. The integration of automated methods into clinical practice emphasizes their importance for enhancing healthcare quality and patient outcomes.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

Acknowledgment

The author would like to express gratitude to the care support workers and elderly individuals who participated in this study, sharing their invaluable insights and experiences. Their cooperation and openness have significantly contributed to the depth and richness of the research findings.

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DIFFUSE INTERSTITIAL LUNG DISEASE (ILD): CLINICAL- RADIOLOGICAL CORRELATION (CASE STUDY)

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ABSTRACT

Diffuse Interstitial lung disease (ILD) includes a whole group of diseases that damage the lung parenchyma and affect the gas exchange processes in the lungs. Some of these diseases occur with similar symptoms in adults and children. They occur with different frequencies in different populations. They are characterized by special features in newborns.

The work aimed to detect interstitial lung disease in early stages in children, correctly diagnose it, develop treatment tactics, and, as a result, improve the duration and quality of life.

The group of interstitial lung diseases includes more than 180 acute and chronic diseases with inflammatory and fibroproliferative changes. Their diagnosis is difficult and cannot be made based on radiological data. It is difficult to distinguish them from bacterial lung diseases, especially pneumonia, and tuberculosis, which often leads to incorrect treatment, disease progression, and a poor outcome.

The article presents a clinical case, the analysis of which was carried out on the basis of diagnostic and disease management criteria available in the literature. The article discusses in detail the main characteristic anamnestic, clinical, and diagnostic criteria of the disease, established based on the results of various clinical studies.

Introduction

Diffuse Interstitial lung disease (ILD) is a heterogeneous group of rare, chronic respiratory diseases, with a prevalence variably reported (from 0.13 to 16.2 per 100,000 children per year) as

a result of a diagnosis that is often challenging. Standardized diagnostic criteria are lacking and the presentation of clinical and pathological is heterogeneous. Even if the term Children interstitial lung disease, child, is conventionally used in the international scientific literature, the term Diffuse Lung Disease, DLD, would be more appropriate to describe these conditions, since many of them do not show exclusive involvement of the interstitium but also alveoli, distal small airways and/or terminal bronchioles.

The severity of chILD presentation is highly variable, ranging from mild nonspecific symptoms, which may lead to a late diagnosis, to a very severe clinical picture. Usually the earlier the onset of the disease, the more severe are the presenting symptoms. Despite the heterogeneity that characterizes chILD (age of presentation, genetic mutations, disease course), there is significant overlap in clinical manifestations. The earliest possible presentation of chILD is shortly after birth, with unexplained respiratory distress in term neonates, who can rapidly require intubation and ventilation. Less frequently, chILD patients are born preterm; in this case, they present with acute respiratory distress which is more severe than would be expected because of prematurity. During the first two years of life, a child's clinical manifestations range from no symptoms to severe respiratory distress usually triggered by viral infections. In most cases, children with chILD have nonspecific respiratory signs and symptoms, such as dyspnea, polypnea, dry cough, wheezing, recurrent respiratory infections, and exercise intolerance. Older children can show tachypnoea, hypoxia, digital clubbing, and/or cyanosis during exercise or at rest. In children, auscultation typically reveals crackles, sometimes coupled with wheezes, but no pathological chest sound can be heard in up to a third of affected children.

The pathogenetic sequence in actuality involves a series of inflammation and fibrosis that extends beyond disrupting the interstitial bed to changing the parenchyma. The diagnosis and management of interstitial lung disease are complex and require an interprofessional team. Once the diagnosis is made, asymptomatic patients may be placed under observation, but all symptomatic patients need treatment. The condition is known to progress to fibrosis and end-stage lung disease, hence long-term monitoring is essential. In addition to a complete medical history and physical exam, thoracic computed tomography (CT), specifically high resolution CTs (HRCTs), plays an essential role in diagnosing diffuse pulmonary lung disease.

Diffuse parenchymal lung disease is a rare disease. According to studies, the incidence per million children was recorded: in Germany 1.52 cases, in Britain - 3.6 cases.

During the first year of life, the disease manifests itself disproportionately between the sexes and is relatively common in boys compared to girls, especially under the age of 2. There are no statistical data on diffuse lung disease in childhood in Georgia.

Case study

An 11-month-old female patient was admitted to the M. Iashvili Children's Central Hospital with a six-day history of illness. The illness began with a sub-febrile temperature (37.9°C), catarrhal phenomena, an attack of a cough, and an excessive amount of sputum. Symptomatic treatment was carried out at home. In dynamics, the patient's condition worsened, the intensity of the cough increased, and abundant sputum was noted, the evacuation of which was difficult. Breathing became more frequent and difficult.

Upon admission to the clinic, the patient's general condition was severe, which was due to acute respiratory failure. T-37.2°C P-168, RR-50. SpO₂-90%. The severity was determined by: abundant catarrhal phenomena, an attack-like cough, with abundant, thick bronchial secretions,

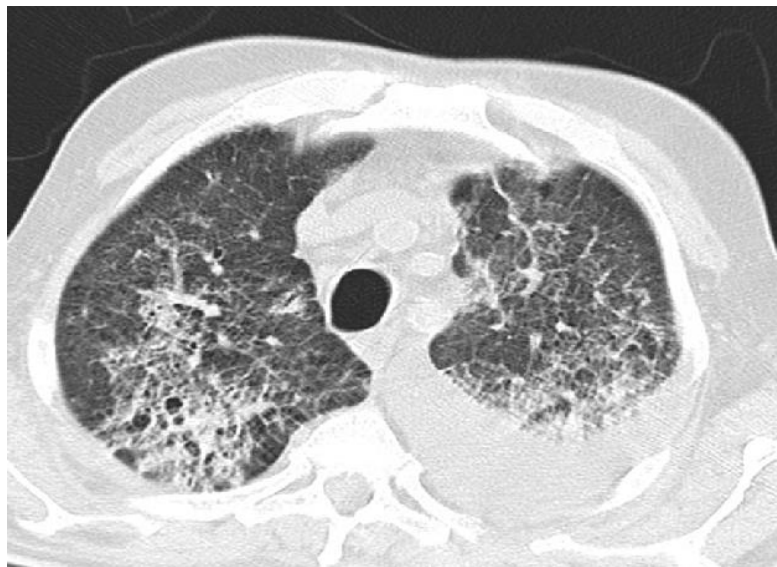
the evacuation of which was difficult. To normalize oxygenation-ventilation, constant oxygen therapy was required. There was pronounced pallor of the skin with a cyanotic tint. Auscultation of the lungs revealed diffuse dry wheezing, abundant wet wheezing of various calibers, and crepitus in the projection area of the right middle lobe. Decreased appetite, sharply distended abdomen, pronounced flatulence, intestinal dysfunction with periodic diarrhea.

During treatment, the patient's condition remained severe, acute respiratory failure persisted, he remained oxygen-dependent, and she received food through a nasogastric tube.

Laboratory studies: peripheral blood count - without pathological changes, CRP-8.52g/l, SARS-CoV-2 Ag (-) negative, respiratory acidosis was noteworthy, high lactate-4.01 mmol/l, hypoproteinemia-42g/l. Bacteriological examination of feces did not reveal changes characteristic of intestinal infection.

Radiological studies: chest Ro-graphy - right perihilar infiltrative changes, high-resolution CT of the chest cavity revealed tracheal stenosis and CT changes characteristic of interstitial pneumonia. Repeated studies on infectious markers, complete blood count, blood gas and electrolyte control, and liver and kidney functions were performed in two days, respiratory acidosis remained noteworthy.

Due to prolonged respiratory failure and the presence of abundant bronchial secretions, a repeat CT scan of the chest cavity with contrast was performed, which revealed central and peripheral interstitial tissue congestion, interlobar and intralobular septa, which gave the lung parenchyma a somewhat mosaic configuration, infiltrative changes of low intensity of peribronchovascular distribution. Thickening of the right upper interlobar pleura, areas of basal linear fibroatelectasis on the same side.



Picture N1. Computed tomography scan showing features of interstitial lung disease.

Based on the clinical and laboratory data, especially high-resolution CT scan, which is the gold standard for diagnosing the disease, the diagnosis of the underlying disease was made. The patient was treated according to the scheme provided in the literature.

Laboratory tests include hematology (complete blood count and biochemical tests should be performed in all infants), search for infectious agents, evaluation of immune function, serology to rule out autoimmune diseases, and evaluation for hypersensitivity pneumonitis. Quantitative immunoglobulin determinations should be considered in most cases except in neonates. Rheumatological evaluation is mainly in older children.

The severity of PDPD is assessed by pulmonary function tests and pulse oximetry. Arterial blood gases may also be measured. Pulmonary hypertension is assessed by echocardiography and cardiac catheterization. The degree of hypoxemia and pulmonary hypertension largely determines the severity of the disease.

Nutritional status and growth trajectory also play a role in assessing the severity of the disease, especially in infants and young children.

Chest radiography is important for diagnosis, usually nonspecific, but rarely specific. Infiltrates are mostly interstitial, but alveolar and mixed are also possible. The exception is neuroendocrine hyperplasia (NEHI), in which chest radiography is often normal or shows hyperinflation or increased density around the bronchial wall.

High-resolution computed tomography (HCV) is more accurate in assessing the extent and severity of the disease than radiography. In some forms of PDPD, chest CT findings are specific and may reduce the need for lung biopsy. MRI findings that may be seen in various forms of PDPD include: septal thickening, ground-glass syndrome, geographic hyperlucency (increased opacity), or mosaic attenuation, pulmonary cysts or nodules, and consolidation.

The prognosis depends on the underlying/comorbid disease. For example, duration of symptoms at initial assessment, weight below the 5th percentile, wet wheezing, clubbed fingers, and family history of PDPD are not associated with poor survival. Whereas, hypoxemia and pulmonary hypertension (which indicate disease severity) are significantly associated with poor survival.

Conclusion

Diffuse Interstitial Lung disease is a heterogeneous group of rare, chronic respiratory diseases, affecting not only the interstitium but also alveoli, distal small airways, and terminal bronchioles. The high variability of clinical manifestations, which range from mild symptoms to a severe onset, leads to a difficult and often delayed diagnosis and treatment. Despite their overall rarity, pediatric pulmonologists must be familiar with these diseases to carry out a timely diagnosis and patient management.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

Acknowledgment

The author would like to express gratitude to the care support workers and elderly individuals who participated in this study, sharing their invaluable insights and experiences. Their cooperation and openness have significantly contributed to the depth and richness of the research findings.

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SYSTEMIC LUPUS ERYTHEMATOSUS IN GEORGIA: SINGLE CLINIC EXPERIENCE AND FUTURE PERSPECTIVES

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ABSTRACT

Systemic Lupus Erythematosus is an autoimmune, multiorgan, and frequently relapsing disease. Pediatric lupus manifests before the age of 18. Compared to the clinical phenotype of adults, the disease in children is characterized by higher activity, polyorgan damage, and, most importantly, a high frequency of kidney damage or lupus nephritis. The rate of lupus nephritis in adults is lower than in the pediatric contingent. In systemic lupus, lupus-nephritis is considered an unfavorable prognostic criteria.

Five cases of pediatric lupus nephritis were recorded in Georgia during the last ten years. The study aims to evaluate the clinical-morphological correlations of these five cases and identify prognostic criteria. The study was conducted at the Central Children's Hospital named M.Iashvili in Tbilisi, Georgia.

We showcase the clinical-laboratory and morphological data of five pediatric patients, whose initial manifestations did not match the symptoms of common pediatric lupus. Additional studies confirmed different morphological classes of pediatric lupus nephritis in all of the cases. Based on these Georgian cases, we built a chart of the activity and chronicity indices of the disease and confirmed that in our cases, the disease is equally active in both genders. Our study showcases that pediatric lupus is more active in prepubescent and pubescent ages, and it is necessary to differentiate it from other kidney pathologies. The treatment decision should depend on the morphological identification of the kidney biopsy. Timely diagnosis and targeted use of treatment protocols are vital in determining the prognosis of the disease and the patient.

Keywords: Lupus Nephritis, Extrarenal Manifestations, Activity and Chronicity indices, EULAR, Kidney Biopsy.

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune, multiorgan, and frequently relapsing disease. Pediatric Lupus manifests before the age of 18. Compared to the clinical phenotype of adults, the disease in children is characterized by higher activity, polyorgan damage, and, most importantly, a high frequency of kidney damage or Lupus Nephritis (LN). In Systemic Lupus Erythematosus, lupus nephritis is considered unfavorable prognostic criteria. The incidence and prevalence of LN depend on the selected population and the diagnostic criteria for defining SLE. The exact prevalence of the disease is unknown in Georgia.

Epidemiologic evidence exists for the association of silica, Epstein-Barr infection, and cigarette smoking with SLE. There are conflicting data associating infections, vaccinations, air pollution, ultraviolet (UV) light, solvents, pesticides, and heavy metals, for example mercury. While UV radiation exposure is known to exacerbate preexisting lupus, it is unclear whether this is a risk factor for its development. Biologic mechanisms linking environmental exposures and SLE include oxidative stress, systemic inflammation, cytokine upregulation, and molecular mimicry to viral antigens.

A combined chain of genetic and environmental factors determines SLE pathogenesis. Environmental factors cause epigenetic changes - DNA methylation, histone modification - and they can cause disease in genetically predisposed individuals. The leading link in pathogenesis is neutrophil apoptosis (NETosis) - a special form of cell death that can be stimulated by pathogens, immune complexes, and cytokines. At this time, decondensed chromatin and protein network structures are released into the extracellular space. This process takes place during SLE. A possible link in pathogenesis is a genetic defect, which is a defect in the opsonization process, and antigen clearance does not occur.

Nuclear antigen binds to Toll-like receptors. They secrete Interferon alpha, a cytokine that activates autoreactive T cells. T cells enhance the synthesis of T and B lymphocytes in the red bone marrow and lymph nodes. B lymphocytes produce autoantibodies that bind to nuclear antigens and form circulating immune complexes (CICs). Involvement of the kidney is due to the deposition of CICs in the kidney tissue. The complement system is activated, and FC receptors of phagocytes bind to the immune complex. Activation of the classical complement pathway produces C3a and C5a proteins that activate neutrophils. Activation of neutrophils leads to ROS, IL-4, TGF- β , TNF- α , and IFN- γ . They cause damage to podocytes, mesangial proliferation, degeneration of endothelial cells - organ damage, and finally, fibrosis develops. In SLE, although autoantibodies can be detected against nearly any portion of the human proteome, the most common antibodies detected are antinuclear antibodies (ANA). However, individuals can test positive for ANA without developing manifestations of SLE. Numerous assays can be used to profile ANA reactivity; specificity for anti-double-stranded DNA or Smith antigen is higher in patients with SLE.

Methods

5 cases of Pediatric Lupus Nephritis were recorded in Georgia, at the Central Children's Hospital named M.Iashvili during the last ten years. The study aims to evaluate the clinical-morphological correlations of these five cases and identify prognostic criteria. There were 2 boys and 3 girls. The ages of boys were 4 and 12 years old. The ages of girls were 13, 15, and 17 years old. All patients' clinical and paraclinical data were analyzed, summarized, and calculated a score according to the ACR/EULAR 2019 diagnostic criteria for systemic lupus erythematosus. Based on the results of the histopathomorphological study, we calculated the indices of activity and

chronicity (AI and CI) of each patient. AI and CI are pivotal prognostic criteria for patients diagnosed with Lupus Nephritis.

Results

Studies confirmed different morphological classes of pediatric lupus nephritis in all cases. An early renal biopsy is helpful in patients with an abnormal urinalysis and reduced glomerular filtration rate, and the results form the basis for therapeutic decisions. All of the patients with SLE developed kidney involvement. Frothy urine, edema, proteinuria, and hypertension which with increased creatinine levels, were the most common manifestations of LN in patients. Disease manifestations and outcomes particularly are heterogeneous. The American College of Rheumatology (ACR) 1997 revised classification criteria for SLE described kidney involvement as persistent proteinuria >0.5 g per day, or the presence of granular casts which may be red blood cell, hemoglobin, tubular, or granular casts, or mixed. A similar criterion is stated by the SLICC classification criteria, urine-protein-to-creatinine ratio, urine protein representing 500 mg protein in 24 hours, and histopathologic findings of lupus nephritis.

The 2019 European League Against Rheumatism (EULAR)/ACR criteria for SLE defines proteinuria as above. and follows the lupus nephritis classification of the 2003 criteria of the International Society of Nephrology/Renal Pathology Society (ISN/RPS). A score of 10 or >10 according to the ACR/EULAR 2019 criteria is the basis for diagnosing lupus nephritis. According to ACR/EULAR 2019, the total score of all patients shows that lupus nephritis in each of them is acute, with multiple renal and extrarenal manifestations. (Table 1). Along with the renal paraclinical manifestations of 5 patients, their common and uncommon extrarenal symptoms are also crucial. All of the patients had extrarenal clinical manifestations. Alopecia, Malar rash, Arthritis, Delirium, Thrombocytopenia, Anemia, and Non-infectious fever, General weakness were the most common extrarenal manifestations. (Table 2). In our patients, activity and chronicity indices were also crucial. Active lesions are amenable to immunosuppressives therapy, while chronic lesions represent nonreversible damage, requiring supportive therapy. The activity index and chronicity index quantify mainly glomerular injury, and the tubulointerstitial activity index quantifies extra-glomerular disease. As in adults, risk factors for poor outcomes in cSLE include activity index ≥ 7 , chronicity index ≥ 4 , and tubulointerstitial activity index >5 . Fibrinoid necrosis and cellular/fibro cellular crescents are weighted as they are historically associated with higher rates of long-term kidney failure. The activity and chronicity indices may not reflect the severity of lupus nephritis, and may not respond to therapy at the same rates as clinical and laboratory findings. We built charts of the activity and chronicity indexes of the disease and confirmed that in our cases, the disease is active in all of the cases.

In all patients, the disease progressed acutely, their activity indices were: 8, 3, 10, 4, and 11. The chronicity indices were 4, 4, 4, 2, and 3. We reviewed the results of a kidney biopsy from one patient who was assigned an activity index of 10 and chronicity of 4. Signs of glomerular activity were rated as a moderate degree of damage, and signs of chronicity as a slight degree. (Table 3) Trials in adults have informed guidelines for the treatment of lupus nephritis in children and adolescents. Treatment is geared to promote remission, limit disease exacerbations/flares, and prevent kidney failure. Response definitions vary between studies, but cSLE definitions have been proposed. Management of lupus nephritis is based on disease severity and risk of progressive kidney damage. Lupus nephritis class I and II are associated with good prognosis. Conservative

treatment is recommended. Although no additional immunosuppressive therapy is needed for nephritis, patients require continued monitoring. The development of worsening proteinuria or elevated creatinine may indicate conversion to other nephritis classes. Class III, IV, V, and mixed (III/IV + V) class lupus nephritis requires therapy with systemic immunosuppression in addition to high-dose corticosteroids. Aggressive therapy is necessary when children present with nephrotic syndrome, or for findings on kidney biopsy of active cellular proliferation and necrosis involving 40% of glomeruli. Two treatment phases are utilized: (i) Induction, which lasts on average 3 to 6 months; and (ii) Maintenance where immunosuppressive treatment is reduced over time. Lupus nephritis class IV is the most severe form of nephritis and requires aggressive therapy.

Remission was achieved in all our patients. The main drugs used were – Cyclophosphamide, Hydroxychloroquine Sulphate, Mycophenolate mofetil, and Prednisolone. (Table 4).

Table 1. Patients with ACR/EULR 2019 scores. (Georgia).

Nº	Sex	Age	ACR/EULR 2019 total score
1	Female	13	33, ANA 1:450
2	Female	15	34, ANA 1:640
3	Female	17	33, ANA 1:320
4	Male	4	25, ANA 1:520
5	Male	12	26, ANA 1:390

Table 2. Extrarenal Clinical Manifestations in Children with SLE. (Georgia).

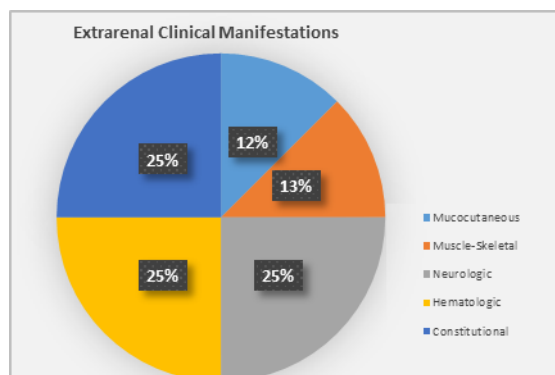


Table 3. Patients with activity and chronicity indices.(Georgia).

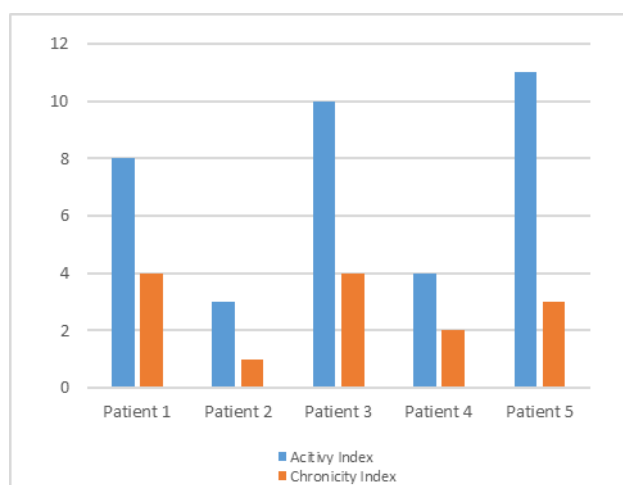


Table 4. This timetable shows our patients' treatment regimes. (Georgia).

Medication	Patient №1	Patient №2	Patient №3	Patient №4	Patient №5
Prednisolone	+	+	+	+	+
Mycophenolate mofetil		+	+		+
Hydroxychloroquine Sulfate		+	+		
Cyclophosphamide	+				+

Conclusion

- Pediatric Lupus Nephritis is more active in prepubescent and pubescent ages;
- It is necessary to differentiate it from other kidney pathologies;
- The treatment decision should depend on the morphological identification of the kidney biopsy;
- Most of our patients had uncommon clinical manifestations, such as delirium, alopecia, and anemia;
- We reached remission in all of the patients in one year. None of the patients have had a relapse;
- None of the patients need kidney transplantation;
- Timely diagnosis and targeted use of treatment protocols are vital in determining the prognosis of the disease and the prognosis of the disease and the patients.

Perspectives

Clinical trials are ongoing on new biomarkers that have not yet been incorporated into routine clinical practice. Potential biomarkers include the determination of circulating BAFF, APRIL, and

cystatin C levels. Also, urine biomarkers that reflect kidney damage are MCP-1, TWEAK, NGAL, and BAFF. Additionally, Medical agitation is necessary due to insufficient knowledge of systemic lupus erythematosus in schools and medical universities in Georgia.

A meta-analysis of the genome of women of Chevropele origin showed that mutation of PDGF protein (proliferates mesenchymal cells) and SLC5A - GLU/Na⁺ transporter (produces a good level of glucose reabsorption) protein genes are associated with the development of lupus nephritis. At the same time, the connection of the first protein gene mutation is more clear, while the second one is still unknown and requires additional research.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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INFLUENCE OF TRICHOMONAS VAGINALIS ON THE PROCESS OF CAPACITATION

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ABSTRACT

Trichomonosis is a dangerous sexually transmitted illness caused by *Trichomonas vaginalis*, a parasitic protozoan. Trichomoniasis has been associated with numerous perinatal problems, male and female genitourinary tract infections, and an increased risk of HIV transmission which largely affects the process of capacity. Trichomoniasis is difficult to detect due to the similarity of its symptoms to those of other sexually transmitted illnesses and the inherent inaccuracy of screening instruments. Despite the efficacy of current nitroimidazole treatment protocols, metronidazole resistance is rising, highlighting the critical need for more antibiotic research. An insufficient understanding of the host immune response to *T. vaginalis* infection has impeded vaccine research. Finding an adequate animal model for conventional research on medication vaccine development and pathogenesis has been challenging. The study would establish the hVECs in culture and examine their interaction with *Trichomonas vaginalis* parasite and these influence the process of capacitas.

Keywords: *Trichomonas vaginalis*, protozoa, STD, Preterm birth, Cytokines.

Introduction

By far, television is the most probable medium to spread the most common non-viral STI in the world. Approximately 276.4 million people were infected in 2008, with more than 90 percent of these illnesses occurring in resource-limited settings. Chlamydia, necrotizing fasciitis, and syphilis all have a higher prevalence than television. While men only watch television at a rate of 0.0 percent, women are more likely to watch than men. Microscopy examinations rather than more sensitive nucleic acid amplification assays were used to estimate these rates, which may be underestimated due to the lack of government surveillance systems (NAAT).

As a sexually transmitted disease, trichomoniasis, a parasitic infection, is among the most common nowadays. Women are more likely to get trichomoniasis, a condition that causes unpleasant vaginal discharge, irritation in the genital area, and difficulty urinating (M.-L.Crouch, et al., 2018). Trichomoniasis rarely affects males. Preterm birth is more likely in women who have trichomoniasis during pregnancy. In order to prevent re-infection, both spouses should be

treated. The most common therapy for trichomoniasis is a single megadose of metronidazole (Flagyl) or tinidazole (Tindamax). When having sex, always wear a condom correctly to avoid infection (Sherrard, 2017).

In 2008, there were an estimated 276.4 million cases of *Trichomonas vaginalis* (TV) worldwide, making it the most common non-viral STI. (STI). The disease affects 22% of girls and 2% of boys in the United States, with regional variations. Only 5.6% and 0.6% of the population in South East Asia are infected, according to the most recent statistics. 6,584 women and 490 men were diagnosed with breast cancer in England in 2016 (Johnson, 2019). Among the UK's black ethnic minority and prisons, television viewing is disproportionately concentrated. Women over the age of 25 are more likely to get infected with a sexually transmitted disease because of television (Tine, et al., 2019).

Flagellated protozoa are transmitted sexually and need intravaginal or intraurethral inoculation, however they can also be disseminated by exchanging sex toys with an infected person. Females' urethras and paraurethral glands are home to the bacteria. Less than 5% of infected women have urethral infection as the predominant location, despite 90% of those infected having urethra infections. A mother who is infected during childbirth can also transmit television. However, trichomonas can also be discovered in the subpreputial sac and penis, where they are more commonly detected in males (Parsamand, et al., 2011).

Methods

Regarding the challenges associated with *Trichomonas vaginalis* the research seeks to examine the influence of *Trichomonas vaginalis* on the process of Capacitas. The objective will be attained using secondary sources. This will examine the specific research outcomes of previous researchers who have specifically adopted quantitative research methods.

Results

The relationship between *Trichomonas vaginalis* on the process of capacitation.

Trichomoniasis can manifest clinically in a number of different ways. Trichomoniasis can induce a variety of symptoms within six months of infection, ranging from carrier status to evident vaginitis. *T. vaginalis*' major target is the squamous epithelium of the genital canal. Men are infected for a brief duration, whereas females are infected for an extended period. This virus is more prevalent in premenopausal and postmenopausal females. The incubation period varies between four and 28 days for nearly half of the people afflicted. According to the degree of the infection, trichomoniasis is classed as acute, chronic, or asymptomatic (Johnson, 2019).

Clinically, leukorrhea-induced vulvitis is observed in patients with acute infections. A mucopurulent discharge of yellow or green color is usual. On the vaginal and cervical mucosa, little hemorrhage patches may occur. Only 2% of people have this "strawberry" appearance, sometimes known as a "spotty" appearance. Menstruation is responsible for the most severe of these seasonal symptoms (Adamski, et al., 2014). Pruritus and dyspareunia are the most prevalent signs of persistent infection, and vaginal discharge may be tiny and mucus-mixed. This disease is crucial epidemiologically, as these individuals are the principal vectors of parasite transmission. Despite the fact that women make up the majority of those affected, *T. vaginalis* infection of the Bartholin's gland is infrequent. *Trichomonas* infection can result in adnexitis, pyosalpinx, endometritis, infertility, premature delivery, and cervical erosion which largely affects the process

of capacitas. Trichomoniasis has been linked to an increased risk of HIV infection (Swygard, et al., 2004).

Although *T. vaginalis* infection is most frequently linked with females, it can also affect men. Men who carry Trichomoniasis vaginalis are asymptomatic carriers. Trichomoniasis in males is characterized as asymptomatic carrier illness, acute trichomoniasis, and minimally symptomatic disease that is clinically indistinguishable from other nongonococcal urethritis causes. According to Parsamand, et al (2011) causes nongonococcal urethritis in 11% of males. The infection is often transient in male patients, lasting no more than ten days in the great majority of instances. Dysuria, a moderate stinging or burning sensation, and a clear to mucopurulent discharge are all prevalent symptoms in symptomatic males. Examples include urethritis caused by nongonococcal bacteria, prostatitis, balanoposthitis (epididymitis), and urethral disease (infertility). Trichomoniasis, which is more prevalent in females, is responsible for less than 5% of urethral infections. The great majority of instances (14 to 60%) are associated with past female companions who were also affected (Swygard, et al., 2004).

It has recently been discovered that glycine and alanine are the end products of glucose metabolism. The trichomonad cell is largely composed of the amino acids alanine and leucine. Normal conditions lead to an increase in amounts of valine, glycine, phenylalanine, and proline. *T. vaginalis* and its environment appear to be in a state of equilibrium based on the concentrations of amino acids in and out of the cell (Adamski, et al., 2014). Aminotransferases, on the other hand, have been shown to have a role in amino acid metabolism. The enzyme aspartate/aromatic amino acid: 2-oxoglutarate aminotransferase was discovered by SHAO & LIN (1995). To further explain why *T. vaginalis* has more of these amino acids, branched-chain and aromatic aminotransferases have been found to be particularly active (Schwebke & Burgess, 2004).

Trichomonas vaginalis Issues on Microscopic and Culture Techniques.

Since Donne's 1836 report on microscopy of motile protozoa in vaginal or cervical secretions, trichomoniasis has been diagnosed using this technique. It is simple to detect a Trichomonad as it moves. This approach has a sensitivity of between 38% and 82%. This is the least expensive diagnostic test available, despite its limited sensitivity, however, it is not the most accurate. Perhaps when protozoa are isolated from the warmth of the body, their particular motility is lost (Kissinger, 2015).

Broth culture, a simple-to-understand method for identifying trichomoniasis, requires just 300–500 trichomonads/ml of inoculum to enable growth in culture and is universally considered as the gold standard. As a result, culture-based diagnosis has significant limitations. *T. vaginalis* is frequently isolated from cultures following a two- to seven-day incubation period during which infected persons can continue to spread the virus. Additionally, doctors may lack access to widely available culture systems. By integrating rapid examination and culture in a single self-contained piece of equipment, a plastic envelope technique was created to boost the acceptability of culture-based diagnosis (Tine, et al., 2019). Regardless of the procedure utilized, wet preparation and culture produce the same results. The two-chambered InPouch device, which resembles a plastic envelope, can be used for microscopic inspections and culturing. According to Sherrard (2017), *T. vaginalis* can be discovered utilizing the InPouch approach. Diamond-modified and Trichosel-modified media have been shown to be significantly more sensitive than this system (Petrin, et al., 1998).

T. vaginalis is cultivated from clinical specimens using a multi-cell line cell culture approach. Garber et al. propagated the disease using McCoy cells, a technology they created, at a concentration of just three organisms per milliliter. Due to the high costs and hassles associated with cell culture, it is rarely employed in the field. Due to the ineffectiveness of cultivation methods and wet-mount preparations, parasite spotting was observed in fixed and unfixed samples. The development of staining methods has resulted in increased sensitivity in direct microscopy (Sherrard, 2017). Papanicolaou (Pap) staining is a frequent gynecological screening test for cytologic abnormalities, particularly in STD-endemic regions. However, a study discovered that when Pap smears were used only for diagnosis and therapy, they were ineffective at diagnosing and treating *T. vaginalis* infection. Another disadvantage of staining *T. vaginalis* is that it may not always emerge in its characteristic pear-shaped form with flagella. Because characteristic morphological traits may be lost during fixation and staining, causal identification of polymorphonuclear leukocytes may be challenging (Adamski, et al., 2014).

How *Trichomonas vaginalis* Antibody-Based Techniques Influence capacitation.

T. vaginalis has been found to have eight distinct serotypes, according to research. Immunoblot analysis, on the other hand, can reveal a wide range of antigenic markers. Antitrichomonal antibodies can be detected by agglutination. Immune system activation, antigen type, state (living or inactivated), concentration of antigen or pathogen in the environment, and frequency and duration all have an impact on the serum or local antibody response to a disease. However, there are a number of things that may be improved upon. The method may not be able to detect low quantities of specific antibodies, or the humoral reaction in the serum may not be sufficient to detect an antibody response in some cases. To distinguish between present and historical infections, *Trichomonas* antibodies may remain in the body for a long amount of time following treatment (SHAIO & LIN, 1995).

T. vaginalis antigens can be detected in clinical specimens using monoclonal antibodies directed against *T. vaginalis* antigens. Using two monoclonal antibodies, Krieger et al. discovered 88 strains of *T. vaginalis* from around North America. Wet-mount preparations and monoclonal antibodies derived from clinical material both yielded similar results in the detection of *T. vaginalis*. Additionally, monoclonal antibodies against *T. vaginalis* immunogens such as CDF (200 kDa) and cysteine protease (60 kDa) can be utilized to detect trichomoniasis. *T. vaginalis* parasite detection was as sensitive and specific as culture approaches using direct immunoassays, which used peroxidase- and fluorochrome-labeled combinations of monoclonal antibodies directed against unique *T. vaginalis* structures (Californio Integrated Diagnostics, Benicia, Calif.) (Tine, et al., 2019). A single patient visit can be used for both diagnosis and treatment because results are available in less than an hour.

T. foetus, a close relative of *T. vaginalis*, has been used as a model to test our current understanding of the immune response to *T. vaginalis* in vitro. Patients who are monitored for 30 percent of the time are re-infected with the same strain of bacteria. People who are infected with *T. vaginalis* produce antibodies that protect them from the disease, according to many immunoassays. Antibodies appear to provide some protection in recent research using vaccinated mice challenged via intravaginal inoculation, which is in line with prior work in mice using subcutaneous or intraperitoneal injections that indicated antibodies may provide some protection (Sherrard, 2017). A parasitic infection causes the generation of antibodies in the reproductive tract and serum.

Parasite-specific immunity has proven to be more difficult to determine. Adhesion-independent host cell destruction was reduced in these mammalian cells as a result of antibodies. Additional anti-soluble parasite components, such as proteases, cytoactive compounds, or lytic agents like phospholipases, may be helpful. " It has been challenging to establish the role of antibodies in eradicating infection or lowering pathogenesis in vivo because of the lack of an acceptable experimental animal model for vaginal infection investigations. Antibodies, on the other hand, do not appear to be adequate for infection elimination, according to the current consensus (Swygard, et al., 2004). *T. vaginalis* infection cannot be studied in mice or any other experimental animals as a result. Mice have been injected with parasites and lactobacilli via intravaginal injection, but these infections are rare. It has been possible to successfully inoculate mice with or without estradiol with the parasite *T. foetus*, a bovine reproductive tract parasite. Anti-*T. vaginalis* antibodies can be tested in the same way as *T. foetus* antibodies if their modes of action are similar.

Helper T cells have been primed by parasite-specific IgG and IgA responses, but the antigens responsible for these responses and the precise actions of antibodies against parasites are yet unknown. As previously stated, parasites use adhesion molecules to facilitate their proximity to their hosts' cells, which has been proven to be successful in destroying the hosts' cells, as has been previously stated (Petrin, et al., 1998). The adhesion of *T. vaginalis* to the epithelial cells of the vagina has also been linked to the presence of four antigenic molecules on the *T. vaginalis* surface. *T. vaginalis*-mediated cytotoxicity was prevented by antibodies directed against these molecules, suggesting that antiadhesion immune responses may be crucial in protecting against *T. vaginalis* detrimental effects.

Many questions remain regarding immunity to *T. vaginalis*, such as whether or not it can be acquired and, if so, what function it plays in decreasing or eradicating infections. In experimental animals, vaccination gives some protection, but it does not appear to have a major protective effect in humans. Compared to people infected with both HIV and *T. vaginalis*, there was no evidence of a rise in parasite levels or a longer duration of parasite infection.

Biochemistry of Virulence and Pathogenesis.

Trichomoniasis pathophysiology relies heavily on the parasite's ability to adhere to human cells, and various adhesion molecules have been identified. The pathogenic role of Ad has been demonstrated in coculture experiments, where antibodies against Ad have been shown to reduce parasite adhesion and, as a result, cytopathic effects [CE] on host cells. The parasite flattens its shape and laminates to the host cell when *T. vaginalis* interacts with mammalian targets, according to additional studies. Adhesion to the parasite appears to be dependent on the presence of cysteine proteinases. DNA regions that are iron-sensitive have been demonstrated to affect the transcription of Adp65-1 (adhesion protein 65,000), which suggests that iron may also influence Ad expression. Because of this, it seems that the ad family of molecules is regulated on multiple levels. When *T. vaginalis* attaches itself to mammalian cells, we hypothesize that cytotoxicity and cell-cell interactions will be enhanced. Other functional carbohydrate groups other than Ad may be required for *T. vaginalis* to connect to human vaginal epithelial cells, although their specific roles in parasite adhesion and CE remain unknown. Knockout or RNA interference methods will be employed to determine if adhesins are necessary for a meaningful CE. Unknown trichomonad adhesion molecules may, however, target laminin, as some data suggests.

Major complications in capacitation

Premature birth has been linked to the STD *T. vaginalis*, which was previously considered a "minor" one. A large multicenter investigation found that disorders were related to rupture of the premature membrane, and low-weight birth after controlling for demographic, behavioral, and microbiological factors. According to Kissinger (2015), trichomoniasis is strongly linked to early labor and delivery. In Georgia the exact prevalence of this disease is unknown. We studied the medical histories of 14 patients with *Trichomonas vaginalis* and 14 healthy patients. We confirmed that pregnancy-related preeclampsia was more common in *T. vaginalis*-infected women than in non-infected women. There was a correlation between *T. vaginalis* and preterm birth and low birth weight in another research on adolescent mothers.

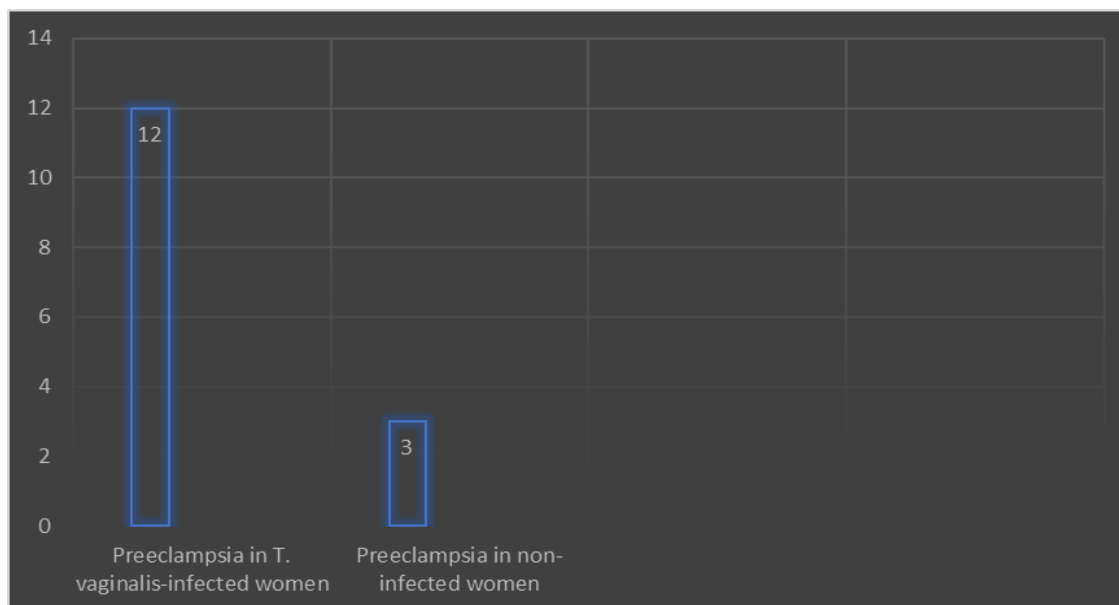


Chart N1. Pregnancy-related preeclampsia was more common in *T. vaginalis*-infected women than in non-infected women.

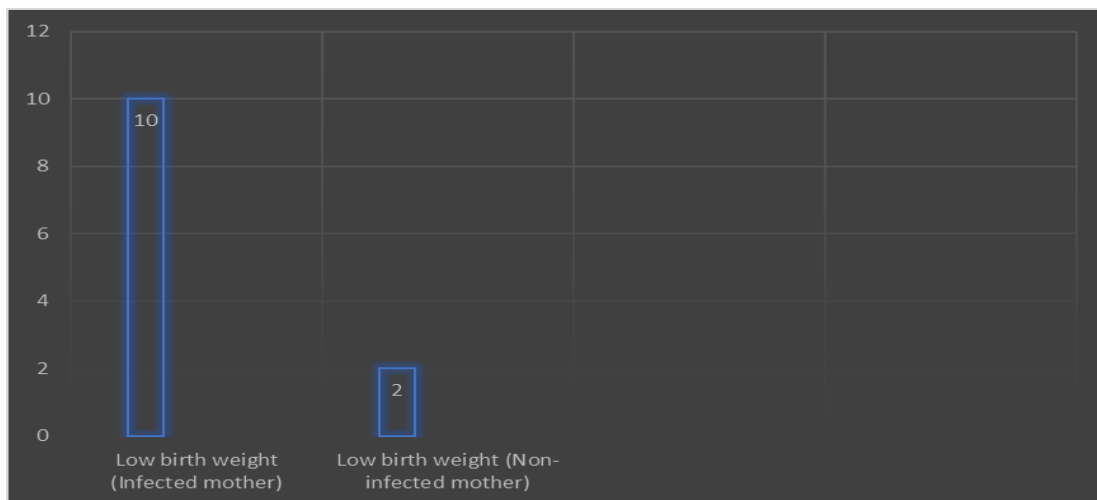


Chart N2. Correlation between *T. vaginalis* and low birth weight.

Veterinary research suggests that *Trichomonas* infections may contribute to pregnancy complications. For bovine trichomonas-infected cattle, immunization with *Trichomonas* has been shown to reduce abortion rates. Preterm labor and colonization or infection of the lower gastrointestinal tract during pregnancy are not known to be associated specifically in pregnancy. The majority view holds that infection triggers the production of local cytokines, which in turn triggers the onset of labor. Infections of the lower genital tract in pregnant women have been linked to vaginal fluid. Endotoxin, interleukin-1 alpha, and phospholipase A2 are also on this list, as is sialidase. Other bacterial infections, such as bacterial vaginosis and *Chlamydia trachomatis*, have been associated to elevated trichomoniasis levels in vaginal or cervical secretions. Premature labor has been linked to elevated cytokine levels in amniotic fluid, according to the study. At or before 34 weeks of gestation, Hillier et al. studied women who were afebrile, had intact membranes, and gave birth preterm. Preterm birth and infection of the amniotic fluid, histologic chorioamnionitis, and cytokines have all been linked. Women with disorders of the lower genital tract, such as trichomoniasis, are more likely to experience chorioamnionitis and preterm birth when there are cytokines present in the amniotic fluid.

There is no benefit to treating trichomoniasis during pregnancy in the hopes of avoiding preterm births, according to prospective studies. Preterm birth was shown to be more common among women who took metronidazole during the second and third trimesters of pregnancy as compared to those who took a placebo. The prescribed dose of metronidazole, on the other hand, was four times the amount that was used. Due to a lack of subjects and an increasing risk of premature birth in the therapy group, the experiment was halted early. Pregnancy-induced prematurity has been linked to the treatment of trichomoniasis in two distinct investigations. It was not possible to assess if *T. vaginalis* medication during pregnancy affects preterm birth rates in a subgroup analysis of the overall trial. Unanswered questions persist in this matter.

As a result of parasite-induced inflammation, many African studies have found a link between HIV and trichomoniasis. Prevalence of trichomoniasis in Rwandan pregnant women with and without HIV infection was considerably different from that in women without HIV infection. A multivariate analysis conducted on a Zairean cohort of women by Crouch, et al., (2018) indicated

trichomoniasis to be a significant risk factor for HIV infection (odds ratio, 1.9). Transmission of HIV is increased when *T. vaginalis* is co-infected. According to a Malawian study, males with trichomoniasis had significantly higher median HIV RNA concentrations in their seminal fluid than those with symptoms of unexplained urethritis. Anti-HIV medication decreases the HIV RNA levels in the body to the same level as in healthy people (Tine, et al., 2019).

Conclusion

T. vaginalis has complicated pathogenesis, according to the study, with components such as hemolysis and cell-detachment factor, as well as adhesion and hemolysis, all contributing to the disease's pathogenesis. The ability of *T. vaginalis* to adapt to its continually changing environment is related to its close association with the indigenous vaginal flora, an advanced immune evasion mechanism, and unique stress responses. The research sought to examine the influence of *Trichomonas vaginalis* on the process of Capacitas.

Trichomonas infection is prevalent and has been associated with many public health problems, including an increase in HIV transmission. Metronidazole is a safe and efficient treatment choice; however resistant strains are becoming more prevalent. The immunology, pregnancy hazards, appropriate diagnosis, and public health control of this sickness remain unknown.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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POSSIBLE ROLE OF THE SOMATIC HYBRIDIZATION IN MALIGNANT TRANSFORMATION OF DIFFERENT CELLS AND NEW APPROACHES TO PREVENT FORMATION OF PRECANCEROUS CELLS

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ABSTRACT

On the initiation stage of carcinogenesis, normal somatic cells after the fusion process form dikaryons, carriers of high carcinogenic potency, and then after karyogamy - hybrid synkaryon (precancerous cell). The mechanism of malignant transformation of the precancerous cell into a cancer cell has molecular and sub-cellular conditions: gene amplifications and chromosomal aberrations. Malignant tumors have a clonal origin and in initial stage consist of genetically identical cells. Cellular populations are constantly formed on tumors without any obvious regularity, and in any other tumor, there can coexist phenotypically and genotypically different cells. We suggest using molecular hydrogen as plasma membranes' stabilizing substance (to avoid perforations) and for inhibition of cell adhesions to prevent frequent cell fusion events.

Keywords: Carcinogenesis, initiation, Promotion, Progression, Invasion, Metastasis, Fusion, Karyogamic theory, Molecular hydrogen.

Introduction

Among the theories and hypotheses dedicated to the problem of carcinogenesis, karyogamic theory belongs to those rare theories which deal with both the etiology and pathogenesis of cancer formation. [1]. This theory may be considered as general theory of carcinogenesis, which includes the principal aspects of the most popular and acceptable theories [2] and hypothesis for today. [3]. Based on this theory it was suggested that the influence of diametrically different carcinogens on target cells is adequate. After their influence, cells' fusion originates as a result of cytoplasmic membrane perforations. [4].

Polypotent cells or other committed cells sensitive to carcinogenic effects and capable of proliferation form firstly dikaryons (hetero- or homokaryons) and then hybrid cells (synkaryons) by means of fusion with another cell of the same organism, in particular, with differentiated and non-differentiated cells of corresponding tissue or with cells capable to migrate (macrophages, lymphocytes, granulocytes of different maturity and so on). In all probability, during the perforation or modification of the plasma membrane, i.e., after the formation of pores, induced by different carcinogenic agents and factors, the total charge of the plasma membrane changes and

cells develop the ability to come closer to each other, which frequently, especially upon coincidence of the perforated parts, will probably be the prerequisite to a fusion process. [5]

Precancerous (initiated, immortal) cells- sinkaryons in phenotypic respect, in most cases, are indistinguishable from normal cells of these tissue, as they retain morphology similar to the one of the parent cells. Only in rare cases, because of intermediate heredity, precancerous cells may have morphology of both parent cells simultaneously, i.e., intermediate morphology. These sinkaryons differ from normal cells only by their genotype, having tetraploid chromosome set at the initial stage of fusion, and then hypotetraploid, hyperdiploid set of chromosomes.

Taking into consideration the plurality and variety of environmental carcinogenic agents and factors around us, and also a fact that the polypotent cells, stem cells, lymphocytes, macrophages and committed cells exist in all tissue of macro-organism, one can suppose that precancerous cells can often be formed in many tissue and organs simultaneously. Thus, theoretically, we can expect that in all tissue of one organism can be simultaneously developed tumors of different localization and histogenesis. [6]

Thus, on initiation stage of carcinogenesis, normal somatic cells form dikaryons, carriers of high carcinogenic potency and giant polykaryocytes. These last cells in most cases, are nonviable cellular formations, i.e., in the genetic respect, they probably are defective peculiar forms, with the lost abilities to enter in S-period of cellular cycle and mitosis. It is necessary to take into consideration that the appearance in certain tissues and organs polykaryocytes can signify presence of conditions for cells' hybridization and consequently, possibility of appearance of tumorous dikaryons and then sinkaryons.

The mechanism of malignant transformation of the precancerous cell into a tumorous one probably has the molecular and sub-cellular foundations. On the promotion stage, after the influence of complete carcinogens or promoters on tissue, where precancerous sinkaryons preexist, in these cells the chromosomal aberrations of different types and gene amplifications may arise. [7]. In majority of cases, because of unsuccessful mitosis, elimination of precancerous sinkaryons probably takes place at stage of transformation into tumor sinkaryons. In rare cases, in result of specific (reciprocal or nonbalanced) translocation, duplications and following genes' amplifications, these cells may undergo irreversible alterations and may transform into true tumor cells (sinkaryons of stage2).

As known, complete carcinogens and initiators can induce damage on level on genes. Such damages are: gene amplification, protooncogene activation, violations of DNA physiological methylation and so on. Violations can be brought on chromosomal level as well. Such alterations are chromosomes structural aberrations, such as translocations (reciprocal and nonbalanced), deletions, duplications, inversions. Chromosome number alterations, ultimately make conditions for aneuploidy of a chromosome set attribute loss or addition of separate chromosomes, [8] what takes place because of their incorrect divergences in mitosis. [9]

Out of numerous dikaryons and sinkaryons formed after the influence of carcinogenic agents, only a few precancerous cells can acquire the potency of unlimited proliferation. In the overwhelming majority of cases, they seem to die in the phase of transformation into tumorous cells due to lethal mitosis. Specifically, due to the imbalance of karyotypes, they either never rich mitosis or are unable to complete it due to disturbance in spindle organization or chromosomes motion. Therefore, true tumorous sinkaryons are probably formed very rarely. Any combination of cancer cell with other differentiated or nondifferentiated normal somatic cells are possible. This

is the reason for different histogenesis and heterogeneity (morphologic, cytogenetic, antigenic and etc.) of tumorous cells.

In the case of progression, generalization of tumor process, exacerbation, a transition to a more malignant stage take place. The progression stage should be conditioned by two radically different properties of a tumor cells, which is being manifested in the ability to develop invasion process, in the one case, and the metastatic process, in the other case. These two processes, i.e. invasion and metastasis, significantly differ from one another by their development, cellular mechanisms and so on. In particular, in the invasion process, inclusion by tumor cells of the neighbor new normal cells in the fusion process takes place, as a result of which tumor cells of new phenotype and genotype are formed. In contrast to it, in the metastasis process, the development of secondary tumors in a macro organism takes place, as a result of breaking-away of some cells from the initial tumor. In the case of invasion and metastasis, a great importance is seemingly given to a changeable electric charge value. However, if in the case of metastasis, the electric charge on the tumor cell's surface counts during almost the whole process, in the case of invasion such charge will count only upon a contact between a tumor cell and its neighbor normal somatic cell, which enables the convergence and further adhesion of these cells.

Separate clones of specific malignant tumors can differ from each other in many abilities, including their metastatic potency, antigen composition, sensitivity to different factors and so on. The origin of clonal divergence may be the consequence of genetic instability of tumorous cells, what unlimitedly leads to tumor progression. We can assume that the possible mechanism of morphological, cytogenetical, etc., heterogeneities of cancer cells and tumor invasion consistent in the further involuntary somatic hybridization of these cells.

Thus it may be supposed that a possible mechanism of invasion process is the hybridization of somatic normal cells, i.e., the already formed tumorous cells can often be hybridized both with the same cells and with normal cells. [10] After the fusion with other tumorous cells or with normal cellular elements, formation of dikaryons may take place, in which one nucleus can be represented by tumorous cells, and the second, by normal cells (in case of fusion of tumor and normal cells). After synchronous mitosis or mechanical assembly of nuclei in such cells, a hybrid cell-synkaryon can be formed. This cellular type is represented with new genotypic (and in some cases phenotypic, as well) signs.

Only some cells of the primary cancer are able to metastasize. Once the cancer cell is detached from the primary tumor, it will penetrate blood vessels, retaining viability under the damaging and lethal to it influence, such as blood turbulence and contacts with the immune system cells. Further, by passing the basement membrane, it will go from the blood-vessel endothelium to the target organ. In order to perform such a complex migration, it is necessary that essential alterations of electric potential on the plasma membrane of the cancer cell take place, which should be associated with the hydrogenous index (pH) changes. In the case of a relatively suppressed metabolism of cancer cells, the environmental pH increases. In the case of high pH, a cancer cell may develop a high negative charge, which suppresses its adhesion with the tumor bulk and can lead to its detachment and migration in the macro organism. In the event of enhanced metabolism of a cancer cell, the environmental pH is suppressed, as a result of which cancer cells acquire a relatively low negative, neutral or even a positive charge, its attachment to a new place and the formation of new cancer cell populations will be quite real. In contrast to metastasis, invasion process should take place only if cancer cells have a low negative, neutral or positive charge.

From the view of karyogamic theory of carcinogenesis we are trying to answer one of the most complex questions in oncology: are the chromosomal aberrations the cause or the consequence of the cancerous growth? We think that during initiation (formation of precancerous cells) chromosomal aberrations are on the third place after the perforations of the plasma membrane and fusogeny (formation of dikaryons and then synkaryons). During promotion chromosomal aberrations are on the first place before gene amplification. In the case of progression (formation of cancerous cells with a new genotypes and phenotypes) the sequence should be the same as for the initiation (perforations, fusogeny and after that -chromosomal quantitative aberrations). So, the role of chromosomal aberrations differs at the different stages of carcinogenesis, but there are no doubts about their causative connections: at the stages of initiation and progression chromosomal aberrations are among the main causative factors (after the plasmatic membrane perforations and fusogeny), while at the stage of promotion, the main causative factor is the structural chromosomal aberrations.

In our opinion the “theory of two synkaryons” contains principal postulates of other theories and hypothesis dealing with the above-mentioned problem. At the same time, the theory provides a comprehensive interpretation of different aspects of clinical and experimental oncology unexplained or insufficiently explained until now by other hypothesis and theories. Thus, given that a tumor cell represents a hybrid originated because of the spontaneous or induced fusion of two normal somatic cells and the subsequent karyogamy, it can be assumed that inhibition of the approaching and the further adhesion process of normal somatic cells will suffice for preventing this fatal disease.

To achieve the set objective, it would be ideal to use the cell plasma membranes’ stabilizing substances (to avoid perforations) or the low-molecular disaggregates(for inhibition of adhesion).This substances might be administered to the person permanently in small harmless doses.

For this purposes, molecular hydrogen can be used. Molecular hydrogen has been accepted to be an inert and nonfunctional molecule in our body. Molecular hydrogen reacts with strong oxidants such as hydroxyl radicals in cells and proposed its potential for preventive and therapeutic applications. This molecule rapidly diffuses into tissues and cells. It stimulates energy metabolism and can prevent cell fusion processes. [11]. For this purposes extensive clinical examinations using model animal organisms should be used.

Conclusion

In our opinion the theory of two synkaryons contains principal postulates of other theories and hypotheses dealing with the abovementioned problem. At the same time, the theory provides a comprehensive interpretation of different aspects of clinical and experimental oncology unexplained or unsufficiently explained until now by other hypotheses and theories.

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ATYPICAL PRESENTATION OF HSV-INDUCED ERYTHEMA MULTIFORME WITH PREDOMINANT ORAL MUCOSAL INVOLVEMENT, PROMINENT SYSTEMIC MANIFESTATIONS, AND SUBTLE CUTANEOUS LESIONS

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ABSTRACT

Erythema multiforme (EM) is an inflammatory skin and mucosal disease related to multiple factors, including infections. This report presents a case of HSV-associated EM in a 21-year-old male, characterized by severe oral mucosal involvement, prominent systemic manifestation, and mild cutaneous lesions. The patient, with a history of recurrent herpetic eruptions, developed severe oral mucosal lesions and a few scattered targetoid rash on upper extremities and chest. Treatment with acyclovir and corticosteroids led to significant clinical improvement and full recovery. This case highlights the importance of recognizing atypical presentation of erythema multiforme. Often following a self-limiting course, it can significantly affect the quality of life, especially if it is recurrent. Prompt identification and treatment with antiviral therapy and corticosteroids can alleviate symptoms and facilitate recovery.

Introduction

Erythema multiforme (EM) is an acute immune-mediated reaction with various etiological factors such as medications, autoimmune disorders, and infections, including herpes simplex virus (HSV) being the most common trigger [1,2].

The annual incidence of EM is approximately 1%, most commonly affecting adults under the age of 40. Although there are multiple etiologic factors for erythema multiforme, including infections, medications, etc., the underlying mechanisms are different. Herpes simplex-associated erythema multiforme (HAEM) happens when the immune system targets HSV antigens in the skin lesions.

In HAEM, the immune response is stronger, with more HSV-specific antibodies and a greater presence of CD4+ T-cells in the affected skin. In contrast, drug-induced EM mainly involves CD8+ T-cells [3].

EM is typically characterized by targetoid skin lesions, but in some cases, the condition may also cause significant mucosal involvement and systemic symptoms. EM is clinically classified into EM minor and EM major. EM major is characterized by severe mucosal involvement (involvement of ≥ 2 mucosal sites, may be associated with systemic symptoms, such as fever and arthralgia). Erythema multiforme minor refers to EM without (or with only mild, involvement of ≤ 1 mucosal site) mucosal damage (and without associated systemic symptoms) [1,2]. Fuchs syndrome is a type of skin sparing erythema multiforme major, with only mucosal involvement [3].

This case report describes an atypical presentation of HSV-associated erythema multiforme, where oral involvement was the primary feature, and systemic manifestations were prominent, while the cutaneous lesions remained limited.

Case Presentation

A 21-year-old male presented with symptoms that began two weeks ago, following a recent herpetic eruption. He initially experienced mild fever, headache, malaise, a non-productive cough, and rash, which he first noticed on his right upper extremity. It was described as raised, itchy, mildly painful, with a central erythematous area surrounded by a lighter ring and a darker, well-defined border, giving it a targetoid appearance. On the next day, painful vesicles appeared on the lips and buccal mucosa, which later progressed to erosions (Figure 1). Within a few days, his condition worsened, with high fever and more extensive oral mucosal lesions that interfered with his ability to ingest food and drink. The patient also reported a history of herpetic eruptions, with the most recent episode occurring approximately a week prior to the onset of his current symptoms. He described it as a few painful vesicular lesions in the perioral angular area, following exposure to cold weather. However, it had completely subsided before the onset of his current rash. Notably, he hadn't taken any medications prior to this presentation, ruling out a drug-related etiology, and there were no underlying medical conditions, such as Mycoplasma-induced pneumonia or other respiratory infections, that could explain the symptoms. Thus, attention was focused on HSV reactivation as the likely underlying cause. Due to worsening of his symptoms, he was subsequently admitted to our hospital.

Upon admission, the patient had a fever (38.5°C), tachypnea (25 breaths per minute), tachycardia (110 beats per minute at rest), and an oxygen saturation of 95%. He also complained of arthralgia, myalgia, and painful, bleeding oral mucosa. On examination, skin rash on the right upper extremity and chest had a central crust, surrounded by a ring of erythema and a second, slightly lighter-colored ring, resembling healing EM. The cutaneous involvement was minimal and poorly defined. However, his oral mucosal lesions were more severe, with numerous erosions that were abundantly bleeding and extremely painful, making it difficult to even open the mouth.



Figure 1: Mucosal erosions with hemorrhagic crusting involving the lips.

Diagnostic Workup

X-ray imaging showed no abnormalities. Laboratory results indicated an elevated neutrophil count and percentage - $9.37 \times 10^9/L$, 87.7% (normal: $2-7 \times 10^9/L$, 50.0-70.0%); along with a decreased lymphocyte percentage - 9.5% (normal: 20-45%). C-reactive protein (CRP) was elevated at 50 mg/L (normal <5). Liver function tests revealed mild elevations in ALT- 64.5 U/L (normal ≤ 50), GGT 93 U/L (93 U/L, normal 8-61); slightly elevated LDH (243 U/L, normal 135-225). Procalcitonin levels were within normal limits.

The serology test for HSV-1 was performed and showed a two-fold rise in IgM titers and more than a 60-fold increase in IgG titers. Although the IgM titer was not extremely high, it was still elevated, indicating a recent infection.

These findings, in combination with the patient's clinical history and physical examination, suggested HSV-triggered erythema multiforme.

Management and Outcome

The treatment was initiated with acyclovir (400 mg, PO, three times daily for 2 weeks), dexamethasone (20 mg, PO, twice daily for 5 days, followed by a tapering dose of 20 mg, once daily for an additional 7 days), topical glucocorticoid, triamcinolone (applied twice daily for 10 days) and omeprazole (20 mg, PO, for 12 days).

Acyclovir reduces viral replication. Dexamethasone manages the inflammatory response, with the tapering dose designed to avoid the complications of prolonged, systemic corticosteroid use while ensuring adequate control of symptoms. The topical corticosteroid is applied to affected skin areas for localized symptom relief. Omeprazole reduces the risk of gastrointestinal (GI) side effects associated with high dose steroid use.

By day three, the patient's fever decreased to 37.5°C, his general condition improved, and the oral lesions, though still bleeding, showed no new eruptions. By day ten, the patient was discharged, with normalized blood test results and only faint remnants of the rash remaining. In our patient, assuming prompt treatment and management, the short-term prognosis is generally favorable, with full recovery expected. However, considering the potential recurrence risk, especially in HSV-related EM, close follow-up is recommended. If the patient experiences future episodes, a prophylactic antiviral regimen could be considered to prevent or minimize outbreaks [1,4]. This approach can help reduce the risk of further recurrences and improve quality of life.

Discussion

This case presents an atypical presentation of HSV-associated erythema multiforme. On the one hand, involvement of only the oral mucosa and mild skin manifestations resemble erythema multiforme minor. On the other hand, the systemic manifestations and the severity of the oral mucosal damage, which severely impaired food and fluid intake, are more consistent with erythema multiforme major, particularly Fuchs syndrome, which does not require extensive skin involvement for diagnosis [1,3,5]. The prominent oral mucosal involvement severely impacted the patient's ability to eat and drink, resembling EM Major. However, the poorly defined, a few scattered targetoid rash didn't correspond to the classic EM Major manifestation.

Given the mucosal involvement and associated flu-like symptoms, Stevens-Johnson Syndrome (SJS) was considered in the differential diagnosis [5]. However, the mild cutaneous manifestations and the absence of the severe systemic features typical of SJS made it less likely. This case emphasizes the importance of considering a broad spectrum of erythema multiforme manifestations, as they may not always follow classical patterns and fit exactly into established classification categories (Table 1).

Table 1: Unclassifiable Presentation with Overlapping Characteristics.

Differential Diagnosis	Pros (Supporting Features)	Cons (Contradicting Features)
Erythema Multiforme Minor	Minimal cutaneous (<10%) and only oral mucosa involvement	Severe oral mucosal involvement; Systemic symptoms (fever, malaise) more severe than typically seen in EM minor.
Erythema Multiforme Major	Patient has severe oral lesions that make it difficult to eat and drink. Systemic manifestation	Only oral mucosa involved, mild cutaneous manifestation*.
Stevens-Johnson Syndrome (SJS)	Severe mucosal involvement is characteristic of SJS, Flu-like symptoms (fever, malaise) are also present.	No widespread skin sloughing, systemic involvement not severe enough.
* Fuchs syndrome - erythema multiforme major with only mucosal and no cutaneous involvement		

Although the rash was described as having a targetoid shape initially, the mild expression, likely due to the healing phase at the time of admission, and the limited number of lesions, primarily on the hands and chest, made it challenging to immediately recognize erythema multiforme. However, the anamnesis of recurrent HSV eruptions became a clue in identifying the diagnosis.

Although polymerase chain reaction (PCR) wasn't performed, it could provide valuable information for confirming the diagnosis. HSV DNA has been detected in patients with HSV-related EM (ranging from 36% to 81%) using PCR [5]. Thus, even if negative, it would not exclude HSV association, as the development of erythema multiforme is primarily driven by an immunological mechanism, and the patient's most recent herpetic eruption occurred about three weeks ago (a week prior to the onset of his current symptoms). This timeline also explains the relatively modest IgM antibody titer.

A critical aspect of managing such cases is the need to rule out other conditions that may mimic or complicate the presentation. Flu-like symptoms raised concern for an upper respiratory tract infection (URI) or potentially pneumonia. As high-dose corticosteroids were considered as part of the treatment plan, clinicians must be cautious about initiating immunosuppressive therapy without excluding undiagnosed infections [6]. In this case, chest X-ray did not reveal any abnormalities, and no lower respiratory tract involvement was present, but it remains essential to carefully assess clinical signs and perform appropriate imaging to avoid complications. Corticosteroids, especially at high doses, can exacerbate infections, including HSV, by suppressing the immune response and complicate early recognition of infection for the same reason. While the benefits of corticosteroid therapy typically outweigh the risks, particularly in patients without known immunocompromising conditions, increased caution is still warranted. Monitoring for signs of infection, both before initiating and during treatment, remains crucial [7]. Regarding acyclovir administration, some studies suggest that antiviral therapy during acute EM does not alter the clinical course of the disease [4], that sounds quite logical considering the immune-mediated mechanism of EM. However, even if HSV itself is not a common culprit in EM flare-ups, its administration is still justified. As mentioned before, high-dose steroids can trigger viral reactivation, and suppressing its replication during such a vulnerable period seems appropriate.

Conclusion

This case describes atypical presentation of HSV-associated erythema multiforme, that doesn't fit the classic EM classification. Early intervention with antiviral agents and corticosteroids can significantly expedite recovery, but clinicians must remain cautious and ensure a comprehensive assessment to avoid complications, such as HSV reactivation. Given the potential for recurrence, close follow-up is essential, and prophylactic antiviral therapy may be indicated to reduce the risk of future episodes.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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EXPLORING THE PROFOUND ENVIRONMENTAL CONTAMINATION BY PHARMACEUTICAL RESIDUES, THEIR ACTION ON ECOSYSTEMS: HEALTH RISKS, COMPLEX INTERACTIONS, ASSESSING RISKS, COMPREHENSIVE MITIGATION STRATEGIES AND THE IMPERATIVE FOR ENHANCED RISK EVALUATION

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ABSTRACT

Aim of the research was to study the profound environmental contamination by pharmaceutical residues, their action on ecosystems: risks, complex interactions, assessing risks, comprehensive

mitigation strategies and the imperative for enhanced risk evaluation. Pharmaceutical residues in the environment have become a growing concern due to their potential impact on ecosystems and human health. These contaminants, often originating from human and veterinary medicine, are found in water, soil, and air, and pose significant risks through their complex interactions with other environmental pollutants. Despite their widespread presence, current environmental risk assessments typically focus on individual substances, potentially underestimating the broader ecological implications. This study explores the profound environmental contamination caused by pharmaceutical residues, emphasizing their effects on aquatic and terrestrial ecosystems. It also discusses the risks associated with the accumulation of these substances, their interactions with other pollutants, and the potential for synergy or additive effects. Furthermore, it highlights the urgent need for more robust and comprehensive risk assessments, including the consideration of transformation products, indirect effects, and the long-term consequences of pharmaceutical exposure. The paper advocates for the development of improved mitigation strategies, such as enhanced waste treatment technologies, better pharmaceutical disposal systems, and more effective regulatory frameworks. Ultimately, this research calls for a multidisciplinary approach to address the environmental challenges posed by pharmaceutical contamination, aiming to safeguard both ecological and human health in the face of growing global concerns. Pharmaceutical contamination of the environment is an increasingly significant concern that demands urgent attention. The presence of pharmaceutical residues in natural systems, primarily from human and veterinary drug use, leads to contamination of water, soil, and air, where their persistence can disrupt ecological balance and potentially harm human health. Current environmental assessments often fail to consider the complex interactions between pharmaceutical residues and other pollutants, leaving many potential risks overlooked. A key issue is the difficulty in predicting the cumulative effects of these contaminants, especially when pharmaceuticals are mixed with other toxic substances in the environment. The impacts are not limited to direct toxicity but may include indirect effects, such as changes to microbial communities and disruptions in ecological processes, like nutrient cycling. Moreover, the transformation products of pharmaceuticals, which may be more persistent or toxic than the original compounds, remain poorly understood and under-researched. Given these challenges, the existing risk assessment frameworks, which often focus on single-substance exposures, are insufficient. A more holistic approach is necessary to account for the interactions, transformations, and cumulative risks posed by pharmaceutical residues. Effective mitigation strategies will require a combination of improved waste management practices, targeted regulatory policies, and advanced treatment technologies. Understanding the full scope of pharmaceutical contamination and its ecological and human health implications is essential for developing proactive, sustainable solutions. The uncontrolled release drugs into the environment may be wastewater and atmospheric emissions from enterprises producing finished drugs and pharmaceutical substances. the environmental safety of such production is usually regulated by law. However, accidental releases of drugs into the environment or those that violate existing norms and regulations that occur in industry, are nevertheless not systematic. Moreover, there is a general trend towards a reduction in the environmental load on the part of pharmaceutical production, primarily in developed countries of the world, due to a consistent increase in the technological effectiveness and organization of the production process, the introduction of increasing quality standards and environmental safety, and control by authorized government bodies . It is also necessary to take into account that pharmaceutical production is localized

geographically, and if an accident occurs at the enterprise or there are violations of environmental legislation, then such emissions are exclusively local in nature and pose a danger only to specific regions. For all the reasons listed above, such sources are not the subject of analysis in this review, although they contribute to environmental pollution. Other sources of drugs that are practically uncontrollable and are formed mainly by people who use drugs for medical purposes, as well as in animals, pose a great danger to the environment. The contamination of the environment by pharmaceutical residues presents a critical challenge to both ecosystem health and human well-being. The widespread presence of these substances in water, soil, and air underscores the need for a more comprehensive understanding of their environmental fate and effects. Current risk assessment approaches, which often examine individual compounds in isolation, are inadequate in addressing the complex interactions and cumulative risks posed by pharmaceutical pollutants, especially when combined with other environmental contaminants. Furthermore, the potential dangers of pharmaceutical transformation products, which may exhibit greater toxicity or persistence, remain underexplored. To address these concerns, a paradigm shift is required in environmental risk assessment, incorporating multi-substance interactions, long-term ecological impacts, and the effects of transformation products. The development of robust mitigation strategies—such as advanced waste treatment technologies, improved pharmaceutical disposal practices, and more stringent regulatory frameworks—must be prioritized. By adopting a more integrated, precautionary approach to pharmaceutical contamination, we can better protect ecosystems and human health from the growing threat posed by these persistent pollutants. Future research and policy initiatives should focus on improving our understanding of these substances, developing innovative solutions to reduce their environmental impact, and ensuring sustainable management practices for pharmaceuticals.

Keywords: Drug, pharmaceuticals, medicine, ecology, environment, human health.

Introduction

The presence of pharmaceutical residues in the environment has emerged as a significant global concern, as these substances increasingly contaminate water, soil, and air systems. The widespread use of pharmaceuticals in human and veterinary medicine, along with improper disposal practices, has led to the accumulation of pharmaceutical compounds in various environmental compartments. These residues, often detected in trace amounts, are not only persistent but can also have profound ecological and human health implications. The environmental impact of pharmaceuticals extends beyond direct toxicity, as they can disrupt ecosystems, alter microbial communities, and interfere with natural processes such as nutrient cycling and waste decomposition [1-2].

While some studies have identified individual pharmaceuticals in the environment, the complexity of interactions between multiple contaminants—such as pharmaceuticals, pesticides, and industrial chemical remains insufficiently understood. Current risk assessment frameworks primarily focus on single-substance exposure, which may fail to account for the cumulative or synergistic effects that arise when pharmaceuticals interact with other environmental pollutants. Additionally, the potential risks associated with transformation products, which may be more persistent or toxic than the parent compounds, have been largely overlooked [3-5].

Given these concerns, there is a pressing need for a more integrated approach to the study and management of pharmaceutical residues in the environment. This includes the development of more robust risk assessment models that consider multiple substances, the environmental behavior

of transformation products, and their potential long-term ecological impacts. Furthermore, effective mitigation strategies, including improved waste management, disposal practices, and regulatory measures, are essential to address the growing issue of pharmaceutical contamination. This paper aims to explore the environmental contamination caused by pharmaceutical residues, assess their risks and interactions, and highlight the need for improved frameworks to better understand and mitigate their impact on both ecosystems and human health [6-8].

The environmental contamination caused by pharmaceutical residues is an increasingly complex and critical issue that threatens the health of ecosystems and poses risks to human well-being. The widespread use of pharmaceuticals in both human and veterinary medicine, combined with inadequate disposal practices, has led to the persistence of these substances in various environmental media, including water, soil, and air. While pharmaceuticals are essential for human health, their unintended release into the environment raises concerns due to their potential ecological impacts. These compounds, often present in trace amounts, can accumulate over time and exhibit a range of adverse effects on aquatic and terrestrial organisms, including the disruption of microbial communities, alterations in biodiversity, and interference with critical ecosystem processes such as nutrient cycling and soil fertility [9-10].

Pharmaceutical residues in the environment are particularly concerning because they can have multiple modes of action, which can interfere with the natural functioning of ecosystems. Some pharmaceutical compounds, such as antibacterial, have been shown to affect soil microbes that play an essential role in processes like pesticide degradation and manure decomposition. The potential for synergistic or additive effects among pharmaceuticals and other environmental pollutants, such as pesticides, biocides, and industrial chemicals, adds further complexity to the issue. While individual pharmaceuticals have been studied in isolation, little is known about how they interact with other chemicals in the environment, which may lead to underestimated risks [11-12].

Current environmental risk assessments often focus on single substances, neglecting the combined effects of pharmaceuticals in the environment. This approach may overlook the potential for greater toxicity when multiple substances interact or the unanticipated consequences of transformation products, which can be more persistent or toxic than their parent compounds. For example, the breakdown products of some pharmaceuticals may persist in the environment for extended periods, increasing the long-term ecological risks. Moreover, the potential for these transformation products to migrate through the food chain and impact human health remains largely unexamined [13-15].

The lack of comprehensive understanding of pharmaceutical pollution in the environment is further compounded by inadequate data on the long-term effects of low-level, chronic exposure to these compounds. Despite significant advances in detecting pharmaceutical residues in environmental matrices, only a small fraction of the thousands of active pharmaceutical ingredients used globally have been adequately studied. This gap in knowledge makes it difficult to assess the full scope of the risks posed by pharmaceutical contamination [16-18].

To address this growing environmental challenge, there is an urgent need for an integrated, precautionary approach to risk assessment that considers the complex interactions between pharmaceuticals and other pollutants. A more nuanced understanding of how pharmaceuticals degrade in the environment, how they interact with other chemicals, and how these compounds affect ecological functions and biodiversity is essential. This requires an expansion of ecotoxicity testing to incorporate a broader range of subtle biological effects, such as behavioral changes,

physiological disruptions, and alterations in biochemical processes. Advanced technologies, including genomics, proteomics, and high-throughput screening, could play a pivotal role in improving the assessment of pharmaceutical pollutants.

Moreover, effective mitigation strategies must be developed to reduce pharmaceutical releases into the environment. These strategies could include improved waste management practices, such as source control, better disposal systems for unused pharmaceuticals, and more advanced wastewater treatment technologies. Additionally, regulatory frameworks must be strengthened to ensure that pharmaceutical contaminants are adequately managed and that new drugs are evaluated for their environmental risks before they are widely used. Such efforts would require collaboration among scientists, policymakers, and the pharmaceutical industry to develop sustainable solutions that minimize the environmental impact of pharmaceutical residues [19-21].

This paper aims to delve deeper into the environmental contamination caused by pharmaceutical residues, exploring their ecological impacts, the complexity of their interactions with other pollutants, and the urgent need for more comprehensive and integrated risk assessments. Furthermore, it will highlight the critical role of advanced mitigation strategies, innovative treatment technologies, and regulatory measures in addressing the growing environmental threat posed by pharmaceuticals. By fostering a greater understanding of pharmaceutical pollution, we can better protect ecosystems, safeguard human health, and mitigate the long-term risks associated with pharmaceutical contamination in the environment [22-24].

Goal

Aim of the research was to study and analyzed the profound environmental contamination by pharmaceutical residues, their action on ecosystems: risks, complex interactions, assessing risks, comprehensive mitigation strategies and the imperative for enhanced risk evaluation.

Methodology

The material of the article was the data from scientific publications, which were processed, analyzed, overviewed and reviewed by generalization and systematization. Research studies are based on a review/overview assessment of the development of critical visibility and overlook of the modern scientific literature. Use the following databases: (for extensive literature searches to identify the profound environmental contamination by pharmaceutical residues, their action on ecosystems: risks, complex interactions, assessing risks, comprehensive mitigation strategies and the imperative for enhanced risk evaluation.). PubMed, Medline, Web of Science, Scopus, Web of Knowledge, Clinical Key, Tomson Reuters, Google Scholar, Cochrane library, and Elsevier foundations, national and international policies and guidelines were also reviewed and as well as grey literature.

Results and Discussion

Human drugs, hormones, antibiotics, analgesics, antidepressants and anticancer drugs indicate environmental risks. When it comes to veterinary products, hormones, antibiotics and parasiticides are often considered environmentally sensitive. These results are consistent with findings from the open scientific literature on approaches to environmental drug prioritization. Promising approaches such as environmental risk assessment of pharmaceuticals play an important role in minimizing the problems caused by pharmaceuticals in the environment. However, the regulatory framework for environmental risk assessment can be improved by

integrating the environment into the risk-benefit analysis of drugs for human use, (ii) improving risk management capabilities, collecting data on existing drugs, and improving the availability of data for environmental risk assessment. In addition, more general and integrative stages of regulation, legislation and research have been developed and presented in this article. To minimize the amount of pharmaceuticals in the environment, they should strive to improve existing pharmaceutical legislation, prioritize pharmaceuticals present in the environment, and (iii) improve the availability and collection of pharmaceutical data. So, the presence of pharmaceuticals in the environment has received increasing attention. Medicines are released into the environment and can have harmful effects [25-27].

It is clear that priority must be given to environmentally relevant pharmaceutical substances. Existing pharmaceutical substances for which environmental data are lacking, as well as substances being considered for monitoring campaigns, need to be given priority attention to identify and minimize their environmental risk. According to the World Health Organization, concentrations of pharmaceuticals in water systems are expected to increase as the use of pharmaceuticals is expected to increase as they become more accessible to a growing world population. To be proactive, it is necessary to identify and prioritize the most important substances for the environment, which has become a challenge in recent years. Depending on the chemical properties of the substances, different approaches have been proposed. Most often, a combination of exposure and exposure data is used to prioritize environmentally significant chemicals. Several approaches have proposed using toxicological data to predict adverse effects on aquatic organisms (comparisons of several, but not all, approaches are included). Most published approaches to prioritization indicate the high environmental potential of various drug classes. Human medicines are often a priority, with all attention paid to hormones, antibiotics, psychotropic, anti-inflammatory and cytostatic substances, as well as beta blockers. In addition to hormones, antibiotics and parasiticides have proven to be environmentally important in veterinary medicines [28-30].

The origin and possible effects of human and veterinary drugs on aquatic and terrestrial organisms are relatively new topics. However, in recent decades, a large number of studies have been published indicating the varied effects of drugs on organisms and the occurrence of drugs in different environmental areas on a global scale. It is now recognized that the environmental impact of pharmaceuticals is a global issue and not just a problem in developed countries. The general public, industry, research or regulatory authorities, do not want bioactive drugs to end up in the environment and therefore potentially in their drinking water. Therefore, the amount of pharmaceuticals in the environment needs to be minimized using all available strategies. Promising approaches such as ERA play an important role in minimizing problems before drugs enter the environment. These strategies need to be strengthened and adapted to minimize the amount of pharmaceuticals entering the environment [31-32].

Regarding environmental risk assessment, (i) include the environment in the risk-benefit analysis of pharmaceutical products for human use, (ii) improve risk management capabilities, (iii) collect data on existing pharmaceutical products, and (iv) improve environmental availability risk. These assessments represent some important next steps. The biological effects to environmental exposures promise interesting results, although very few studies have been conducted on wild animals or caged organisms, such as in the wild or in ecologically significant environments. This may be due to the lack of analytical method protocols as well as the variety of pharmaceutical structural features that are not easy to handle but need to be taken into account [33-35].

Various policies need to be implemented throughout the life cycle of pharmaceutical products, including source-oriented, consumer-oriented and waste management-oriented activities. The most effective solutions must be implemented at the source, before drugs enter the environment. These measures include rational drug consumption, prescribing more environmentally friendly drugs and developing harmless and easily biodegradable drugs. Improved disease prevention, personalized medicine, improved package sizes, and PC redistribution markets may go some way to avoiding drug waste. The next step is to prevent unavoidable waste from entering the environment. Therefore, correct collection and disposal of is critical and must be adapted to national and local conditions. Finally, education of health care professionals and the public, as well as partnerships between environmental scientists and clinicians, paharmacists are important at all stages of the pharmaceutical product life cycle. All joint efforts must be guided by a One Health approach to combat pharmaceutical waste and improve the health of people, animals and the environment, which are closely linked. To reduce contamination levels when consuming medicines should be: Creation of a system for collecting drug waste generated by the population; Conducting awareness-raising work with the population, employees of healthcare institutions and other target groups on the topic of environmental pollution by drug waste; Taking into account environmental factors when choosing and prescribing treatment. At the same time, there is no need to put environmental protection above the human need for treatment; Development and implementation of wastewater treatment systems. It should be taken into account that urban wastewater has an unstable composition in terms of names and concentrations of drugs. A higher priority is to prevent drug residues from entering the city sewer system [36-38].

Medicines play an important role in the treatment and prevention of diseases in humans and animals. But it is due to the very nature of drugs that they can also have unintended effects on animals and micro-organisms present in the environment. Although side effects on human and animal health are typically studied in extensive safety and toxicology studies, the potential environmental impacts of drug manufacturing and use are less well understood and have only become recently a topic of research interest. Some of the effects of various compounds, including veterinary anthelmintics and antibacterial therapeutics, are already known, but there are many other substances that can affect organisms in the environment. The situation is further complicated by the fact that some pharmaceuticals can have effects on bacteria and animals well below the concentrations usually used in safety and effectiveness testing. Additionally, degradation products and the combination of different biologically active compounds can have unexpected effects on the environment. Although it is reasonable to assume that these substances do not significantly harm humans, we have only recently begun to investigate whether and how they affect a wide range of organisms in the environment and what this means for health environmental.

The scale of this potential problem should not be underestimated. More than several million women use oral contraceptives, which eventually end up in the environment. A wide range of human drugs are produced and used, including antibiotics, statins, and cytotoxins used to treat cancer, some of which are produced in quantities of several thousand tons per year. Information on the quantities of drugs used by humans is difficult to obtain, but recent data from Canada indicate that the most commonly used drugs include acetaminophen, aspirin, ibuprofen, naproxen, and carbamazepine. Large quantities of veterinary drugs, such as antibacterials, antifungals, and parasiticides, produced in aquaculture and agriculture can also contribute to environmental stress,

especially because they are often found directly in soil and surface water, unlike human drugs, which typically pass through wastewater treatment plants first.

Human and veterinary drugs enter the environment through a variety of pathways. Residues generated during manufacturing may eventually end up in surface waters. After administration, human medications are absorbed, metabolized, and then discharged to sewers. They typically pass through wastewater treatment plants before ending up in water or on land through the application of sewage sludge. Antibacterial agents used to treat fish or shrimp in aquaculture end up directly in surface waters. Veterinary drugs used to treat grazing animals end up in soil or surface waters. When intensively treated livestock are treated, these drugs may end up indirectly in the environment through the application of slurry and manure as fertilizer. Other minor pathways include air emissions and disposal of unused medications and containers.

Pharmaceuticals have been entering the environment for decades, and researchers have only recently begun to quantify their levels in the environment. Using information from different countries and uses, several prioritization exercises have identified pharmaceutical products that are most likely to end up in the environment. Annual veterinary drug use was combined with information on routes of administration, metabolism and ecotoxicity to identify drugs that should be monitored under a national recognition programme. New analytical techniques such as liquid chromatography coupled with tandem mass spectrometry (LC-MS-MS) have provided a better understanding of the behaviour of drugs in the environment and have determined their concentrations in wastewater treatment plants, soil, surface water.

Once released into the environment, pharmaceuticals will be transported and distributed by air, water, soil or sediment. Their distribution will be influenced by a number of factors, such as the physicochemical properties of the compound and the characteristics of the receiving environment. The extent to which a pharmaceutical product is transported between different environmental media depends primarily on the sorption behavior of the substance in soils, sludge and wastewater systems, and wastewater treatment plants, which varies considerably between products. pharmaceuticals. Additionally, unlike other organic substances such as pesticides and industrial chemicals, the sorption behavior of many pharmaceuticals cannot be simply inferred from the hydrophobicity of the substance or the organic carbon content of the material. solid. Pharmaceutical substances can also be degraded by biological organisms in processing systems, water bodies and soils, as well as by abiotic reactions. Typically, these processes reduce the effectiveness of medications; however, some degradation products have the same toxicity as their original compounds. Additionally, degradation varies considerably depending on chemistry, biology and climatic conditions. For example, the half-life of the antiparasitic ivermectin is six times longer in winter than in summer, and the compound breaks down more quickly in sandy soils than in sandy loam soils. The natural estrogens 17β -estradiol and estrone are degraded in both aerobic and anoxic reservoirs of activated sludge systems, while 17α -ethinylestradiol is only degraded under aerobic conditions. All of this adds to the complexity of the problem and requires customized solutions for individual pharmaceuticals and applications.

In some studies have found low levels of a wide range of pharmaceuticals, including hormones, steroids, antibiotics and parasiticides, in soils, surface waters and waters. underground. Reported concentrations are generally low, but what is even more alarming is that many therapeutic substances have been found under a wide range of hydrological, climatic and land use conditions, and many substances have been detected throughout of the year. The study results raised

questions about how this mixture of veterinary and medicinal drugs, abundant in soil and surface waters, affects beneficial organisms in the environment and human health.

Comparison of these data with information on therapeutic doses, drinking water restrictions, and health advisories shows that concentrations of therapeutic compounds in surface waters are well below levels of concern to human health. Therefore, indirect exposure to pharmaceuticals through the water supply is unlikely to pose a risk to humans. However, risks from other exposure routes, such as ingestion of crops through soil and biomagnification through the food chain, have not yet been quantified and cannot be completely excluded. Environmental health effects are more difficult to assess. Human and veterinary drugs are required by law to undergo an environmental risk assessment for their effects on aquatic and terrestrial organisms before a product can be marketed, and the EU has introduced similar requirements. These environmental impact studies examine the potential adverse effects of manure on fish, daphnia, algae, bacteria, earthworms, plants, and invertebrates. Most of the data are publicly available (many environmental assessments are posted on the FDA website) and provide a reasonable data set for further study. However, legitimate questions arise about the real value of these studies. Risk assessments typically use standard ecotoxicity tests, which are often short-term and focus primarily on mortality as an endpoint. In addition, aquatic tests typically focus on the aquatic environment and do not take into account pharmaceuticals present in sediment. In general, the effects observed in these studies occur at concentrations significantly higher than those measured in the environment. Less well known are the more subtle effects that therapeutically active substances may have on organisms in the environment, such as growth, fertility, or behavior. Pharmaceutical compounds are designed to be either highly active and receptor-reactive in humans and animals, or toxic to many infectious organisms, including bacteria, fungi, and parasites. However, this does not mean that they affect only these life forms. Many lower animals have receptor systems similar to those of humans and animals used in agriculture. In addition, numerous groups of organisms that affect human and animal health, and to which pharmaceutical products are directed, play a critical role in the functioning of ecosystems. It is therefore possible that pharmaceuticals have subtle effects on aquatic and terrestrial organisms that are not detected in standard tests. And because human drugs are released almost continuously into the environment, wild organisms are exposed for much longer periods than those used in standard tests. Researchers have therefore begun to study some of the more subtle effects caused by long-term, low-dose exposure to pharmaceuticals. A wide range of subtle effects have been reported, including effects on oocyte and testis maturation, effects on insect physiology and behavior, effects on faecal decomposition, inhibition of growth or stimulation of aquatic plant and algal species, and the development of antibacterial resistance in soil. There is strong suspicion that steroids in contraceptives affect the fertility and development of fish, reptiles, and aquatic invertebrates. Similarly, human and veterinary antibiotics have effects on soil microbes and algae.

Macrocyclic lactones can affect invertebrate larvae in faeces at relatively low concentrations; earthworms appear sensitive to parasiticides used in veterinary medicine, and plants may be sensitive to many antibiotics. In addition, macrocyclic lactones have been shown to cause numerous sublethal responses in dung-feeding invertebrates, such as reduced feeding, water imbalance, decreased growth rate, inhibition of pupation, and impaired mating. Since livestock faeces contain a diverse fauna and provide a fruitful habitat for other species, macrocyclic lactones may therefore indirectly affect other species by depleting the quality and quantity of their

food source. Sediment-related effects of pharmaceutical products have also been considered. Carbamazepine affects the emergence of chironomid midges.

Additionally, pharmaceuticals are not the only pollutants of environmental systems. Aquatic and terrestrial organisms are exposed to a mixture of drugs and other substances, including pesticides, biocides and common industrial chemicals. A recent study discovered the antibacterial agent lincomycin in combination with other additional chemicals. The study focused only on selected compounds, so many other synthetic substances could be present. Therefore, interactive effects are possible, such as the additivity of substances with similar modes of action and synergy. Because current environmental risk assessments focus on individual substances, it is possible that these assessments underestimate exposure. It is also possible that the environmental behavior of a substance changes in the presence of other substances. For example, antibacterials have been shown to affect soil microbes that play an important role in the breakdown of pesticides. For example, research shows that veterinary antibacterial medications can influence the reduction of sulfates in soil and inhibit the decomposition of manure. If an antibacterial veterinary drug was applied as a slurry to an agricultural field prior to pesticide application, it is possible that the environmental impact of the pesticide would be dramatically altered.

Because very little is known about the effects of pharmaceuticals on environmental health and the interactions of various compounds, some workers are taking a precautionary approach and developing methods to reduce releases of these substances into the environment. Various approaches have been proposed, including source control of pharmaceuticals, source separation, waste treatment to remove pharmaceutical compounds, implementation of breeding practices, and improvement of drug disposal systems. expired medicines and waste containers. Source control includes marking, controlled disposal and separation of urine. Separating sources of pharmaceuticals, such as hospital wastewater, which are likely to be heavily contaminated with pharmaceuticals and antibiotic-resistant bacteria, should allow treatment resources to be focused on the most contaminated waters.

Pharmaceuticals may be removed by treatment with physical processes such as sorption or volatilization, biodegradation, or chemical reactions such as ozone treatment. The significance of the different options is likely to be very specific to each substance. For example, the antibiotic ciprofloxacin is removed by strong sorption to suspended solids in sewage sludge, whereas diclofenac and 17 α -ethinyl estradiol undergo significant biodegradation in aged activated sludge. A range of measures to reduce emissions is therefore likely to be required. Many treatment methods that eliminate pharmaceuticals may also produce transformation products that are more persistent and more mobile than the parent compounds, some of which may also have similar or increased toxicity. Little work has been done to assess the environmental impacts of these transformation products. Clearly, a wealth of data on the levels of pharmaceuticals in the environment and their effects on aquatic and terrestrial organisms has become available in recent years. However, many issues remain to be resolved before it can be determined whether residues in the environment pose a threat to human health and the environment. First, there are risks associated with substances that have not yet been studied. Due to resource limitations, only a small proportion of pharmaceuticals in use today have been studied, and there is an urgent need to understand how other substances affect the environment. Second, we can better assess ecotoxicity. Current standard ecotoxicity tests are likely inadequate to assess the effects of many pharmaceuticals. The use of more subtle parameters such as behavioral changes, physiology, and biochemistry is of particular interest. Further work is needed to identify these subtle effects. It is

likely that many of the technologies currently used by molecular biologists, such as proteomics and genomics techniques or large-scale DNA or protein microarrays, can make a significant contribution to this task. Third, ecotoxicity data are relevant to the real world. Although many subtle effects have been demonstrated following exposure to pharmaceuticals at environmentally realistic concentrations, we need to establish the significance of these data in terms of ecological functioning. Fourth, there are risks associated with mixtures. Pharmaceuticals are unlikely to occur alone in the environment, so the current single-substance risk assessment approach may underestimate environmental impacts. This also includes potential indirect effects. Little has been done to determine the absorption of pharmaceuticals into organisms and throughout the food chain. Such studies are critical to determining the potential indirect impacts of environmental exposure on the ecology and human health. A related question is: should we be concerned about transformation products? Much of the work to date has focused on the parent compounds; however, we know that transformation products are produced in the environment and during processing. It is important that we begin to understand the potential impacts of these substances. Future work should therefore focus on understanding the biotic and abiotic processes underlying the release, fate, and environmental impacts of pharmaceuticals. Finally, certain environmental exposures lead to greater resistance to antibacterial drugs. A wide range of antibacterial agents have been found in water and soil, many of which persist for some time. It is possible that such exposures could lead to the development of resistant microbes that could pose a serious threat to human and animal health.

The future work should focus on understanding the biotic and abiotic processes underlying the release, environmental fate, and effects of pharmaceuticals. Such an understanding should ultimately enable the development of new modeling approaches. A comparative plasma concentration model linking mammalian and fish species, which could provide useful information on the likely effects of pharmaceuticals on fish. Other modeling approaches, such as quantitative structure-activity relationships, could help estimate the environmental impacts of pharmaceutical products based on their chemical structure. Read-across approaches, in which data from closely related compounds are used to determine the effects of an untested compound, can also help improve environmental assessment. Improved tools should provide a better understanding of the environmental impacts of pharmaceutical products. At the same time, we must strive to improve the way we use, handle and process medicines to minimize their release into the environment.

The contamination of various components of the environment (water, soil and air) by pharmaceutical residues poses an environmental problem. Human consumption of medicines ranges from 50 to 150 g per person per year in the EU. Veterinary drugs are used in smaller quantities, but pets are a growing segment of the veterinary drug market. In most EU Member States, around 50% of unused human medicines (3-8% of total sales) are not collected.

The problem is that we do not have a comprehensive understanding of what happens when these drugs are released into the environment, and further characterization of possible pathways of human exposure is needed. Residues of different types of drugs (hormones, anti-cancer drugs, antidepressants, antibiotics, etc.) have been found in various environmental elements, raising the question of whether this poses a risk to exposed plants, animals and microbes or to the man.

This study characterizes the extent of the environmental impact of pharmaceutical products outside of personal care products. The aim was to identify non-legislative and legislative reasons for their presence in the environment and to suggest ways to adapt legislation to address this problem. 30 to 90% of an orally administered dose of the drug is generally excreted as active

substance in the urine of animals and humans. A large proportion of medicines are flushed down sinks and toilets and end up in the environment. Inappropriate and excessive consumption can also lead to unnecessary emissions.

In the EU, the contribution of manufacturing facilities to emissions of medicines and/or their residues is generally considered negligible.

Once in the environment, drugs are transformed and transferred between its different parts (surface and groundwater, soil, air). Highly fat-soluble drugs also have the ability to accumulate in the fatty tissues of animals and can thus be introduced into the food chain. These products can be broken down either through digestion and metabolism by organisms or through physicochemical processes in soil and water. Some degradation products may persist even after wastewater treatment and cause concern.

For a number of pharmaceutical products, the environmental risks can be quite minor because they do not remain in the environment for long and are low in toxicity. However, it is increasingly clear that certain drugs, notably antiparasitics, antifungals, antibiotics and (xeno)estrogens, which can have ecotoxicological effects, in some cases present environmental risks. For example, the vulture population in the Indian subcontinent has declined due to poisoning with diclofenac, a painkiller found in the carcasses the vultures fed on. For humans, the possible consequences are less obvious than for the environment. Residue levels in drinking water or food are very low and are not considered to pose a risk to humans, but long-term exposure to low levels may occur through these routes.

There are currently no legal restrictions on human medicines potentially present in products of animal origin, this route of exposure being considered minor, even if it is currently not well characterized. For example, in Europe, only very low concentrations of veterinary antibiotics are found in dairy products.

Until 2005, the registration process for medicines did not include an environmental risk assessment (ERA), and therefore much relevant information was missing. Even for new products, the ERA was often incomplete. A number of regulatory frameworks for chemicals marketed and used in Europe now include an assessment of the potential for persistence, bioaccumulation and toxicity (PBT), but there is no specific guidance for veterinary and human medicinal products.

There are currently no European regulations covering the assessment of risks associated with contaminated soils and product residues transferred to animals, including fish, or present in wastewater sludge from wastewater treatment plants.

Key legislative steps to address these limitations include, among others, strengthening environmental risk assessments, which could also target “old” pharmaceuticals. The Water Framework Directive could explicitly take into account the results of the ERA for active pharmaceutical ingredients. Relevant legislative instruments could also establish a special label for the “green” pharmacy. The main non-legislative solutions focus on consumption and waste management through a better understanding of the ecotoxicity of medicines and encouraging the recruitment of ecotoxicology-trained staff to regulatory agencies. At the same time, training sections for doctors could be organized, a better match between consumer needs and packaging sizes could be considered, while increasing the role of pharmacists in collecting unused medicines and organizing public information campaigns. The main improvements in waste management could focus on more efficient collection systems for unused human and veterinary medicines and on monitoring their effectiveness.

Impact of climate change on the use of medicinal pharmaceuticals in the Northern Hemisphere. As climate change alters environmental conditions, the prevalence and global distribution of human diseases will change. Climate-related environmental changes are associated with an increase in chronic diseases already common in the Northern Hemisphere, such as cardiovascular disease and mental illness. The increase in these diseases is leading to an increase in the use of already widely used Western drugs. People with respiratory diseases may experience a worsening of symptoms due to changing environmental conditions, such as increased pollen counts, leading to an increase in the demand for drugs used to control these symptoms. Toxic substances and respiratory, waterborne, and foodborne infections, including vector-borne infections, may become more common in Western countries, Central and East Asia, and across North America. As new disease threats emerge, a significant increase in the use of pharmaceuticals seems inevitable, particularly for pharmaceuticals not currently in wide use (e.g., antiprotozoal drugs). This study found that the use of drugs to treat common symptoms, such as painkillers, may also increase. Understanding which diseases, and therefore which drugs, may be used in the future is important so that toxicologists, environmental scientists, policymakers and legislators can focus their efforts, implement mitigation measures and plan training, education and treatment.

The chemical pollutants such as pesticides, biocides or industrial chemicals, the release of pharmaceuticals into the environment must be regulated to ensure adequate information and transparency about the environmental impacts of pharmaceuticals; adequate and reliable assessment of environmental risks of pharmaceutical products; prevent pharmaceutical products from entering the environment throughout their entire life cycle and control releases of pharmaceuticals into the environment when prevention is not possible.

Consumption of medicinal products for human and veterinary purposes has impacts on terrestrial and marine environments and ecosystems. Increased environmental awareness regarding pharmaceutical activities has led to the development of policies and measures aimed at mitigating negative environmental impacts. Various measures have been taken to promote environmentally friendly production and practices, leading to the development of alternative methods and processes benefiting both the environment and industry. Distributors and pharmacists can make a difference by effectively managing daily operations, including improving inventory and rotation, consolidating supplies and reducing unused medications.

Pharmaceutical products are essential to human health, but they become an environmental problem when they enter the environment, which occurs when residues are excreted from the body after consumption or when unused pharmaceutical products are improperly disposed of. Although no method has been developed to detect all drugs entering an ecosystem, certain groups have been shown to have negative impacts on ecosystems, including increased mortality of aquatic species and changes in physiology, behavior, or reproduction. Particular attention is paid to these groups of drugs and their impact on the environment. In this review, the authors propose measures to reduce the amount of unused pharmaceutical products in the environment, with a focus on prevention. Various policy measures are recommended throughout the life cycle, including source-oriented, user-oriented and waste management measures, to prevent the generation of household pharmaceutical waste and ensure environmentally sound disposal of household pharmaceutical waste. Preventive measures include rational drug consumption, prescribing more environmentally friendly drugs or developing safe and easily biodegradable drugs, better disease prevention, personalized medicines, better packaging sizes and markets for the redistribution of unsafe drugs. The next step is to prevent inevitable waste from entering the

environment. Therefore, it is extremely important to collect and properly dispose of unused medicines. Finally, education of healthcare professionals and the public, as well as partnerships between environmental scientists and clinicians, are essential at all stages of the pharmaceutical life cycle. Reducing drug levels in the environment will benefit human life.

Demographic, epidemiological and lifestyle changes, such as the aging of the population, the increase in chronic diseases, the availability of cheap generic treatments and easy access to a large number of over-the-counter medications, have become key factors in the growth of the pharmaceutical industry. The global increase in drug consumption has led to greater international awareness of the problem of unused pharmaceuticals (UPs) in households and the harmful environmental and health consequences of their improper disposal. Drugs in the environment are challenging because they are designed to interact with a living system and produce a pharmacological response at low doses, making them dangerous to the environment even at low concentrations. Secondly, drugs are designed to be stable in reaching and interacting with their target molecules, meaning that they degrade very slowly or that their continued use results in a constant, slower release into the environment, that is, as quickly like decomposition. In addition, conventional wastewater treatment plants are not designed to completely remove pharmaceuticals from wastewater.

Pharmaceutical products enter the environment through two main routes: excretion and insufficient elimination. In both cases, pharmaceuticals end up in sewage treatment plants, which are generally not designed to remove these pollutants from wastewater. Drugs have been found mainly in surface water, but also in groundwater, soil, manure and even drinking water. The presence of drugs in freshwater and terrestrial ecosystems can lead to the release of drugs into wildlife with the possibility of bioaccumulation. People are then exposed to drugs through drinking water and their residues in crops, fish, dairy products and meat. The effects of pharmaceuticals entering aquatic environments are of increasing concern, with impacts ranging from molecular changes to population-level effects.

The environment is everything that surrounds us: the air we breathe, the water we drink, and the land on which all living creatures live, the plants we use for food thrive. Development is what we do with these resources to improve lives. Our actions to make our lives more comfortable change the environment

One of the achievements of the United Nations in the field of environmental protection is the Kyoto Resolution on the Climate Change Convention (1997). In 2004, it passed into law, requiring countries to reduce emissions of dangerous greenhouse gases by 5.2% by 2012. The United Nations Convention on Biological Diversity (1992) obliges states to preserve the rich diversity of plants and animals necessary for human existence.

Environmental pollution leads to the increase of toxic substances in the human body and its environment - air, water, soil, animal and plant world - beyond the permissible norm, which is followed by a sharp increase in various chronic diseases.

The interaction between the organism and the environment takes place in two main directions. One of them refers to those biochemical changes in human organisms that are caused by the demands of environmental conditions or arise in the process of human impact on the environment. It is necessary to specify the impact processes of men, women, children and entire groups. The environment is that part of living and non-living nature that surrounds organisms and directly or indirectly affects their existence, development and reproduction.

Pharmaceutical and personal care products (PPCP) in the environment are a hot topic. Veterinary antibiotics, prescription drugs and cosmetic products are discarded from a variety of sources and regularly enter the environment, where they occur in small quantities in wastewater, surface and ground water, silt-laden agricultural soils, aquatic and terrestrial biota, and wet drinks Water. The public should become aware of this and is calling on the scientific and regulatory community to assess the potential risks to human health and the environment and take appropriate action if necessary.

Chemical pollutants are known to have specific effects on organisms, for example: Organotin compounds (used in anti-fouling paints on ships) affect marine life. However, there is another very diverse group of chemical compounds that can be harmful but have received relatively little attention as potential environmental pollutants. These include drugs, including drugs for humans and animals, as well as illegal (recreational) drugs.

Thousands of tons of pharmacologically active substances are used worldwide every year, but surprisingly little is known about the fate of most drugs after their intended use. Most of the administered dose is excreted unchanged from the body, and metabolites can be converted back into the active ingredient by bacteria. In addition, the public often throws unused medicines down the drain. Based on published prevalence data, it is likely that a significant portion of municipal wastewater is contaminated with narcotic compounds that vary only in the type and content of substances present.

Modern research has shown that many drugs are not completely eliminated from the body in wastewater treatment plants. The presence of drugs in surface systems, soil and even marine systems has been confirmed in concentrations ranging from high ng/liter to low mg/liter, which are similar to the concentrations of some pesticides. Pharmaceutical compounds discarded in household waste can end up in landfills and pose a risk to surface and ground water. Additionally, unlike more regulated contaminants, which often have a longer half-life in the environment, pharmaceuticals can become pseudopersistent due to prolonged exposure to wastewater, with unknown consequences for aquatic organisms that may be continuously exposed.

The potential consequences of the presence of pharmaceuticals in aquatic systems are unknown and have therefore received increasing attention as potential pollutants in recent years. The fact that an industrial chemical can end up in the environment is not surprising in itself. What's interesting about drug contamination is that it does not primarily arise from manufacturing, but rather from the widespread and ongoing use, isolation, and improper disposal of drugs for human and veterinary use.

Pharmaceuticals are potentially ubiquitous pollutants as they are present in all human environments. There is currently little evidence that pharmaceuticals are present in the environment in sufficient quantities to cause significant harm, although their use is expected to increase as the Human Genome Project is completed and the population ages. Drugs and their metabolites are increasingly being found in water bodies in areas adjacent to anthropogenic activities.

The biggest concern at the moment is that antibiotics in wastewater treatment plants may lead to increased resistance of natural bacterial populations. There are many isolates of microorganisms resistant to antibiotics in the environment, and although the issue remains controversial, the significant increase in the number of bacterial strains resistant to multiple antibiotics is often attributed to the misuse of antibiotics and the increase in their discharge into wastewater. Three known mechanisms of gene transfer (conjugation, transduction, and transformation) are thought to

occur in aquatic environments; As a result, streams and rivers can become a source and reservoir of resistant genes, as well as a means of their dissemination. In addition, some non-target organisms (eg cyanobacteria) may be exposed to antibiotics, which may have indirect negative effects on the aquatic food.

The problem is further complicated by the fact that exposure to only one drug or toxic substance at a time is likely to be a rare event. Laboratory studies have shown that mixtures of just a few compounds have effects on ecosystems, but it is unknown what happens in the wider environment. Most organisms are constantly exposed to various substances, the concentrations of which vary little in time and space. Therefore, the limits of your tolerance depend on the duration of exposure to chemical and non-chemical stressors, many of which have the same mechanism of action and whose effects can result in additive effects. Thus, risk estimates that ignore possible cumulative drug effects will almost certainly lead to significant underestimation of risk.

Increasing demand for global water sources will likely lead to increased indirect and direct water reuse in the future. Drinking water is a direct route to the human body, including drugs and other contaminants that may be present there. Advanced water treatment technologies such as granular activated carbon (GAC) and reverse osmosis (RO) can remove drugs from drinking water until they are invisible, but these processes are not widely used. Due to the lack of appropriate technology and the need for significant economic investment, municipal wastewater is never treated in this way. In addition, large-scale monitoring programs to test these compounds would be extremely expensive and time-consuming due to the large number of different compounds and the diversity of their properties and effects.

Given that the extent and consequences of the presence of drugs in aquatic environments is largely unknown, more research is needed before a clear picture of the true nature and importance of the problem can be formed. Therefore, it would be unwise to claim that these compounds have significant environmental impacts until convincing evidence is available. To this end, future emphasis should be on adequate and sufficient scientific knowledge to determine occurrence, exposure, sensitivity and consequences in order to make informed decisions regarding human health and the environment.

When evaluating drugs, benefits to human health must take precedence over potential harm to the environment. Therefore, it may be beneficial to focus on reducing or eliminating problems at their source by developing clearer drug labeling and more effective guidelines for the disposal of pharmaceutical compounds by patients and healthcare professionals. The potential benefit of this approach would be improved consumer health (by minimizing the consumption of active substances) as well as reduced healthcare costs. Given the enormous importance of the pharmaceutical industry to both human health and the economy, any increased control could have serious economic and social consequences. If pharmaceuticals turn out to be problematic contaminants, collaboration between health professionals and environmentalists will be mutually beneficial, as much research remains to be done before the problem can be fully understood.

Ecology, which directly affects the health of society, is one of the most important factors in the modern era of civilization. Factors affecting population health are the biggest social problem. The health and illness of society are determined by the environment in which a living organism is located and develops. Man is a biosocial being. Environmental factors affect organisms in different ways. It can be irritating, limiting or determining the existence of the organism in specific conditions; the danger of disturbing the natural balance is associated with pollution of the atmosphere, water, soil and food products with nitrates, pesticides, radionuclides and other

harmful substances. The environment is saturated with psychotoxins, chemical waste, biological damaging agents (drug-resistant bacteria, fungi, viruses, parasites resulting from mutations). causing death of plants and animals and illness in humans. Therefore, it is clear what a great danger an environmental disaster poses.

An environmental disaster has a direct impact on public health. Society and the environment are in constant relationship. Therefore, the health and illness of society are determined by the environment in which a living organism is located and develops. Factors affecting population health are the biggest social problem.

There is a danger of disturbing the natural balance. Pollution of the atmosphere, water, soil and food products with nitrates, pesticides, radionuclides and other harmful substances leads to the death of plants and animals and diseases of people. Therefore, it is clear what a great danger ecological disaster causes.

The most serious consequence of biosphere pollution is the manifestation of genetic disorders. As a result of increased radioactive background and chemical pollution of the environment, the number of pathologies, malignant tumors, mental disorders, etc. increases. number. Mutagens in the form of chemical compounds, ionizing radiation penetrate the cell and cause disruption of the genetic program, causing mutations in somatic cells.

Diseases and conditions caused by climate change will also impact demand in the healthcare system and pharmaceutical industry. The pharmaceutical industry may see a change or increase in demand for drugs. For example, an increase in temperature can trigger asthma due to increased pollen levels. This increase in asthma cases will, in turn, lead to an increase in demand for medications to control asthma. Changing demand for medicines could create opportunities for the pharmaceutical industry to make the most of climate change and incorporate green chemistry principles into the development of new medicines.

The production and consumption of pharmaceuticals results in the presence of active pharmaceutical ingredients (APIs) in the ecosystem. Active ingredients enter the marine and terrestrial environment through release from manufacturing facilities, into wastewater after consumption of the drug in question, or through improper disposal of expired or unused drugs. The use of medicinal products in veterinary medicine may also result in the release of active substances into the environment, for example through the use of wastewater for irrigation, agriculture, aquaculture or the disposal of animal carcasses treated with veterinary drugs. The presence of APIs in the ecosystem can have a number of side effects, such as: Bacterial resistance to antibiotics and changes in the activity of digestive glands in marine life, reproductive toxicity in amphibians and feminization of fish. Another striking example of the impact of APIs on the ecosystem is the sharp decline in vulture populations due to the presence of diclofenac residues in cattle carcasses.

Based on data from the World Health Organization, an analysis of the impact of environmental factors on human health was published, which revealed large differences between countries and showed that human health can be improved by reducing exposure to environmental factors such as: pollution, ultraviolet radiation, noise, climate, ecosystem change and dangerous work environment. More than 10% of deaths in 23 countries of the world are related to the environment with two risk factors: 1) polluted air and water; 2) low sanitary and hygienic indicators.

The industrial agriculture, municipal wastewater treatment, and the introduction of municipal sewage sludge (biosolids) as major sources of pharmaceuticals and personal care products in the environment. To compensate for this, indicators of veterinary antibiotic use are provided by both

the agricultural industry and interested scientists. Personal care products are divided into fragrances and musks, cleansers and disinfectants.

Pharmaceutical products intended for human use are included in the UNESCO list of emerging pollutants. Their identification and elimination represent a decisive step towards achieving the goals of the Sustainable Development Program. Concentrations of drugs found in the environment are below therapeutic levels. In waters receiving treated wastewater, drugs are found at concentrations below 100 ng/L. These low concentrations make it difficult to assess their toxic effects on ecosystems and human health. The vast majority of pharmaceutical products have not been adequately studied regarding their long-term toxic effects, presence and fate in the environment. However, certain classes of drugs, such as beta blockers, antibiotics, anticancer drugs, and endocrine disruptors, have been shown to have devastating effects on the ecosystem, including increased mortality and disruption of the physiological and reproductive functions of aquatic species. Moreover, since it is impossible to separate humans from nature, this has devastating consequences for human health. However, the extent of the problem remains largely unknown due to the large number of drugs available and difficulties in assessing the risks associated with exposure to multiple compounds at low doses over long periods of time. The drugs on the market pose a potential risk to the environment. Although there is no established method for detecting all pharmaceuticals entering an ecosystem, some are widespread and have been shown to have negative impacts on ecosystems. These groups include hormones, antibiotics, antidepressants, anti-inflammatory and pain relievers, beta blockers and anti-cancer drugs.

Antibiotic resistance is a global public health problem, especially given the increased use of antibiotics during the COVID-19 pandemic, which has led to the exhaustion of the last line of antibiotics. It has been established that the use of antibiotics in medicine, veterinary medicine and agriculture is associated with pollution of various parts of the environment, which has contributed to increased antibiotic resistance and the occurrence of ecotoxicological effects. Failure to properly dispose of antibiotics through sewers by patients also poses a growing environmental threat to public health. Additionally, high levels of antibiotic contamination after long-term exposure can negatively impact human health, especially in patients with chronic diseases such as obesity, diabetes and asthma.

Antidepressant contamination has increased significantly worldwide during the COVID-19 pandemic. To this day, antidepressants can be found in urban and suburban water supplies. Many aquatic animal species bioaccumulate various antidepressants in their tissues, resulting in cytotoxicity, genotoxicity, impaired stress response, weight and length gain/loss, and liver and kidney damage. Because there is significant overlap between human and animal environments, exposure to antidepressants (sertraline, fluoxetine) in the environment also affects human neurological development and various mental illnesses. Although psychotropic drugs are usually present in wastewater at subtherapeutic levels, they can have biological effects at low doses, and combinations of multiple psychotropic drugs are often present, especially in the environment, increasing the risk of toxic effects.

Pharmaceutical compounds are used in modern society for various beneficial purposes, but at the same time, the pharmaceutical industry releases highly toxic pollutants into the environment either directly or after chemical modification. Additionally, pharmaceutical compounds can enter the environment through various routes such as treated wastewater discharge, seepage into landfills, sewer pipes, animal waste, etc. Although a number of physical and biological processes occur in an aquatic ecosystem, they can lead to depletion of many lead to pharmaceutical

compounds. Traces of human and veterinary drugs and their metabolites were found in several bodies of water. Objects such as surface water, groundwater and drinking water sources. Several industries, including pharmaceuticals, chemicals, paints, etc., are rapidly developing in India, with wastewater being discharged into water bodies either directly or after partial treatment. Pharmaceutical compounds have been found to be released into the environment and may be considered environmental pollutants. Several pharmaceutical plants have been found to be sources of much higher concentrations in the environment than those resulting from drug use. Typically, the pharmaceutical industry generates a large amount of waste during production and service. Drugs have been found in sewage treatment plant wastewater and drinking water. Trace amounts of drugs in drinking water can have serious adverse effects on human health and aquatic life over long periods of time, even when drug concentrations in drinking water (in the nanogram per liter range) are orders of magnitude below the minimum therapeutic dose.

Pathways through which drugs may be exposed to the environment include manufacturing plants and hospital wastewater, land use (eg, biosolids and water reuse), etc. Wastewater treatment services are not always successful in removing active chemicals from wastewater. Therefore, drugs enter the aquatic environment, where they have a direct effect on aquatic organisms and can be absorbed into the food chain.

Higher concentrations of antibiotics can lead to changes in microbial community structure and ultimately affect food chains. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen and diclofenac, are widely used and therefore often found in wastewater systems, both surface and groundwater. Ibuprofen, ketoprofen, naproxen, indomethacin, diclofenac, acetylsalicylic acid and phenazone were detected in the surface water system. However, after clofibric acid, the most common drugs found in aquatic environments are diclofenac, ibuprofen and propyphenazone. Diclofenac has also been shown to be highly toxic to vultures and livestock. NSAIDs such as ibuprofen, naproxen, and aspirin are the most commonly used medications and are often found in effective amounts in municipal wastewater.

Many pharmaceutical companies are responsible for the generation of toxic wastewater during their operations. The wastewater generated from these facilities contains solids, biodegradable and non-degradable organic compounds, etc. Pharmaceutical wastewater provides basic information about the reliability of the aquatic environment of the rivers and streams into which it is discharged. An important indicator of industrial wastewater contamination is the oxygen content of chemical oxygen demand (COD) and biological oxygen demand (BOD), with nutritional status measured by the amount of nitrogen and phosphorus in the wastewater.

Long-term exposure of coastal biota to lower concentrations of complex drug mixtures can result in acute and chronic damage, behavioral changes, tissue accumulation, reproductive impairment, and inhibition of cell proliferation. Several studies have shown that fish exposed to sewage may experience reproductive problems. In addition, fish exposed to trace amounts of contraceptive drugs in the concentration range found in the environment show dramatic reductions in reproductive success, suggesting that population-level effects may be possible.

Around the world, the drug residues in the environment poses risks to humans, aquatic animals and wildlife and is becoming a major concern for both regulatory authorities and the pharmaceutical industry. Significant progress on this issue is simply not possible with the current limited knowledge about the transport, fate, and environmental impact of pharmaceuticals. It is necessary to take into account the possible potentiating effects of different drugs acting on the

same receptors. Risk assessment of pharmaceutical chemicals involves identifying the hazards associated with each step and assessing the risks associated with those hazards.

Currently, pharmaceutical compounds are regularly released into the environment in extremely large quantities, and the current emission control system is unable to control untreated or partially treated pharmaceutical wastewater. The effects of drugs permeate and impact ecosystems, biota and humans. Adverse health effects on humans, aquatic animals and livestock should be investigated through careful toxicological and safety studies. Serious efforts are needed to reduce this problem, and appropriate regulations are needed to monitor and control it. Water quality guidelines in India should include analysis of the most commonly used pharmaceutical compounds in drinking water sources. In addition, pharmaceutical industrial wastewater treatment plants need to implement new corrective measures to prevent long-term environmental and health risks [7].

Water sources contaminated with pharmaceutical contaminants are found in agricultural lands, surface water, groundwater, and drinking water. Water flows to plants, which affects the quality of soil and crops grown using this contaminated water. Pharmaceutical contaminants are considered external environmental factors that affect crop quality. Drugs enter plants as pollutants, either through the soil or the air. Pollutants enter the plant from the soil through the roots and are transported through the stem. Plants also absorb pollutants from the air, and leaves can absorb pollutants from the atmosphere. Pharmaceutical contaminants such as B-lactams, aminoglycosides, macrolides, tetracyclines, sulfonamides, herbicides including sulfonylureas, triazines, imidazolinone, phenylurea and bisphenol (BPA) have been found to cause toxicity in plants. Polychlorinated biphenyls (PCBs) affect plant growth, reproduction and productivity [8]. Most pharmaceuticals we use are excreted via urine and feces in unchanged form or as metabolites and eventually end up in the drain. The pharmaceutical residues can then reach lakes, the sea and groundwater, despite passage through wastewater treatment plants, as the wastewater treatment plants are not built to clear pharmaceuticals. Pharmaceuticals affect biological processes. They are also often designed to withstand biodegradation and can therefore remain in the environment for a long time. There are reports of effects on fish, as well as that measured concentrations of antibiotics in wastewater treatment plants can select for antibiotic resistance.

Chemicals play an important role in healthcare as they can be used as disinfectants, cleaning agents, laboratory reagents, sterilants, pesticides, pharmaceuticals, and in medical devices and equipment. They also offer great animal welfare benefits. However, there is growing awareness and concern about the consequences of mishandling drugs and chemicals on human health and the environment [9].

Pharmaceuticals are also biologically active substances specifically designed to provide pharmacological effects on living organisms. They affect the health of wildlife and ecosystems if not managed in an environmentally sound manner.

Active pharmaceutical ingredients (APIs) are the biologically active components of a drug. These APIs are sold to pharmaceutical companies that manufacture end products for patients around the world. More than 5,000 active pharmaceutical ingredients are used in prescription, over-the-counter and veterinary products worldwide. From a chemical and waste management perspective, environmental and health issues in this sector are mainly related to the release of pharmaceuticals into the environment: Waste ends up in rivers, lakes and underground aquifers. In addition, when used in livestock production and when manure is used as fertilizer, veterinary drugs end up in the

soil and environment. This leads to soil contamination and biomagnification due to leaching of drugs into food crops [12].

Sources of drug release into the environment include direct emissions from drug manufacturing, patient and animal feces, aquatic agriculture, and disposal of unused or expired drugs. Medicines designed to degrade slowly, or even non-degrade to resist chemical breakdown as they pass through the human or animal body, pose a particular risk if ingested, stored, or distributed into the environment. When released into the environment, the biological activity of persistent pharmaceutical pollutants in the environment can have direct negative effects on non-target organisms such as wildlife and have long-term impacts on the health and sustainability of ecosystems. The latter occurs through population-level reproductive effects that persist into future generations of non-target organisms. Pharmaceutical contaminants that are persistent in the environment are frequently and increasingly used in consumer products. However, significant gaps remain in knowledge about the environmental and health impacts of these pollutants.

Some pharmaceuticals have been found in low concentrations in drinking water, which is a warning sign that the current handling of pharmaceuticals may lead to health and environmental problems in the future.

Access to healthy water is a prerequisite for good health. Since society's use of chemicals, including pharmaceuticals, is continuously growing, the risk is also increasing that these chemicals will return to us in our food and water supply through nature's ecocycle.

There are little knowledge of the long term effects that continuously supplied trace quantities of pharmaceuticals and other chemicals could have on our development, our ability to resist disease and wellness in general. Therefore caution is advisable. The pharmaceuticals in nature can cause health problems. According to the precautionary principle, measures can be taken if there is reason to believe that a product or a method of production involves unacceptable risks to the health of human beings, animals, plants and the environment – even if there is no definitive scientific proof of such an effect [9].

Drug residues are found in various environmental components around the world, and there is growing concern about the harm they may cause to human health and the environment. In nature, drug residues were found in urban wastewater, rivers and lakes. Effective measures must be taken to prevent further contamination of the environment by drugs. First of all, it is necessary to create a system for collecting drug waste from the population. Undoubtedly, drugs enter the environment during the production process through wastewater from pharmaceutical plants, municipal wastewater through natural human excretion, wastewater and manure from the use of veterinary drugs and as a result of improper handling of drug waste [19,36].

The review defines each of these sources and steps that can be taken to reduce drugs' environmental impacts. In the European Union, since 2004, the obligation to organize a system for collecting drug waste from the population has been established. For the successful operation of such a system, information work with the population about how drugs affect the environment and how to properly dispose of them is important. Residents of all European countries can bring drug waste to a pharmacy or hazardous waste collection point. However, in some countries there is a lack of widespread awareness-raising, which leads to inefficient collection systems and most waste ends up in the trash or drained into sewers. In some countries, drug waste generated by medical and pharmaceutical organizations is neutralized in pharmacies, clinics, hospitals and manufacturers. At the same time, pharmacies and hospitals have the right to transfer expired medicines to the manufacturer [36].

In most countries where the system operates successfully, the costs of collecting and neutralizing drug waste are shared by pharmaceutical companies, drug manufacturers and local authorities. The main problem is the very existence of unused drugs. So, generally many patients buy more medicines than they need. The best way to reduce their number is seen in optimizing the practice of prescribing drugs, so that only the necessary amount of drugs is prescribed, giving preference to more environmentally friendly ones, as well as improving information interaction between doctors and patients. The pharmaceutical industry must also provide for the production of drug packaging adapted to various treatment regimens [10, 19].

Every participant in the drug supply chain, from the pharmaceutical industry to the patient, plays an important role in reducing the environmental impact of pharmaceutical activities. The International Pharmaceutical Federation has highlighted the different roles that each person plays in the pharmaceutical supply chain to minimize the environmental impact of pharmaceutical products. The pharmaceutical industry plays an important role in the environmental impact of pharmaceutical products.

Educating pharmaceutical personnel and the public is an important aspect of helping to create a healthy environment and reduce activities that contribute to climate change. The implementation of green practices in the pharmaceutical sector is already included in the curricula of EU Countries countries universities. Pedagogical input helps to recognize the importance of such practice early in professional development.

Consumer education is also important as it plays an important role in reducing the amount of drugs in the environment. Consumers should be discouraged from storing medications to avoid wasting them when not in use. They should also be taught how to properly store and dispose of unused and expired medications that may end up down the drain [13,28].

The world's population is aging, which will lead to an increase in drug use. Various measures need to be taken to minimize the release of active pharmaceutical ingredients into the environment and reduce the carbon footprint of the pharmaceutical sector. Small contributions from many people can synergistically have a positive impact on the environment [7,18].

There are several sources of release of active pharmaceutical ingredients (APIs) into the environment. The main ones are: wastewater from cities, hospitals, pharmaceutical plants and landfills. The vast majority of the active pharmaceutical ingredients (API) of drugs taken orally is excreted in the urine of animals and humans. Some pollution comes from the use of veterinary drugs in livestock and fish farming. However, it is not yet possible to evaluate this contribution, because there is no control and accessible reporting of the use of veterinary drugs. The most vulnerable to the effects of active pharmaceutical ingredients (APIs) are amphibians, fish, some animals and birds.

The main source of drugs entering the environment is wastewater from pharmaceutical enterprises (from product washing, waste acidic and alkaline wastewater, wastewater from cleaning equipment and production facilities, etc.) and liquid waste that is allowed to be discharged into the sewer system. Currently monitored parameters in pharmaceutical wastewater are biological oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids, ammonia and ammonium ions, phosphates, chlorides, sulfates, petroleum products, iron, anionic surfactants and pH value. This list may include other chemical compounds, including active pharmaceutical ingredients (APIs), but their content is not regulated or controlled at this time. Currently, the countries of the European Union have prioritized the most environmentally stable active pharmaceutical ingredients (APIs) - diclofenac, hormonal drugs of the estrogen group (ethinyl

estradiol), antibiotics of the macrolide class (erythromycin, clarithromycin, azithromycin) and etc [29].

Assessment of environmental risks of both original and generic drugs. In European countries, for some drugs such an assessment is carried out, as well as an assessment of the level of resistance, bioaccumulation potential and toxicity. Currently, providing information about environmental hazards when registering drugs in the countries of the European Union is voluntary. In some countries has been created an online database of drugs, which describes their environmental risks and expanding the responsibility of drug manufacturers throughout the entire cycle from production to neutralization.

After drugs enter the body, they are destroyed, neutralized, metabolized and converted into new compounds. However, some of them are excreted unchanged or in the form of metabolites, ending up in the sewer system. Municipal wastewater treatment does not involve removal of APIs. Some of them are concentrated in sewage sludge from treatment plants, which is stored in filtration fields, while the rest ends up in rivers. The Challenges in this matter are also hospitals, where there is a high level of drug consumption. In the absence of an established system for collecting drug waste generated by the population, it either ends up in the sewer or is thrown into the trash. From landfills, drugs can be carried by animals, birds, or migrate into the soil and groundwater.

To raise animals and fish on an industrial scale, hormonal drugs, antibiotics and other drugs can be used, which can be excreted from the animal's body naturally. Hormones can be used in veterinary medicine and animal husbandry to stimulate the development and growth of animals, improve fertility, digestibility of feed, accelerate puberty, regulate the timing of pregnancy, etc. According to studies in some countries, antibiotic residues were found in manure, in plants grown in fields fertilized with manure, in soils, and in small quantities in groundwater. The use of veterinary drugs in should be regulated by veterinary and sanitary rules for the use, sale and storage of veterinary drugs.

European experience in collecting hazardous waste from the population shows that waste collection is carried out effectively if such collection is organized by a company specializing in the collection of hazardous waste. The same practice works in our country. In the EU, pharmacies are considered only as an area for the installation of appropriate containers and containers for collecting hazardous waste from the population. The containers themselves are installed by specialized companies interested in collecting hazardous waste. It is inappropriate to oblige pharmacies, healthcare institutions or other trade organizations to organize the collection of drug waste from the population.

Pharmacies and medical institutions are places where consumers can obtain the most complete information about drug waste, since these organizations employ personnel with the relevant knowledge. In the country, many pharmacies themselves are located on the territory of various retail facilities, so there may not be places in pharmacies to install a special container for collecting drug waste. When determining places for collecting waste from the population, it is necessary to comply with the criterion of step-by-step accessibility of such places from the places of residence of citizens. In this regard, retail facilities should also be considered as places for installing special containers for collecting drug waste. The decision to organize collection points for drug waste from the population in pharmacies should be made by Health care institutions in every countries.

In the vast majority of countries, all drug waste collected from the population is sent for incineration. At the same time, pharmacies, for example, in Sweden and Lithuania, can only

accept medications without packaging, because it belongs to secondary resources and must be sent for recycling. Low-temperature, medium-temperature (up to 850°C) and high-temperature (at least 1200°C) combustion is used for waste. Hazardous waste, which includes most drugs, cannot be burned at low temperatures. At medium temperatures it is possible in limited quantities and in the absence of high-temperature combustion technology. Cytostatic drugs for cancer treatment can only be burned at temperatures above 1200°C, but the generation of such waste in household use is unlikely. Currently, there is a steady trend towards a decrease in the number of thermal installations for the neutralization of pharmaceutical waste. Incineration of waste is contrary to three principles of international law: precaution, prevention and limitation of transboundary effects. In Europe, resistance to waste incineration manifests itself in the form of the introduction of alternative technologies. Any combustion method requires monitoring of pollutant emissions and the resulting ash. An alternative to conventional methods of thermal treatment of pharmaceutical waste are technologies that provide for the preliminary decomposition of the organic component of the waste in an oxygen-free atmosphere (pyrolysis). When carrying out microwave pyrolysis with heating using microwave waves, toxic gaseous products are converted into less dangerous ones.

In countries where there are no incineration plants or their use is limited geographically, drug waste is disposed of. The main disadvantage of this method is the high probability of soil and groundwater contamination. According to recommendations of the World Health Organization, only non-hazardous drug waste (vitamins, herbal-based drugs, biodegradable drugs) can be sent to the landfill. Hazardous waste, including cytotoxic drugs, must be pre-sealed, i.e. placed in a metal capsule and filled with plaster and cement.

Liquid waste of drugs classified as non-hazardous (syrups, herbal preparations, solutions based on salts, amino acids, lipids or glucose) can be poured into the sewer after diluting with water. It is necessary to prevent the discharge of large quantities of disinfectants into the sewer system, because they can affect the quality of biological wastewater treatment. Discharge of drugs that are persistent in the environment, capable of biological accumulation and have toxic properties into the sewer system leads to environmental pollution with active pharmaceutical ingredients. According to studies conducted in many countries, existing wastewater treatment systems do not eliminate such pollution and drug residues are found in wastewater cleaning sludge, and to a greater extent in water after cleaning, which is discharged into natural watercourses.

Some drugs pass through the human body, exit unchanged or in the form of metabolites, while maintaining their stability in wastewater and the environment for a long time. In addition, improper disposal of medications and disposing of them down the drain increases the concentration of hazardous APIs in water. Wastewater from pharmaceutical plants is also discharged into the city sewer system after local treatment. The active pharmaceutical ingredients are present in municipal wastewater above detection limits. Traditional mechanical and biological wastewater cleaning methods are unable to neutralize the active pharmaceutical ingredients in water. The issue of purification efficiency, the formation of drug metabolites and their behavior, the interaction of some drugs with others is still under study. Among the methods being developed and implemented in the countries of the European Union one can highlight physicochemical methods, aerobic/anaerobic biological cleaning in membrane bioreactors. Effective technologies for purifying wastewater from medicinal components include oxidation with ozone or hydrogen peroxide and the use of carbon filters. However, such technologies are currently expensive to implement and use. At the same time, more and more attention is being

paid to preventing the entry of drugs into wastewater, including during production. The main problem is the very existence of unused drugs [15,19,22].

One of the most obvious sources of uncontrolled release of drugs into the environment may be wastewater and atmospheric emissions from enterprises producing finished drugs and pharmaceutical substances. The environmental safety of such production should be usually regulated by law. However, accidental releases of drugs into the environment or those that violate existing norms and rules that occur in industry, are nevertheless not systematic. Moreover, there is a general trend towards a reduction in the environmental load on the part of pharmaceutical production, primarily in developed countries of the world, due to a consistent increase in the technological effectiveness and organization of the production process, the introduction of increasing standards of quality and environmental safety, and control by authorized government agencies. It is also necessary to take into account that pharmaceutical production is localized geographically and if an accident occurs at the enterprise or there are violations of environmental legislation, then such emissions are exclusively local in nature and pose a danger only to specific regions. Other sources of drugs that are practically uncontrollable and are formed mainly by people who use drugs for medical purposes, as well as in animals, pose a great danger to the environment.

For the most part, drugs are xenobiotics, and many of them are metabolized in the human body. The task of metabolism, as a rule, is to impart polarity to lipophilic substances in order to facilitate subsequent excretion. Metabolic parameters are individual for each substance and depend on gender, race, age and physiological state of the human body. There are two phases of metabolism, the numbering of which does not necessarily reflect their actual sequence. In the first phase of metabolism, a redox or hydrolytic transformation of the molecule occurs, increasing its polarity. In the second phase of metabolism, the xenobiotic is conjugated with endogenous molecules that improve the transport properties of the metabolite. During metabolism, inactivation of the active substance often occurs, which can lead to its inability to further exert a biological effect. However, many drugs are either not subject to metabolism or are subject to it only to some extent. And this leads to the fact that the active molecule of the active substance is excreted unchanged either in the urine or in the feces and is capable of further exerting a biological effect. In addition, as research results show, glucuronide transport complexes of active molecules of some drugs, formed during the second phase of metabolism, are easily destroyed during sewage treatment processes and release unchanged active substance into the aqueous phase or sewer sludge. We can also mention the route of release of drugs into aquatic environments due to their transport through the skin or leaching of drugs for external use during swimming in open waters. But from the point of view of quantitative indicators, this path is of little significance.

During metabolism, inactivation of the active substance often occurs, which can lead to its inability to further exert a biological effect. However, many drugs are either not metabolized or only to some extent. And this leads to the fact that the active molecule of the active substance is excreted unchanged either in the urine or in the feces and is capable of further exerting a biological effect. In addition, as research results show, glucuronide transport complexes of active molecules of some drugs, formed during the second phase of metabolism, are easily destroyed during sewage treatment processes and release unchanged active substance into the aqueous phase or into sewage sludge.

We can also mention the route of release of drugs into aquatic environments due to their transport through the skin or leaching of drugs for external use during swimming in open waters. But from the point of view of quantitative indicators, this path is of little significance.

The increasing the availability of drugs, for the general development of health care systems, the consumption of drugs for medical purposes increases and, as a result, their content in the environment increases. This process is poorly managed and poses a potential danger to human health and other biological organisms. Contamination of the environment with drug residues has a global character and is actively studied in the developed countries of the world. However, this problem remains insufficiently worldwide [26].

The best ways to reduce their number are to optimize the practice of prescribing drugs, so that only the required amount of drugs is prescribed, giving preference to the least environmentally hazardous ones, as well as improving information interaction between doctors and patients. The pharmaceutical industry must also consider producing drug package sizes tailored to different treatment regimens. One key measure is to encourage the pharmaceutical industry to develop harmless drugs that quickly break down into harmless compounds in the environment. For example, currently in European countries, when registering a new drug, environmental characteristics such as ecotoxicity, biodegradability are indicated.

The comparing drugs that are equally safe and well suited for treating a patient, it is recommended to take into account, in addition to their pharmaceutical properties, their environmental impact. To do this, recommend using environmental drug classifiers.

Large quantities of nonsteroidal anti-inflammatory drugs, including acetaminophen, acetylsalicylic acid, ibuprofen, diclofenac, and naproxen, are significant contributors to environmental pollution, especially because they have been detected in nanogram and microgram quantities in soil, wastewater, surface water, and drinking water, groundwater. These drugs have chronic ecotoxic effects because their stable chemical structure makes them very resistant to biological changes in the environment. It is now known that they primarily damage the organs of invertebrate and vertebrate animals, cause oxidative stress and interfere with the activity of detoxification enzymes. These drugs may also cause cardiovascular effects, hepatotoxicity and affect oocyte maturation through unknown mechanisms [5,19].

Beta blockers are very long-acting drugs that are toxic to the environment. Although there is no data on their adsorption in the environment, these drugs are known to have moderately high water solubility and are present in surface waters at $\mu\text{g/L}$ concentrations. These compounds are extremely resistant to hydrolysis, bioavailable and mobile in the environment. Therefore, its accumulation in the environment can have unexpected consequences for many living organisms. According to European Union Directive, metoprolol and propranolol are compounds harmful to aquatic organisms. This is evidenced by the results of tests with green algae.

Anticancer drugs interfere with cell growth and division, and when released into the environment, they disrupt the ecosystem, impair fertility and cause significant genetic changes in living organisms. Anticancer drugs are prescribed in smaller quantities, but their effects are destructive even at concentrations in the ng/L range and include mutagenic, carcinogenic and teratogenic effects on aquatic life. Cytostatics are frequently found in the pharmaceutical industry and hospital wastewater due to improper use and disposal. The detection rate of anti-cancer drugs in oncological hospitals wastewater is big amount and cisplatin is considered one of the most dangerous drugs. The presence of cisplatin in water, even at concentrations of ng/l , can have a toxic effect on aquatic flora and fauna [28].

Environmental pollution caused by pharmaceuticals is a complex public health problem that is scientifically controversial and affects multiple stakeholders with different interests and at different organizational levels: governments, non-governmental organizations, academic institutions, manufacturers, industries and families.

In keeping with the idea of protecting the environment, the pharmaceutical industry must develop promising concepts to minimize secretions while still ensuring sufficient pharmacologically effective concentrations in the patient. The potential of developing new pharmaceutical products that are more biodegradable and less harmful to the environment. There are already some examples of the development of greener pharmaceuticals, such as glufosfamide and green drug delivery systems. Scientists are currently developing an effective and environmentally friendly version of the antibiotic ciprofloxacin, a very stable drug. Using computer modeling, an existing active ingredient is analyzed and theoretically modified to improve biodegradability and reduce toxicological effects. The most promising candidates have been synthesized and tested in vitro [37].

Limited consumer awareness of best recycling practices weakens their influence on recycling practices in many countries. Information campaigns can increase awareness and use of environmentally friendly pharmaceutical waste disposal methods in households. A good example is the Meds disposal campaign, a European initiative jointly coordinated by several European health and supply chain organizations and supported by media campaigns in different languages. The aim of the initiative was to combat the negative impact of mishandling of pharmaceutical products on the environment, raising consumer awareness of correct disposal routes and collection systems in a number of European countries.

In addition, greater awareness and behavior change can be achieved through specific recycling instructions on the product's outer packaging or information leaflet, which are mandatory in EU countries. In addition, eco-labels that reflect the environmental impact of various pharmaceutical products can influence consumer choice and awareness, as well as help physicians make prescribing decisions. Instructions on how to properly dispose of medications should also accompany medication dispensing at regular intervals. Pharmacists can play a key role in educating their patients about proper medication disposal.

Human activity has the most negative impact by releasing pollutants. Pollutants are considered to be all those substances that enter the atmosphere, soil, natural waters and cause disruption of the biological, physical or chemical processes taking place there. Radiation and thermal radiation are also pollutants. As a result of human activities, carbon dioxide (CO₂), carbon monoxide (CO), sulfur dioxide (SO₂), methane (CH₄), nitrogen oxides NO₂, NO, N₂O are released into the atmosphere. As a result of aerosol use, chlorofluorocarbon enters the atmosphere, and hydrocarbons from transport emissions. Water bodies are polluted not only by waste from industrial production, but also by organic and mineral fertilizers and pesticides used in agriculture. In the same way, sea water is being polluted. Rivers carry millions of tons of chemical waste into the sea every year. Millions of tons of oil spill into the oceans every year as a result of tanker and oil rig accidents, killing marine animals. Burial of nuclear waste at the bottom of the sea, sunken ships with nuclear reactors and weapons also pose a danger [7,19,28].

Radioactive contamination of the soil creates a great danger, since radioactive substances from the soil enter plants, and from there into the body of humans and animals, where they accumulate and cause various diseases. Chemicals pose a particular danger, specifically, organic compounds used in agriculture to control weeds, pests and diseases.

The uncontrolled release drugs into the environment may be wastewater and atmospheric emissions from enterprises producing finished drugs and pharmaceutical substances. the environmental safety of such production is usually regulated by law. However, accidental releases of drugs into the environment or those that violate existing norms and regulations that occur in industry, are nevertheless not systematic. Moreover, there is a general trend towards a reduction in the environmental load on the part of pharmaceutical production, primarily in developed countries of the world, due to a consistent increase in the technological effectiveness and organization of the production process, the introduction of increasing quality standards and environmental safety, and control by authorized government bodies . It is also necessary to take into account that pharmaceutical production is localized geographically, and if an accident occurs at the enterprise or there are violations of environmental legislation, then such emissions are exclusively local in nature and pose a danger only to specific regions. For all the reasons listed above, such sources are not the subject of analysis in this review, although they contribute to environmental pollution. Other sources of drugs that are practically uncontrollable and are formed mainly by people who use drugs for medical purposes, as well as in animals, pose a great danger to the environment [14].

For the most part, drugs are xenobiotics, and many of them are metabolized in the human body. The task of metabolism is generally to impart polarity to lipophilic substances in order to facilitate subsequent excretion. Metabolic parameters are individual for each substance and depend on gender, race, age and the physiological state of the human body. There are two phases of metabolism, the numbering of which does not necessarily reflect their actual sequence. In the first phase of metabolism, a redox or hydrolytic transformation of the molecule occurs, increasing its polarity. In the second phase of metabolism, the xenobiotic is conjugated with endogenous molecules that improve the transport properties of the metabolite [25,29].

The impact of pharmaceuticals on the ecology and human health. Currently, increasing attention is being paid to the presence and fate of active pharmaceutical ingredients, solvents, intermediates and raw materials that may be present in water and wastewater, including pharmaceutical wastewater. Traditional wastewater treatment methods, such as activated sludge, are insufficient to completely remove active pharmaceutical ingredients and other wastewater components from these waters. Pharmaceutical wastewater has direct and indirect impacts on the environment and health, especially near pharmaceutical industrial sites. Although pharmaceutical factories produce untreated or partially treated wastewater, drinking water sources are contaminated. Various classes of pharmaceutical compounds such as analgesics, antidepressants, antihypertensives, contraceptives, antibiotics, steroids, hormones, etc. To protect the environment and lifestyles from health risks, the concentration of pharmaceutical compounds in medical wastewater entering drinking water sources should be regularly monitored. This article highlights the toxicity, health risks, and environmental risk assessments associated with pharmaceutical contaminants. To reduce contamination levels when consuming medicines should be: Creation of a system for collecting drug waste generated by the population; Conducting awareness-raising work with the population, employees of healthcare institutions and other target groups on the topic of environmental pollution by drug waste; Taking into account environmental factors when choosing and prescribing treatment. At the same time, there is no need to put environmental protection above the human need for treatment; Development and implementation of wastewater treatment systems. It should be taken into account that urban wastewater has an unstable composition in

terms of names and concentrations of drugs. A higher priority is to prevent drug residues from entering the city sewer system.

Incorporating green practices into the pharmacy curriculum provides future pharmacists with the skills and competencies needed in the field to reduce the environmental impact of processes and medications. A more environmentally conscious workforce in the pharmaceutical industry is creating the necessary ripple effect for the adoption and implementation of green principles across various pharmaceutical environments. Patients should also learn to avoid accumulating medications and disposing of them safely and correctly. Adopting environmentally friendly practices leads to a reduction in the use of chemicals and waste generation, which in turn leads to a reduction in the pollutants that contribute to climate change.

The increasing production and use of pharmaceutical and veterinary products has had an impact on the environment over time. Drug production processes have a significant impact on the environment, which affects the value of chemistry to society. The pharmaceutical industry impacts the environment through the carbon footprint generated during the production of pharmaceutical products and throughout the supply chain, which can lead to climate change. Climate change may alter the incidence of vector-borne diseases by altering the population of species that act as disease vectors. Another consequence of climate change is the emergence of infectious diseases caused by pathogens that would otherwise be dormant.

Currently, increasing attention is being paid to the presence and fate of active pharmaceutical ingredients, solvents, intermediates and raw materials that may be present in water and wastewater, including pharmaceutical wastewater. Traditional wastewater treatment methods, such as activated sludge, are insufficient to completely remove active pharmaceutical ingredients and other wastewater components from these waters. Pharmaceutical wastewater has direct and indirect impacts on the environment and health, especially near pharmaceutical industrial sites. Although pharmaceutical factories produce untreated or partially treated wastewater, drinking water sources are contaminated. Various classes of pharmaceutical compounds such as analgesics, antidepressants, antihypertensives, contraceptives, antibiotics, steroids, hormones, etc. were detected in water samples ranging from mg/L to µg/L. Although the quantities detected are very small, they are highly toxic to humans, animals and aquatic life. To protect the environment and lifestyles from health risks, the concentration of pharmaceutical compounds in medical wastewater entering drinking water sources should be regularly monitored. This article highlights the toxicity, health risks, and environmental risk assessments associated with pharmaceutical contaminants.

Residues of many pharmaceutical products can be found in drinking water, plants and fruits, as well as in the tissues of fish and shellfish. Thus, people are exposed to these residues when they drink contaminated water and eat contaminated food. Pharmaceuticals in the environment can also influence the provision of important ecosystem services and have indirect effects on human health and well-being. Found the evidence that drug residues in drinking water and food affect human health, as well as the indirect effects of drugs on human health. Available evidence suggests that the risks of direct toxicity are low, but there are scenarios in which indirect effects are possible. Much remains to be done regarding the wider range of drugs and exposure pathways, and the links between the presence of drugs in the environment and the provision of ecosystem services.

Conclusions

The contamination of the environment by pharmaceutical residues presents a critical challenge to both ecosystem health and human well-being. The widespread presence of these substances in water, soil, and air underscores the need for a more comprehensive understanding of their environmental fate and effects. Current risk assessment approaches, which often examine individual compounds in isolation, are inadequate in addressing the complex interactions and cumulative risks posed by pharmaceutical pollutants, especially when combined with other environmental contaminants. Furthermore, the potential dangers of pharmaceutical transformation products, which may exhibit greater toxicity or persistence, remain underexplored. To address these concerns, a paradigm shift is required in environmental risk assessment, incorporating multi-substance interactions, long-term ecological impacts, and the effects of transformation products. The development of robust mitigation strategies—such as advanced waste treatment technologies, improved pharmaceutical disposal practices, and more stringent regulatory frameworks—must be prioritized. By adopting a more integrated, precautionary approach to pharmaceutical contamination, we can better protect ecosystems and human health from the growing threat posed by these persistent pollutants. Future research and policy initiatives should focus on improving our understanding of these substances, developing innovative solutions to reduce their environmental impact, and ensuring sustainable management practices for pharmaceuticals.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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THOR HEYERDAHL AND AZERBAIJAN

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ABSTRACT

This article investigates the hypotheses of the famous Norwegian scientist and traveler Thor Heyerdahl about the historical and cultural ties between the peoples of Azerbaijan and Norway. Having visited Azerbaijan and observing petroglyphs in Gobustan, Heyerdahl comes to the conclusion that there are historical and ethnic ties between the two countries and that Norwegians and Azerbaijanis had the same roots in ancient times. The author of the article, in addition to highlighting the research of the famous traveler, attempts to provide some explanations for the Turkic roots of Odin, the chief god of Scandinavian mythology, based on the comments made by Azerbaijani and Turkish researchers. At the same time, he draws attention to the fact that the World Tree, which is characteristic of the mythology of the Turkic peoples, also exists in Scandinavian mythology and provides a description of some words of Turkic origin in the Norwegian language. In the end, the author concludes that the arguments put forward by Thor Heyerdahl are completely reasonable and well-founded.

Keywords: Thor Heyerdahl, Azerbaijan, Norway, petroglyphs, Odin, World Tree, mythology, words of Turkic origin

Thor Heyerdahl in Azerbaijan

Ethnographer, scientist, archaeologist, professor, famous traveler Thor Heyerdahl is one of the personalities who made great contributions to world science. He is a famous traveler who traveled a great distance from South America to the Tomato Islands with his expedition. He wrote more than a dozen books and monographs by writing down the issues he observed and researched, as well as his impressions and memories. Those who read the books of Thor Heyerdahl, who wrote about the study of primitive man and ancient civilizations, witnessed an extraordinary treasure.

Continuing the traditions of world-famous travelers such as Christopher Columbus and Ferdinand Magellan, the author was the organizer and leader of the famous Kon-Tiki expedition. Thor Heyerdahl confirmed the possibility of transoceanic migration of peoples between the Old World and the New World, and proved that the Polynesian islands were inhabited by people coming from America. As a result of his archaeological researches, the origin of ancient man and the customs of peoples were studied. The author's books based on expeditions have gained wide fame. The books "In Search of Paradise", "American Indians in the Pacific Ocean", "The Secret of Aku-aku Easter Island", "Easter Island Art", "Kon-Tiki Expedition", "Tigris Expedition", "From Kon-Tiki to Ra" are the author's famous books. These significant works prove that he has great experience and a broad outlook.

His inexhaustible energy, scientific talent, and adventurous spirit have been met with great interest when he visited Azerbaijan as well as other countries. While in Azerbaijan, he began to lay the foundations of a new hypothesis based on his observations. This new hypothesis reflected Scandinavian-Turkish ties. Academician Hasan Aliyev invited the author to this country to show him the ancient settlements of Azerbaijan. The first visit of the famous scientist to Azerbaijan

took place in 1981. The rocks of Gobustan deeply amazed him. Information about this meeting says that Thor Heyerdahl looked at the petroglyphs and took notes and did not speak. He finally said these words after an intense work process:

“These are descriptions of reed boats. It looks a lot like boats I've seen in the Middle East. For now, I see the difference in the fact that in those boats they showed the Sun in the form of a disc or a person. On the Gobustan rocks, the Sun is carved completely naturally on the top of the boat”.

His next visit to Azerbaijan coincided with 1994, the period of independence. During this visit, he met with the President of the Republic of Azerbaijan. The traveler, who was received with the previous sincerity and hospitality, expressed these thoughts:

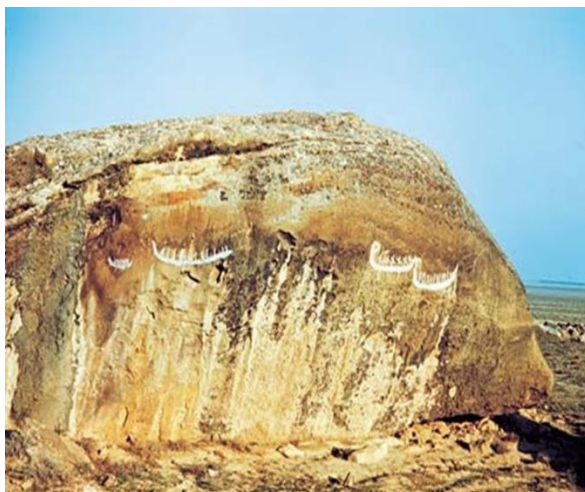
“The first time I came to Azerbaijan was in 1981. At that time, the Iron Curtain existed and there were not many visitors from outside. I was invited by the Azerbaijan Academy of Sciences... On my first visit, I came to study reed boats that resembled ancient Mediterranean boats. But on my second visit, I learned that people in Azerbaijan call themselves Azeri. I remember from my school years that we have legends that are so intricately connected with Norwegian history that when we read them, we did not know where history began and mythology ended. But the written history of Norway goes back to more than 800 years. Oral traditions about the original homeland of our ancestors were recorded around the year 900 in Iceland and that we are descendants of the land of the “Aser” [1].

During his last visits to Azerbaijan in 1999-2000, he began to expand his research on the Scandinavian-Turkish ties. Thanks to his many visits to Azerbaijan, he came to the conclusion that it is necessary to explore the roots of contacts between our countries through the river systems – from the Caspian Sea to the Volga and Don rivers, and from there through the Baltic Sea to Norway. He confidently said that regardless of where we live in the world, we call ourselves "Caucasian type" from the point of view of anthropological structure. We are proud that we are connected to a region with such an ancient and rich culture, especially Azerbaijan. He always admitted with great love that the culture of Azerbaijan is as old and rich as the culture of China and Mesopotamia. His biggest wish was to travel around Azerbaijan and explore the similarities, kinship, and commonalities of Gamigaya paintings with Norwegian petroglyphs and stone monuments. He considered the Gobustan rock paintings as a symbol of the Azerbaijani people. He wished very much to go to Nakhchivan and see Gamigaya with his own eyes. However, this dream did not come true. Thor Heyerdahl died in April 2002.

The beginning of Scandinavian history.

Heyerdahl thinks that the actual years for the lineage of historic kings began around the year 800 AD. He is based on the fact that the mythology starts with the God named Odin. From Odin it took 31 generations to reach the first historic king. The history of Odin says that he came to Northern Europe from the land of Asers. Snorri Sturluson, a 13th-century Icelandic historian, who recorded these stories, said that the homeland of the Asers was east of the Black Sea. [2] He wrote that this was the land that chieftain Odin had a big country. He gave the exact description: it was east of the Black Sea, south of a large mountain range on the border between Europe and Asia, and extended southwards towards the land of the Turks. The author mentioned a “skin boat” with a rather short and bulky hull. According to the Ynglinga Saga, Odin was an immigrant hierarch who came in a vessel called Skithblathnir (Skidbladner) which could be folded together like a cloth. He came from the land of the “Aser”, and is, therefore, frequently referred to as “Asa-

Odin". In fact, in the 5th century B.C., the Greek historian Herodotus described such marvelous foldable boats used precisely in the area referred to in Asa-Odin's saga as the home of the Aser, namely the land of the present day Azeri.

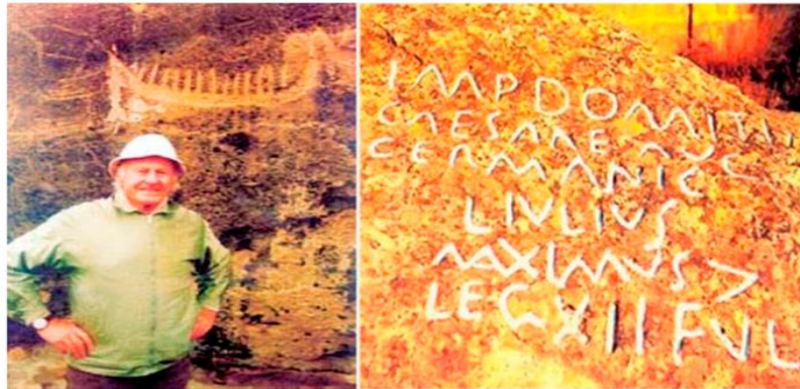


Sickle-shaped boats in Azerbaijan petroglyphs



Sickle-shaped boats in Norway petroglyphs

Sturluson explains the reason for Odin's migration to the north with the Roman attacks on the region. Deciding to protect himself from these attacks, Odin had to take his priests and chiefs and moved to the north of Europe. There is a stone slab in Gobustan with Roman inscriptions. These words are written there: **IMP Domitiano Caesare Avg Germanico Lvcivs Ivlivs Maximvs Legionis XII FVL** – Lusius Yulius Maximus. The XII Fulminata legion under the leadership of St. Caesar Germanicus Domitian.



*Thor Heyerdahl at the Gobustan
petroglyphs in Azerbaijan - 1994*

*Roman inscription at Gobustan rocks indicating that
Roman troops were in the region around 97 AD.*

Indeed, there are enough historical sources about the march of the Roman Empire to the Caucasus and its main country, Albania (now Azerbaijan), in order to expand its territory. The Albanian army was led by King Oroys and his brother Cozis. Although the Albanian army strongly resisted the Roman army, the Roman army won both battles because it was experienced and strong.

The author describes that the As tribe left the city of Turova (Troy) and first came to the country of the Saxons in the north of Europe, then mixed with the local population and multiplied and spread to the northern regions to the present-day Sweden and Norway. It is known from European history that they went to Iceland. That is, a thousand years after the ases left Troy, their descendants in Northern Europe went to Iceland.[3]

The author writes that the local population welcomed these beautiful aliens from Asia, who did not look like the people they had seen before, and gave them territory. As young men married local girls, the number of ases gradually increased. Sturluson notes that long after that period, written sources preserve the names that the Ases brought from Asia. Professor Firudin Jalilov notes that there are such sentences and phrases in the Ynglinga Saga:

“Troy is a Turkish country”,[4] “he left the country of the Turks”,[5] “the ases who came to Europe brought here the Turkish customs and the laws used by the Turks were applied here”.[6]

Thor Heyerdahl considers that there is a logical way to find out when these words were written. It had to be written after the year 84 AD and before the year 97 AD. If this inscription is compared with Snorri’s record, it would mean that Odin left for Scandinavia during the second half of the 1st century AD. Then he counted every king up to the grandfather of the king that united Norway into one kingdom. Such information is available - around 830 AD. In antropology it is considered 25 years per generation of ruling kings. In modern times, a generation extends up to 30 years, but on average the length of a generation in early reigns is 25 years per generation. When we multiply 31 generations by 25 years, we come back to the second half of the 1st century AD. So it proofs that these inscriptions carved by the Romans in stone coincide with the written history almost 800 years ago in Iceland.

Swedish Prof. Sven Lagerbring wrote in his book titled “Similarities of Swedish with Turkish”: “Our ancestors are Turks who are comrades of Oden. We have got enough evidence on this subject. There are people who want to fool you into thinking they are Goths, or Tyrks. I don’t care whether it will be discrediting for me or not. Oden and his comrades were Turks” [7] In the

Turkish translation of the book, the two ravens and two wolves of Odin are also mentioned. The crows were named: Hugin (thought) and Munin (memory). The king of Uighurs whose name was “Buku Tegin” (which probably means Prince of Magic or maybe even Prince of writing or reading) can be seen in Turk epics and it's known that he had three crows.

Who is Odin?

Heyerdal tries to explain the origin of the word Odin in the form of Uti, the name of the Udins living in the territory of Azerbaijan. He wanted to meet the Udi and learn more about their history, and visited to Gabala. Thor Heyerdahl was twice (1999, 2000) in Nich village of Kabala and met with members of the Udi community. He appreciated Udins as the phenomenon of rich Albanina cultural and religious heritage. As the result of this visit with the financial support of Norwegian donor organizations in 2003 the Kish temple and in 2006 the Cotari church in Nich were reconstructed. The Udis have been one of the tribes living in Caucasian Albania for centuries. Their names are probably related to the “uti” listed in ancient sources. The Udis live in the city of Oguz, the administrative center of Oguz region, and in Nic settlement of Gabala region. The fact that they also historically worshiped the Sun and the Moon proves that Heyerdahl's assumptions are quite reasonable. Placing a bust of Thor Heyerdahl in front of St. Elyus Church near Kish village of Sheki city is a bright expression of respect and esteem of Azerbaijanis for the outstanding scientist.

This is how the chief god Odin is described in Scandinavian epics: “On Odin's head is a winged golden helmet, and in his right hand he holds the spear of Gungnir. This spear never misses its target and instantly kills anyone it hits. The eight-legged gray stallion Sleipnir, the horse of the father of the gods, can gallop not only on the ground, but also in the sky. The ruler of the world often walks around the world with this stallion, participates in their battles without being seen by the eyes of the people, and helps the worthy to win. Odin also likes to walk. A poor traveller, wearing an old broad hat and an equally old blue cloak, goes out to see the world and is received with hospitality by all”. Odin was the great magician among the gods and was associated with runes. He was also the god of poets. In outward appearance he was a tall, old man, with flowing beard and only one eye (the other he gave in exchange for wisdom). He lives in the city of Asgard”. [8]

The Odin is called Wodan, Woden, or Wotan. The roman historian Taitus stated that the Teutons worshipped the greek god Mercury and because dies Mercury (Mercury's day) was identified with Wednesday (Woden's day) there is a little doubt that the god (The earlier form of Odin) was meant. However, those who claim that Odin is of Turkish origin say that this name is derived from the Turkish word “od” (the fire). Indeed, it is said in the epic that at first there was darkness in the whole world, and the sun and the moon did not yet exist, so the seeds did not sprout in the fields, and the trees did not bloom in the gardens. Odin and his brothers took fire from Muspelheim and made the moon and sun to light the earth”. The fact that Azerbaijan, the homeland of Ases, is called the Land of Fire, and the fact that the people of Ases were fans of fire and worshipped the fire, is a matter of great interest. Carl J. Becker, in this work, “A Modern Theory of Language Evolution” emphasizes that besides Odin's Asian origin, the word “od” means “fire” in Turkish:

“Odin, together with the Aesir gods, brings a new experience to the northern peoples' experience from Central Asia, from Asgard. In Scandinavian traditions, the Gok-Turks, Scythians, and/or Sarmatians recall the white Elves of Alfheim. Freyr is the king of the white elves in Alfheim.

These elves, like the black dwarfs of Swartalfheim, are skilled in metalworking. This situation is also seen in the Turkish tribes living in the Taurus valleys in Eastern Anatolia. ...When Odin returned from the east, he brought his knowledge of metalworking with him. “Od” means fire in Turkish, and the word “odun” means “wood (firewood)”. In this case, “Odin the Ygg” turns into “Good and young wood”. [9]

In fact, in the Turkic-speaking peoples, the worship of the sun is so widespread that it gradually evolved from the initial belief and began to take the form of a god. This god also had different names in Turkic-speaking peoples. Some of them called the god of fire – Andargan, Odine, some called Odgan, Aggayig, Od-azzi and so on.

Another interesting analogy concerns Odin's own origin. It is said in the saga: “...when the third day ended, a strong and huge Buri came out of the glacier. His son Bjor married the giant Beslay, who gave birth to three sons – Gods: Odin, Vili and Ve...[10] The words Buri and Byor are very similar to the Turkish word bori – wolf. In addition, Odin has two wolf-friends named Freki and Geri. According to Turkish legends, the ancient turks considered the wolf as their totem and believed that they came from the “Wolf-Father”. They took the wolf as an example to the extent that they could learn their own character from the wolf and learn from his life.

In the Hervavar Epic, we come across the following sentences: “... At that time, Asians and Turks came from the East and settled here in the North. Their leader was named Oden. He had eight sons. They all became great and strong men”. In the Bosa Epic, it is also stated that Odin came from the lands of Asia: “... A king named Ring ruled East Gotland. He was the son of Gote, the grandson of the Swedish king Oden. Oden came from Asia, and the most famous royal dynasties of the North were descended from him”.

In their article titled “Alps and Elves: A Case of Heroism in the Turkish and Scandinavian Worlds”, Assoc. Dr. Osman Karatay and Emre Akgun give interesting information about Odin. [11] According to Karatay and Akgun, Odin, who migrated from Turkestan to Scandinavia, was later deified and became the chief god of the northerners. According to them, the name of Odin's tribe is Az, that is, the people in the Kyrgyz neighborhood of the Abakan steppe, who appear as “Az budun” in the Gokturk inscriptions. Again, according to what Karatay and Akgun reported from Nizamuddin Shami, Timur visited the tomb of Oden Ata in this region before he set out on an expedition, prayed and made wishes. Assoc. Dr. Osman Karatay also explained the Turkish origins of Odin in his article “King Odin's Migration from Turkland to Scandinavia”. [12] As the Eurasian shamans he travelled to underworld with his Sleipnir and had two ravens, Hugin and Munin, like shamans all over the world.



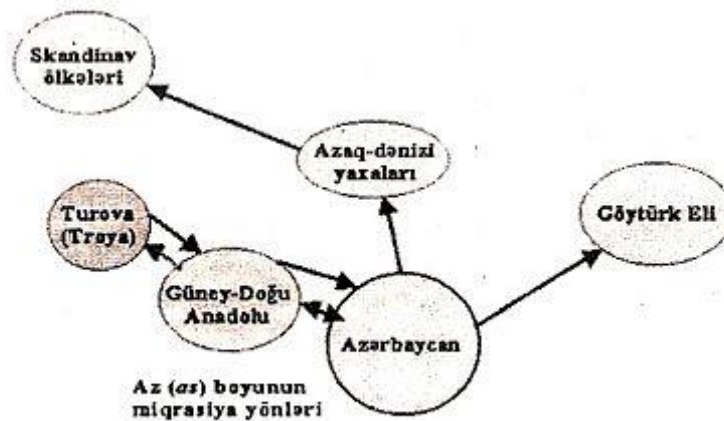
Migration way of Odin according to Osman Karatay

Prominent Azerbaijani mythologist, Professor Mirali Seyidov, in his book “Sources of Azerbaijani Mythic Thinking”, compares the mythical heroes of a number of peoples, Orion, Del, Odin with Oguz, one of the main heroes of Azerbaijani mythology, and finds similarities between them. The author presents the size of these god-giants, hunting, extraordinary abilities, helping people and fighting evil, being on the side of the light as their common features and writes: “Orion, Odin, Del, Oguz as mythological-historical characters have not only external but also internal meaning and idea similarity. Maybe there was a connection between them. This closeness is related, first of all, to the attitudes of tribal groups and peoples who believe in folklore, to life, to individual events, and to the similarity in their lifestyles” [13].

As or Az people

In the saga, it is said that Odin is the father of the ases. But who are these ases or aesirs? Where do their roots go? What role did they play in history? What is known about them?

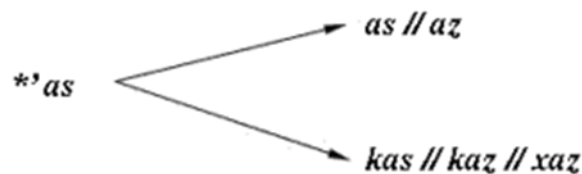
Ases or azes (aesirs) are an ancient people widespread in Europe and Asia. Among the Turkic ethnos that spread throughout Eurasia from time to time, they left their traces in different countries, from the Azikh (Az - oq) cave to the northern, southern, western regions of Azerbaijan and the Azov (Azag) Sea. Azerbaijan was one of the numerous lineages in the Turkic ethnos, which was the main nucleus in the origin of the Azeri tribes at the root of the country's name. Like the parallelism in the name Asia//Azia, the *as* variant of the ethnonym *az* is widespread. The reason for such spread is related to the migration of Az//as tribes from ancient Azerbaijan to western, northern and eastern countries.



Migration territories of as tribes from Azerbaijan to Scandinavian countries, the city of Turova (Troy), southern-western Anadolu, the land of Gokturks.

Professor Firudin Jalilov, who has conducted extensive research on the Az people, writes: “Ethnonyms that attract attention as a division of different Turkic peoples and have the az//as component in their composition are of great interest. For example, the assi lineages named the ases in the Bashkortostan-Katai tribes, the Balkars being called the as, the mention of the as tribe by A. Vamberi among the 32 main tribes of the Uzbeks, the Azig tribe in the Kyrgyz, and finally, the little-known part of the ancient Azerbaijani population was later known as the Azeri tribe leave no room for doubt about their Turkishness. However, the appearance of ases in wide geographical areas has caused some researchers to make a wrong opinion about their ethnic origin”. [14]

In some historical sources, the ethnonym az//as is also used with the forms yaz//haz. Those forms could be thought of as consonants y, h, but there are also forms of this ethnonym that are used with k, x (kaz, kas, khaz). For example, the name of Kasogol (Kas Lake) and the Caspian Sea in the north-west of the Orkhon River represent the name of the Kas//Khaz-ar tribes, just as the Sea of Azag reflects Az tribes. Firudin Jalilov thinks that in this case, there can be no talk of an increase or decrease in sound. Here, only the laryngeal theory can help us to explain the origin of all existing forms. In other words, during the formation of proto-Turkic dialects, the laryngeal vowel 'a', which is pronounced with a throat contraction in the last name as, was purified in one dialect and turned into consonants k, x, h in another dialect.



Further division of Ases according to Firudin Jalilov.

In the ages after the Kura-Araz culture, the minors formed in ancient Azerbaijan experienced a strange fate. Some of them went through Azerbaijan – Asia Minor – Europe to Iceland, and the

other part migrated to North Caucasus and Turkestan. Those who remained in the homeland are scattered in different regions of Azerbaijan.

Of course, there are many toponyms related to the names of ases both in the territory of contemporary Azerbaijan and beyond: Asia, Asturican, Azov, Azych, Asgard, Astarchan, Aslaug, Asdis, Astara, Asparuch, Araz, etc.

In the Scandinavian epics, the Ases are presented as a glorious and powerful people. The king of Sweden, Gulfi, asks a singer who has come to his country to find his immediate family. The woman answers that she is a descendant of ases. Gulfi thinks: "Look at how smart and strong these ases are, that everything in the world is created by their desire. But who can tell me where they get this power from? Perhaps there are greater and wiser gods than them, the ases serve these gods, and in return they give the ases their strength".[15] For this purpose, he comes to Asgard, the city of the ases, and learns from the kings everything about the creation of the world, the glorious deeds and bravery of the ases. After leaving these kings, he realizes that his interlocutors are not kings, but gods.

Ases live in a mysterious city called Asgard. This city is located far above the clouds, at a height unseen by the sharpest human eye. The thin but sturdy Bifryost Bridge connects Asgard to the ground, but disaster awaits those who dare to cross it. People call this bridge rainbow. The red stripe running along the bifryost is an eternal flame that never goes out. This flame, which does not harm the gods at all, burns anyone who dares to touch it. Apparently, here again we see the magnificence of fire. Most likely, this fact is related to the ancient beliefs of the Ases, who were once fire worshippers.

Based on his interpretation of Snorri Sturluson, Thor Heyerdahl organised an archaeological excavation in Azov, which is connected with the name of ases in Russia in 2001. He planned for a subsequent field season in 2002 which was carried out after his death. Scandinavian and Russian archaeological teams worked independently with the purpose of testing the theory proposed by Heyerdahl. Sergey Ivanovich Lukyashenko, the worker of Laboratory of Archeological Research of Azov city says that on the eastern side of Don they know of two cities/settlements that existed around the first century BC, the timeframe that would fit in with Snorri's description. Both of them were situated in the territory of present-day city of Azov. There had been no previous archeological digs, and the dig resulted in a number of artifacts from the period in question. Finally, the excavation findings will be evaluated in light of Heyerdahl's interpretation of Snorri Sturlusson.



It should also be noted that the Azikh cave, named after the Azes, is considered one of the oldest settlements in the world. In 1968, during archeological excavations, a lower jaw bone of a primitive man belonging to the Acheulean culture was found here. It was the first oldest find in the former Soviet Union.

Turkish words that exist in their language today also prove that Scandinavian peoples are of Turkic origin. This is natural, because even though words and phrases undergo phonetic and grammatical changes, they are passed on from mouth to mouth for centuries and continue to remain in the vocabulary of the language, albeit in a different form. Sven Lagerbring's research about similarities between Old Swedish and Turkish were quoted by Abdullah Gurgun from his book "Swedish Turkish Origins". [16]

Turkish	Modern Norwegian	Old Swedish
Adlı	Edel	Adel
Aş	Ete	Aeta
Ata	Edd	Att
Baltalar	Bultar	Bulta (Balta)
Burç	Borg	Burg
Bükmek Böye (s.50),	bulke (bülke)	Biegen
Dip	Dyp	Diup
Er	Herr	Vir
Emek	Innsats	Omak
Erlık	Aerlig	Arlig
Göl	Gyl	Gjöl Sjö
Göm	Gjöm	Göm
Gö mü	Göymsle	
Gülle	Küle	Kula
Hakan	Håkan	Håkan, Hokan, Hakon
Hal	Helse	Halsa?
Han	Han	Han
Hani	Henne	Hanne

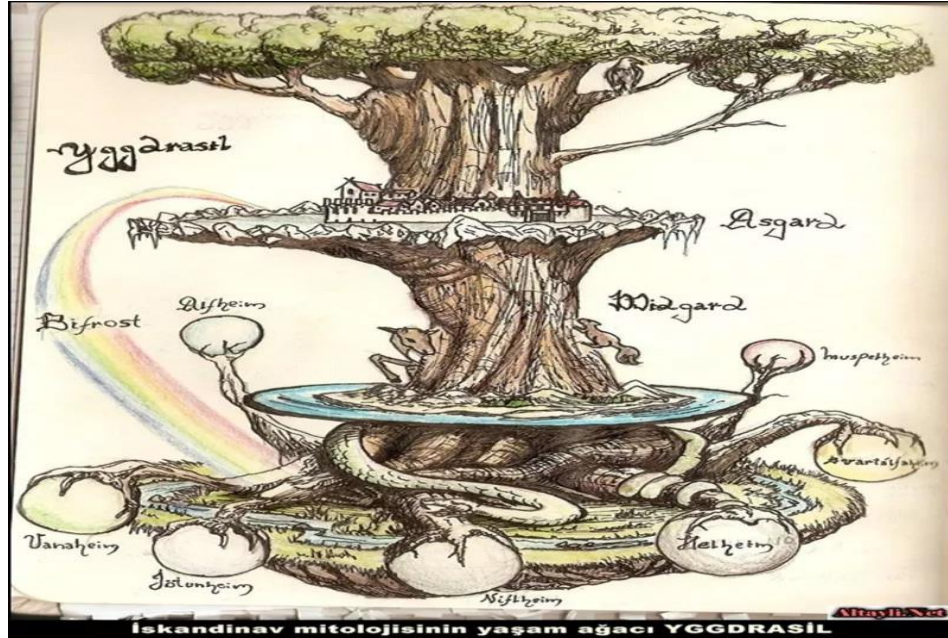


Haydi/Hayda	Kom da	Hejdå
Hun	Hun	Hon
Hey	Hei	Hej
Höyük	Haugen	Hög
Kaan	Konge, Kunge	Konug, Kung
Kandil	Lys	Kyndil
Kap	Kopp	Kop
Kaz	Gås	Gås
Kedi	Katt	Katt
Killer	Kjeller	Kallare?
Köy	Vik	Koja (koya)
Kule	Kull	Kulle
Mana	Mening	Mena
Nam	Navn	Namn
Oda	Hytte	Hydda, uthas
Öküç	Okse	Oxe
Öreke	Rokk	Reck
Peder	Fader	Fader
Pusu	Felle	Puss
Siper	Sperre inne	Spar?(sper)
Sagu	Saga	Saga
Söyle	Seie	Saeledes
Su	Sjö (şö)/ Vann	Sjö (Syö)
Sulu	Sölete	Sölig
Şen	Glad	Shön
Tepe	Toppe	Top
Var, Varlık	Veare?	Vare, Varelse
Yer/Yurt	Gerd, Gård/ Jord (Yur)	Gerd/ Jort (Yort)

The World Tree

Yggdrasil is the sacred tree of life in Norse mythology. It is also called “World Tree”. “Yggdrasil connects the 9 worlds through its branches: Asgard, Vanaheim, Alfheim, Midgard, Nidavellir, Jotunheim, Svartalfheim, Niflheim, Hel. At the top of Yggdrasil is the eagle Vedrfolnir. This eagle watches the whole world from here. Odin hung on the branches of Yggdrasil for nine nights in order to learn the secret of the runes.” [17] Yggdrasil generally represents longevity, fertility, rebirth and knowledge in mythology. According to the Edda, Yggdrasil is a great tree that stretches from the bottom of the earth to the sky. Yggdrasil has nine branches that cover the whole world and three roots that end in the heavens. These roots go deep into the three lands of Niflheim, Jotunheim, and Mitgard. [18] Each of these roots receives its water from a source. One of the roots is under Asgard (home of the Asians), where the Asians live. The main temple where the gods gather is at the bottom of Yggdrasil. Yggdrasil trembles when the heroes are in danger. The presence of holy water (three springs: Gorgelmir, Mimir, Urd) under the roots of Yggdrasil reminds us of the “water of life” of the world tree of Turkish mythology. In Turkish mythology, the world tree is sometimes combined with the belief of “water of life”. For example, in some

Altai legends, the “tree of life” is a “birch tree” on top of the “mountain of the world” rising up to the 12th floor of the sky, and this “water of life” located in the pit below sometimes gave immortality or new strength, and sometimes health or youth.



The concept of “Tree of Life” or “World Tree” also has an important place in Turkish mythology. In Turks, the tree of life was used quite widely as a motif in carpet and rug patterns. It is even possible to see the motifs of the tree of life even on the tombstones. In Turks, shamans used the tree of life to reach the sky god. In Altai mythology, God Bay Ulgen sat on top of this sacred tree. In Norse mythology, in the middle of the Yggdrasil tree is Midgard (Middle Earth), the place where people live. The book “Altay Knowledge” also mentions a “Middle World” where people live in the middle of the Turks’ tree of life: “The middle world we live on is above the Earth. It is said that the middle world consists of two worlds, the visible and the invisible. The flat parts of the middle world (mountain valleys and steppes), i.e. the visible side, belong to people.”

Azerbaijani shamans remember the World Tree together with the Mother Fire when saying applause. “From the day when the blessed birch tree with sixty branches grew, you, our Mother of Fire, fed the hungry, warmed the cold, and built our beds to cook our meals”, “You are resting in the shade of the golden leafed tree”. [19]

The spiritual unity with the tree and plant world, the connection of man, generation, clan, and community with vegetation is not observed in any nation as much as the turks. Tree, plant, sky, flora are important concepts of Turkish culture. The tree symbol is the core of Turkish shamanism, mythology and folklore, ethnography, and folk art. Therefore, the interpretation of the tree symbol is of special importance in the study of Turkish mythological systems. Mythologist Arif Hajili writes: “One such important symbol related to the concept of Gaba it is a tree (“kaba” - high, high - this word is Sumerian “guba” found in the texts - rising, standing comparison with the word is interesting). The World tree – Coarse tree – generation of various image changes.” [20] Found in the poetic phraseology of “Kitabi Dada Gorgud” the phrase “rough tree” came from is undoubtedly related to the world tree, the legend of the Oghuz-Kipchak peoples. The roots of the

coarse tree are the underworld and the past, branches mean sky and the future. The drying of the tree is the death of the offspring, the lineage. On the contrary, the vitality of tree means life. Gorgud Ata's most respectful applauses is "do not cut the thick tree".

Speaking about the tree myth, Alesger Alakbarov notes that belief in the sanctity of trees and even small forests is widespread in Azerbaijan, and sacrifices were made in honor of sacred trees and forests.[21] There are a number of historical sources about ancient Azerbaijanis having special faith in spruce and plane trees. Azerbaijanis worshipped double trees, forty trees, sometimes a forest of trees, and no one dared to break even a single branch of them. They swore by the tree, they worshipped and sacrificed them once a year.

In Turkish mythology, the tree, as a symbol, is closely related to anthropogony (human creation myth) as well as its connection with cosmogony (universe creation myth). The first created human being is protected by a dog under the tree. Ulgen used two elements while creating man. These are: soil and wood. Seven men were created with their bones from clay and their bodies from clay. Later, in addition to these, he created eight people and eight trees with them. Professor Nihat Banarlı thinks that, the number of men is nine:

"According to the Turkish thought about the creation of humanity, God sheltered the nine human species on earth under the shade of a nine-branched tree that he created before these people. He first raised a tree with nine branches from the ground, then created one of the first ancestors of today's humanity under each branch, and gave these nine people shelter in the shade of the tree as a knowledge of creation".[22]

Tarum mummies in China and Scythians

During his visit to Azerbaijan Heyerdal stated in his speech that when he contacted with China they informed him that they had discovered blond-haired mummies in the Tarim Desert deep inside China. These mummies were so perfectly preserved in the cold climate and salty earth that everyone could see the colour of the skin and hair. Chinese archaeologists were surprised to find that these mummies did not belong entirely to the Mongoloid race and began to suspect that they were Vikings. When radiocarbon dating was applied, it was determined that they belonged to the Nordic type, dating from 1,800 to 1,500 years BC. However, the period of Vikings started around 800 AD. Therefore, these mummies were not Vikings who had once come to China. There is a missing link here. Logically, this leads to the idea that the Caucasus is a connecting link as a center of migration.

These mummies were dressed in woven cloth, the colors and woven patterns were very specific. The Chinese first studied the mummies themselves and then invited American experts to study the clothing, who determined that the weaving and clothing were typical of the Celts in Ireland. Old written sagas of Ireland says that their ancestors were Scythians. Heyerdahl thinks that Azerbaijan has been a very important centre, sending people in many directions and attracting people from many directions.

As for the Scythians, it should be noted that already in B.C. in the 1st millennium – B.E. at the beginning of the 1st millennium, powerful states such as Manna, Midia (small Midia), Ishguz (Scythian) kingdom, Atropatena, Caucasian Albania existed in the lands of Azerbaijan. According to the historian Heradotus, the Scythians worshiped only one God – the Sun God. Historian Zaur Hasanov, like other Turkish scientists, believes that the Scythians are of Turkish origin and referring to Heradotus work notes that (part IV of the book "History") Scythians moved to the above-mentioned areas from the Asian continent. Zaur Hasanov in his work "Tsar of Scythians"

which can be considered a serious study of the Scythian and Turkic tribes, writes that the historian Rashid al-Din in his work "General History" refers the history of the ancient Turks to the VII century BC.[23] During this period, a part of the Turks moved from the Asian continent to Western Europe, and the other part settled in the Near East. At first, the Scythians defeated the Cimmerians and settled in the northern areas of the Black Sea coast, on the western shores of the Sea of Azov. In this regard, Zaur Hasanov states that the ancient homeland of the Scythians was the Asian continent, but the other Turkish tribes – Massagets forced them out of there, and they were forced to enter the territory of the Cimmerians. Facts about the arrival of the Scythians to Western Europe and the shores of the Sea of Azov confirm Heyerdahl's idea of a missing link and fill this gap.

SKRUK and Azerbaijani music

SKRUK is a Norwegian choir which was founded in 1973. It has toured all over the country and many parts of the world for more than 35 years with its conductor, Per Oddvar Hildre. SKRUK has a varied repertoire, influenced by Norwegian folk music, spirituals, world music, and jazz.

After Tur Heyerdal put forward the idea that Norwegians are of Azerbaijani origin, in 1995 a collaboration between Norwegian soloists and Azerbaijani musicians called "The Land We Came From" (Landet vi kommer fra) took place. They have created the link between two different musical traditions and cultures. The collaboration is accompanied by traditional Azeri instruments such as tar, saz, ud, kamancha, tutak, balaban, garmon, nagara. Norwegian Bjorn Holum played bass. Azerbaijani singers Brilliant Dadasheva and Ilgar Muradov have been performing the song "Bari bax" (Look at me). Ilgar Mammadov says that Azerbaijan-Norwegian ties are real. "Now I am convinced that Thor Heyerdahl's theories aren't fantasy. When our mugham musicians saw a film about the original Norwegians – the Laps they said: "This is our music and culture". "Many of the expressions in the art and culture of Azerbaijanis are very similar to the same works of art of Norwegians," – Mammadov noted, and was surprised that the "SKRUK" choir could sing Azerbaijani folk melodies so well.

Bjorn A.Wegge, Director of Information for the Norwegian Humanitarian Enterprise, promoted the idea for the CD project. He said that Norwegians have discovered the rich musical and cultural life of Azerbaijan and intend to introduce this music more widely to the outside world. For this purpose, 45 singers of SKRUK came to Azerbaijan in 1997. For ten days, they traveled around the country, visiting cities and villages to get to know the traditions and lifestyle of Azerbaijanis closely. SKRUK gave concerts in different cities of Azerbaijan such as Baku, Shaki and Ganja. This project of the outstanding composer-pianist Siyavush Karimi was awarded the world's biggest "Grammy" award in the music category in 1997.

"It was the Norwegians' idea to make this CD," said Brilliant Dadasheva, a popular soprano vocalist. "We were excited that they wanted to sing our folk songs." She thinks that when the Norwegians and Azerbaijanis were together that month, while recording and touring, they communicated with each other mainly through music.

Per Oddvar Hildre, SKRUK's director commented they have much to learn from Azerbaijanis. Because they found the mugham tradition to be very interesting. When you listen to the same melodies over and over again, you always find interesting, new elements. They found the Azeris receptive to new musical combinations.

The closeness and similarity between Norwegian and Azerbaijani music should be explained by Heyerdahl's theory being true. Indeed, the same spirit is felt in both musics.

Conclusion

In conclusion, we would like to note that every scientific hypothesis is initially met with doubts and criticism. This is natural, because it goes through a great struggle until it is fully proven. Of course, there are many who criticize Thor Heyerdahl and claim that the evidence presented is fantasy. However, the fact that there are so many similarities between the two cultures cannot be accidental. Sometimes, even if the material evidence is not satisfactory, they appear in folklore, traditions, music and various areas of culture and art. Especially in historical science, it takes a lot of hard work and research to construct different narratives based on the evidence available. It is thanks to courageous scientists and brave travelers like Thor Heyerdahl that the truth is revealed.

Although Thor Heyerdahl died, his theories are still of interest in world science today. Although there are those who doubt the Turkic origin of the Scandinavian peoples, the followers of the great scientist continue his work. Norwegian scientists continue to study petroglyphs, they conduct research together with their Azerbaijani colleagues to reveal secrets unknown to science. It is clear from the information about the monuments in the territories of Azerbaijan that the dark pages of history are gradually being opened.

Declarations

The manuscript has not been submitted to any other journal or conference.

Study Limitations

There are no limitations that could affect the results of the study.

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RESEARCH OF THE IMPACT OF CASPIAN SEA LEVEL CHANGES ON COASTAL SOILS AND WAYS OF EFFECTIVE USE (SAMUR-DAVACHY PLAIN LANDS)

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ABSTRACT

The article also discusses the impact of changes in the level of the Caspian Sea on coastal soils, shows ways of efficient use of soils in agriculture. The assessment was carried out on the basis of the analysis of field, laboratory and multi-year research materials. It is noted that the existing natural and ecological conditions in the studied region, both natural and against the background of human economic activity, lead to rapid transformation processes in the morphogenetic properties and diagnostic indicators of soils. This change always changes from north to south and from west to east. Although the selected study region does not have a large area in either the meridional or parallel directions, the differentiation caused by natural and anthropogenic factors in the landscape and land cover is clearly evident. Thus, the ratio of natural and anthropogenic impacts changes from the lower reaches of the Samurchay in the north to the lower reaches of the Sumgayitchay in the south. While the anthropogenic impact on the surrounding ecosystem in the north increases year by year, the impact of natural exodynamic processes increases towards the south, and the anthropogenic impact takes second place. On the Absheron Peninsula, the anthropogenic (technogenic) impact on the environment increases many times. As is known, the Caspian coastal region of Azerbaijan extends from the Samurchay in the north to the Astarachay in the south. The aridity index increases from both the northern and southern ends of the Caspian coastal region towards the Absheron Peninsula, and the anthropogenic impact is weaker than the natural impact. Only in the center, as mentioned, does the anthropogenic impact on the Absheron Peninsula increase again. The study area includes the part of the Caspian Sea coastal region from the Samurchay to the Absheron Peninsula. The Samur-Devachi, Siyazan-Sumgayit and Bogaz plains are located here. Over the past hundred years, research has been conducted in the area on various directions and problems of soil science. These studies reflect the period of the last century. These research works are of great importance for determining the dynamics of soil processes. In the studied area, the desertification process is expanding its territory not only to the north, but also from east to west. Towards the west, the influence of natural factors weakens, but the anthropogenic influence intensifies. This process, in addition to negatively affecting the parameters of the soil cover, has also led to serious transformation of the soil.

Our latest research on natural and anthropogenic degradation of soils covers the years 2016-2019.

Keywords: anthropogenic, transgression, regression, takır, hesitation, climate

Introduction.

Climatic conditions are considered the main factor in the degradation of land cover. Since the study area is geographically located on the north-south path of the general atmospheric

circulation, climatic elements change sharply from north to south and at the same time their negative impact on land cover increases. As a result, the desertification process manifests itself clearly with the formation of various soils at a distance of less than 20 km. The area is associated with a sharp change in climatic elements.

Global changes in nature in modern times are considered one of the important research directions in the system of Earth sciences. It is especially important to analyze these changes in a natural and anthropogenic context. Against the backdrop of climate change currently taking place on the planet, processes in this direction are gaining even greater momentum on a regional and local scale. The fluctuations in the level of the Caspian Sea also have a major impact on the soils of our study area. The level of the Caspian Sea is related to climate change. Climate change, in turn, affects the hydrometeorological conditions of the Caspian basin, including the water balance and annual flow of rivers flowing into the Caspian. Thus, the rivers flowing into the Caspian Sea have also been affected by climate change. In other words, their excessive use in irrigation and exposure to evaporation result in less water being brought to the Caspian Sea. Summarizing the opinions on the fluctuation of the Caspian Sea level, it can be said that the main reasons for the fluctuation of the level are:

- climate of the northern hemisphere,
- atmospheric circulation,
- The climate of the Caspian watershed and the changes occurring in it.

Caspian scholar G. Gul shows that there are connections between the level of the Caspian Sea and the ice caps of the northern Arctic seas.

This once again confirms the change in the water balance in the Caspian basin as a result of global climate changes in the northern hemisphere and the circulation of moisture in the atmosphere. To obtain detailed information about the climate of the area, multi-year data from many meteorological stations was used. These include multi-year and annual average temperatures, the amount of precipitation and possible evaporation, soil surface temperature, relative humidity, etc. In our study area, the annual precipitation is less than 300 mm, and the average annual temperature varies between 13-15⁰. Five months of the year are very hot. The driest months are in the summer. Only 30 mm of precipitation falls during these months. Some places receive even less precipitation than this amount. In our study area, precipitation decreases sharply from north to south over a distance of 150-200 km. High temperatures begin in May and continue until September (Eyyubov: 1984). During this period, the average monthly temperature does not fall below +16.4⁰C. In the south, the annual amount of precipitation on the Absheron peninsula is 227 mm. As a result of analysis of temperature data from meteorological stations over the last hundred years, it has been revealed that the temperature has increased by 0.7-0.9⁰. It is known that precipitation fell by 30-40 mm. Global climate warming primarily affects coastal zones. As a result, the level of the world's oceans is gradually rising (2-3 mm per year). This process is affecting many coastal lowlands around the world. Currently, many scenarios show a rise in global sea levels of 0.5 to 3 m by 2100 (Shashko:1967). At the end of the 20th century (from 1978 to 1995), the rate of rise in the Caspian Sea level was estimated to be 13-15 cm per year. From this point of view, the Caspian Sea coast can be considered the most suitable region for modeling environmental changes. As is known, according to the results of many years of observations, the Caspian coast of Azerbaijan can be assessed as a regressive phase since the middle of the last century, and its continuation as a transgressive phase. From this perspective,

when preparing an article of this type, studies conducted over the last 70-80 years were reviewed (Mamedov:2007).

Object and methodology of the research.

The study area geographically covers the area between longitudes E 49°8'13.2" in the east, E 49°30'4.8" in the west, latitude N 40°45'54" in the south, and latitude N 41°14'2.4" in the north. The elevation varies between 0 m above the modern level of the Caspian Sea (-26.5 m). After the in-house preparation phase, the research was continued with field work and completed with laboratory analysis results. During the field study, observation and sampling sites were selected under semi-stationary conditions, taking into account the physical and geographical conditions of the area, based on the comparative geographical method. The geographical coordinates of the center point of the selected city are given in the analysis and discussion section. A number of physical properties of soils on soil sections in desert conditions were studied using known methods, and the soil samples taken were analyzed using the following methods: humus - by the method of I.V.Ivanov, pH in aqueous solution with a potentiometer, carbonation (CO₂) by the Scheibler method in a calcimeter device, analysis of easily soluble salts in soil [E.V. Arinushkina], hygroscopic moisture by weighing after drying in a drying cabinet at 105 °C for 6 hours, determined by the granulometric N.A. Kachinsky method using Na₂P₂O₇.

Research object and methods.

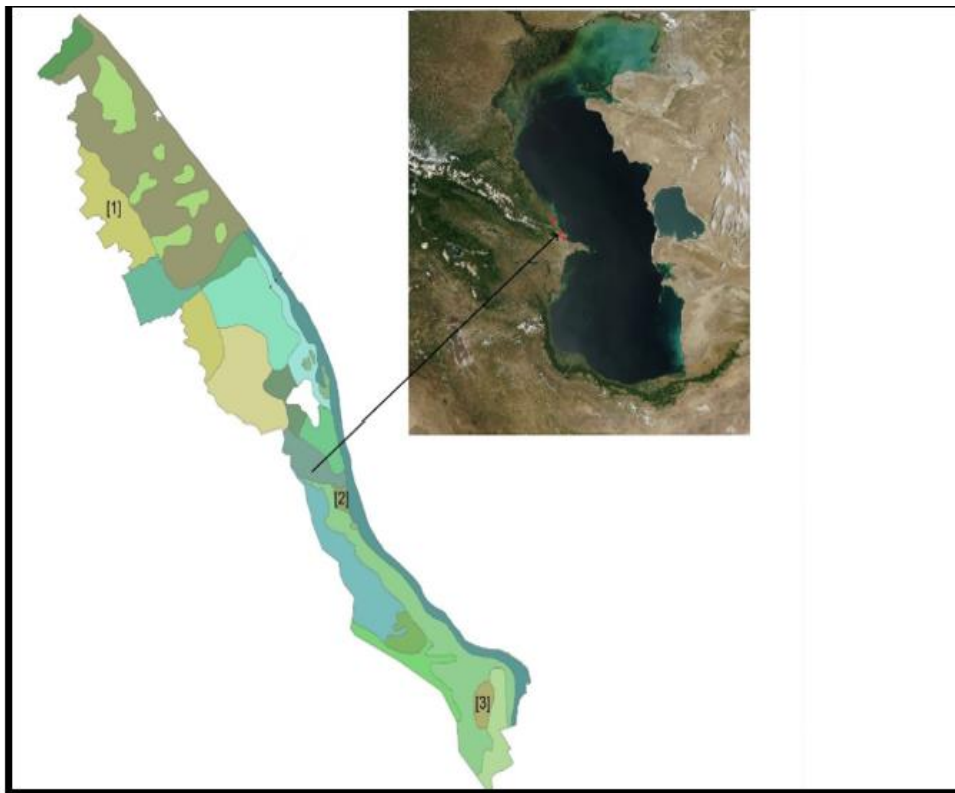
Analysis of the studied area. In the last century, drastic changes have occurred in the evolution of coastal lands due to fluctuations in the level of the Caspian Sea (regression-transgression-stabilization). These changes are more characteristic of the modern and ancient terraces of the sea, especially the coastal zone between the Shurabad settlement and the Mukhtadir settlement. The process of soil formation in the regressive and lagoon-transgressive landscapes of this area has been in the direction of decline and recovery. As a result of sea level rise in the second half of the 20th century, much of the coastal land, including delta and island lands, was submerged under sea water. This situation is also characteristic of the coastal lands of the Russian Federation, Kazakhstan, Turkmenistan, and the Islamic Republic of Iran, which are located on the Caspian coast (Mamedov:2007). Field research was conducted on the first and second accumulative terraces of the coastal areas of the administrative districts (Khizi, Siyazan, and Shabran). The first point was taken 1.5 km west of the village of Shurabad. From this point, the youngest accumulative terrace of the sea begins to the east, and crystalline carbonate layered rocks that actively participated in the nucleation of the Caspian Sea and the soil formation process of the area come to the surface.

It is known from the conducted studies that there have been major transgression-regression phases in the Caspian Sea, and as a result of this numerous activity, it has created major changes in the relief and lithological structure of the coastal zone. In the Caspian coastal zone of Azerbaijan, the modern New Caspian, Upper Khvalyn, Lower Khvalyn and Caspian sea terraces are distinguished. These terraces differ from each other in terms of hypsometric level. From the first "Shurabad" point to the east, modern accumulative marine sediments are formed on crystalline rocks, and the direction of the soil formation process reflects the morphogenetic characteristics of gray-brown soils.

When the level of -25.5 m in 1929 was taken, modern terraces along the coast were covered with Caspian waters and lagoons existed in the area of Shurabad settlement. By the end of the 70s of

the 20th century, these areas were free from sea waters and primitive forms and intrazonal variants of gray-brown soils were formed in their place. Analysis of the results of the analysis of many parameters of soil sections from east to west in these soils allows us to clarify the influence of transgression-regression movements of the sea on the evolution of coastal soils. In general, along with this process, the continental influence on the quantitative and qualitative changes in coastal soils was not less than the influence of exo- and exodynamic processes [5]. During the field study, characteristic and deep soil sections were laid in the Shurabad observation and sampling site in directions parallel and perpendicular to the sea. When selecting the locations of the soil sections, the surrounding relief forms and geobotanical conditions were taken into account. In almost all small areas of the territory, the description of the soil, especially the signs of the salinization process, was noted. Another point that caught our attention was the study of the issues of sulfidation, claying in groundwater, and the amplitude of groundwater level changes. In the first point, the differentiation of the soil profile is weakly noticeable. The amount of humus in the upper horizon does not exceed 1%. The degree of salinization varies from weak to severe. The direction of soil formation and soil composition are greatly influenced by the deflation process characteristic of the territory, the activity of sea waters, extreme climatic conditions, and the heavy granulometric composition.

Figure 1. Observation and site sampling of established characteristic soil plots.



[1]-1st observation and sampling site

[2]-2nd observation and sampling site

[3]-3rd observation and sampling site

Horizontally, the degree of coverage with wormwood-variegated vegetation varies from 10-15% to 50-70%. A very fine layer consisting of small shells and smooth sand grains has formed along the seashore. The great influence of the eolian process is clearly visible in the formation of this layer. Below this, the "A1" horizon has formed, which is light gray in color and the structure is not clearly distinguishable. Since the soil-forming rock is carbonate, this layer boils under the influence of HCl. The soil-forming horizon differs from the horizon above it only in its yellow-straw color. The lower part of the "C" horizon again consists of small sand and shells.

In the profile of many of the soil sections, a sandy-medium loamy, strongly hardened divalent iron compound is found. This layer is the remains of buried lagoon and marsh soils. Here, the groundwater level is very close to the surface. While humus is 0.3-0.4% in the upper horizons of these soils, the amount of humus increases slightly in the buried "C" horizon. The environmental reaction of the soil is alkaline and weakly alkaline. In these soils, the soil formation process was very weak due to extreme conditions. Rapid exodynamic processes create imbalances and stop development.

A significant part of the study area is occupied by takyra-like soils with varying degrees of salinity and heavy mechanical composition. These soils have remained unused for many years. In recent years, the introduction of irrigation in the area has increased the importance of efficient use of soils. However, the specific properties of these soils, including their heavy mechanical composition, the formation of polygonal cracks 15-20 cm thick, poor supply of nutrients, and the process of salinization and salinization, make it difficult to use them for agricultural purposes. From the results of our multi-year field and laboratory analyses, we can conclude that it is necessary to implement a number of agrotechnical measures on these soils. First of all, it is important to add sand to the soil to improve the physical properties of the soil. When applying sand to the soil, it is more effective to add it mixed with finely ground manure. Considering the high Na^{2+} cation in the soil's absorbent complex, it is also important to add gypsum to the soil together with NPK.

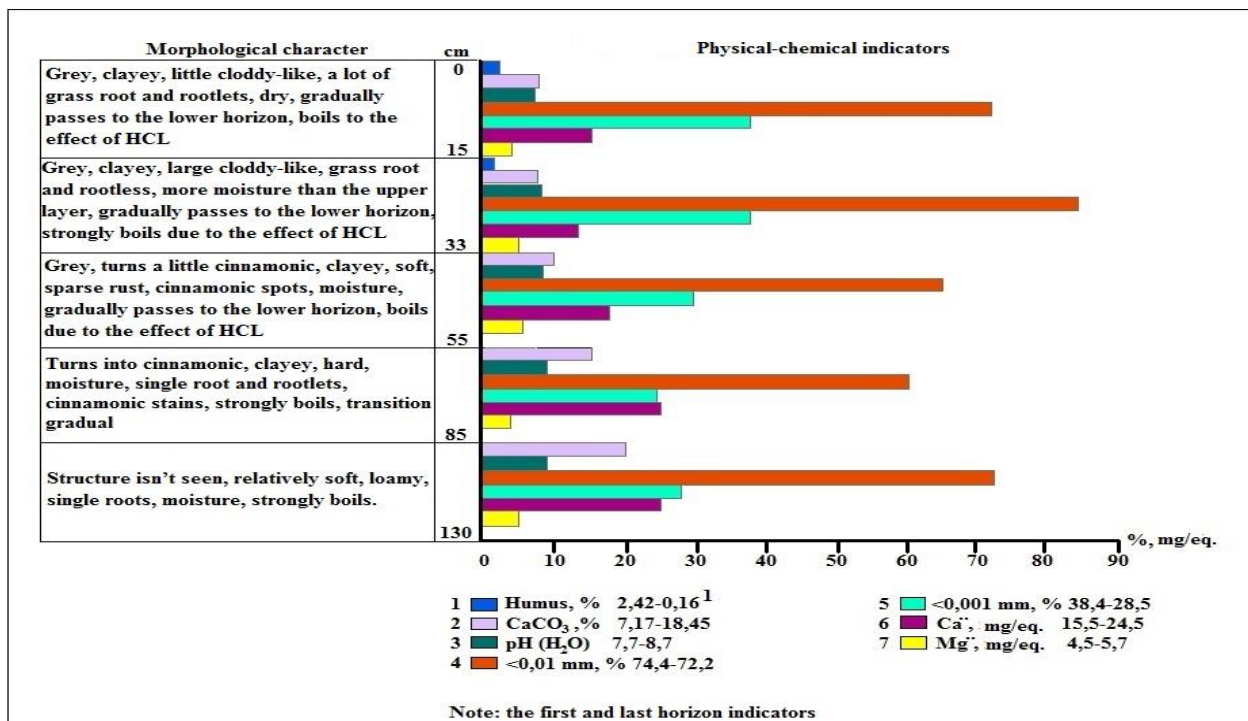
Taking into account the intensity of the sun's rays, irrigation should be carried out in the second half of the day when the sun approaches the horizon. The heavy clayey nature of the soils prevents water infiltration. As a result of evaporation from the surface and heating, the swollen soil is compacted and, as a result, crusts and cracks are formed, which results in a 25-30% loss of productivity. In general, if the above-mentioned measures are implemented at a high agrotechnical level, 25-30 tons of grain can be harvested from these lands under irrigation conditions.

Field work and soil analysis.

A site 1 km east of the center of Shabran district was selected as the second sample and observation site in the study area. The geographical coordinates of the center of the site are N 41°12,800', E 45°01,943'. The absolute altitude is -7 m. The area consists of a flat plain with a slight slope towards the sea. The analysis results of characteristic soil section No. 4, established in this area, are compared with the analysis results of section No. 8, established in gray-brown soils to the south of that area. The geographical coordinates of section No. 8, which was laid out on gray-brown soils to find the changes in absolute altitude from south to north and the influence of the Caspian Sea, are as follows: N 40°59.139', E 49°14.124', absolute altitude is -23 m. When

comparing the physical properties of these soils, the gray-brown soils located in the Siyazan region to the south have a heavier mechanical composition than the grass-gray soils formed in the Shabran region. The amount of physical clay (<0.01) varies between 78.3-83.4% in the upper horizons of the soil.

M.E Salayev shows a change of total humus averagely 2.0-3.5 % in these soils during his research. This index changes by 1.5-2.6 according to our research results. The graphic that reflects morphological and physical indicators of the section I applied in the zone of the Gulami village has been given (Graphic 1). Calcareous gets increased towards depth in these soils. An absorption capacity is 20.5-22.7 mg/eq in absolute dry soil of 100 g. Saturation with bases reaches 96-98 %.



Graphic 1. Morphological and physical-chemical indicators of the meadow-grey soils

This indicator decreases towards the north and is 67.6-75.3% in the upper horizons of section No. 4. The relative lightening of the mechanical composition of the soil is due to the decrease in the influence of the sea and the increase in the influence of continental deposits. In both areas, the increase in natural moisture in the soil profile towards the depth is due to the influence of groundwater. Therefore, after the "A1" horizon, this indicator increases sharply. When paying attention to the salt content of these soils, both the influence of the sea and the degree of mineralization of groundwater increase towards the south. The amount of SO₄ and Cl anions is high in the "A1" horizon of section No. 8. However, in section No. 4, on the contrary, the amount of these anions is low in the upper horizon and increases towards the lower layers. In our opinion, these are related to the geographical factors of the area, as well as human economic activity. The long-standing application of the irrigation system and the presence of a horizontal drainage system in the Shabran region are considered to be the main factors affecting the amount and

distribution of salt content. The application of classical irrigation methods to these lands may increase the salinization process in the area in the future. Therefore, the application of a progressive irrigation system may have a more positive effect.

Conclusion

We came in the following conclusion:

1. As a result of global climate change and atmospheric moisture circulation, the water balance in the Caspian basin is changing.
2. The impact of the transgression and regression phases of the Caspian Sea is clearly visible, and this impact increases from north to south.
3. The anthropogenic impact on the soils of the Caspian coastal plain from north to south is gradually weakening, while negative natural impacts are increasing.
4. The introduction of new irrigation systems to the territory and the correct orientation of human economic activity in the direction of soil evolution can lead to the formation of agrogenic soils in the near future.

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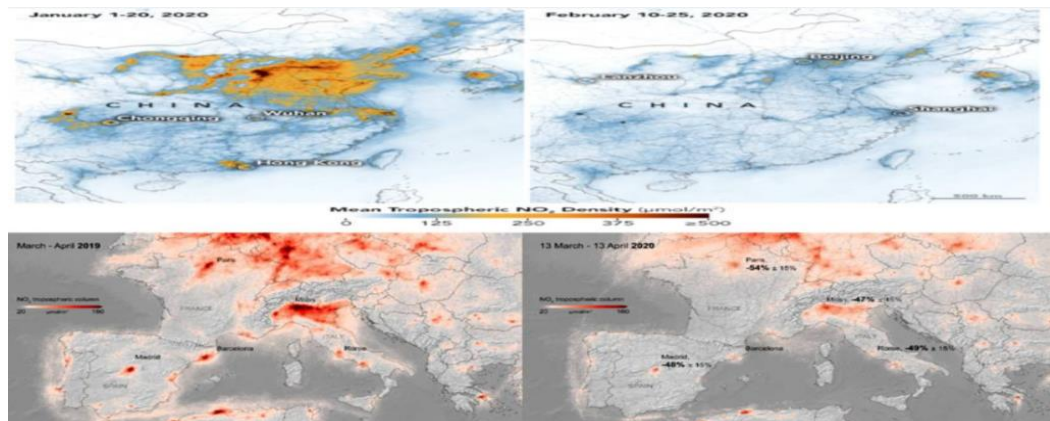


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6. M. Ahmad, "Importance of Modeling and Simulation of Materials in Research", J. Mod. Sim. Mater., vol. 1, no. 1, pp. 1-2, Jan. 2018. DOI: <https://doi.org/10.21467/jmsm.1.1.1-2>

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