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ORAL LEUKOPLAKIA AS A PRECANCEROUS LESION AND PREVENTION OF ITS MALIGNIZATION

Abstract. Leukoplakia, a disease of the mucous membranes, is characterized by pathological keratinization of the protective epithelium, which, as a rule, is a reaction to chronic, mechanical, exogenous irritation of the mucous membranes lined / covered / with stratified squamous epithelium, and manifests as lesions of varying degrees. It is characterized by a different degree of the epithelial layer thickening and the involvement of the lamina propria of the oral mucosa into the inflammatory process.

Keywords: Flat leukoplakia, Verrucous leukoplakia, Erosive leukoplakia, Leukoplakia, Malignization of leukoplakia.

Leukoplakia, a disease of the mucous membranes, is characterized by pathological keratinization of the protective epithelium, which, as a rule, is a reaction to chronic, mechanical, exogenous irritation of the mucous membranes lined / covered / with stratified squamous epithelium, and manifests as lesions of varying degrees. It is characterized by a different degree of the epithelial layer thickening and the involvement of the lamina propria of the oral mucosa into the inflammatory process.

Leukoplakia manifests itself as a chronic hyperplastic inflammatory process in which hyperkeratosis alternates with parakeratosis. When keratinization acquires the character of parakeratosis, the phenomenon of acanthosis is more pronounced.

Inflammatory infiltrate of lymphoid cells and plasmacytes, that often alternate with fibrous and sclerotic lesions, develops in the zone of the oral mucous membrane.

The first clinical description of leukoplakia belongs to A. Bazen (A. Basin 1868), and F. Vidal (F. Vidal 1883) was the first to describe leukoplakia of the oral cavity.

Leukoplakia of varying degrees is observed in 13% of patients with pathologies of the gastrointestinal tract over the age of 30 years. Men of older age suffer from this disease 7 times more often.

Over the past five years, 67 patients with a diagnosis of leukoplakia have been treated at the K. Mardaleishvili Medical Center. Of them, 45(62.9%) patients had a history of gastrointestinal pathogenesis, 51(76.8%) were smokers, and 23(34.9%) were alcohol users.

Leukoplakia of buccal mucosa was observed in 19(29.9%) cases;

On the lateral surface of the tongue – 11(17.6%) cases; in the lip corners – 5(7.8%) cases. Medical histories of 51(76%) patients revealed tumors of different localization, associated with genetic factor.

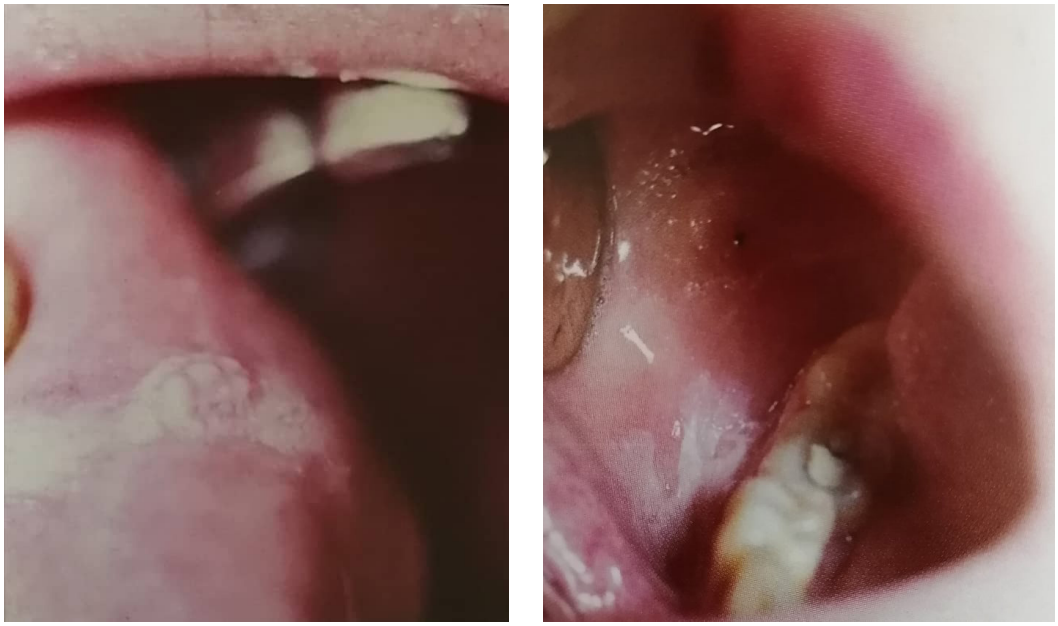

Figure 1. In the mouth cavity floor – 24 (34.7%) cases

Figure 2. In soft and hard palate areas – 8 (11.85%) cases

Chronic mechanical damage caused by a fully removable prosthesis was observed in 14(21.9%) cases. 51(76%) patients did not undergo sanitation of the oral cavity. Pathological occlusion and the formation of leukoplakia on the mucous membrane of the cheek due to constant mechanical injury caused by cheek biting was observed in 12(19.7%) cases. 9(13.9%) patients underwent one or more episodes of conservative treatment for leukoplakia lesions on genitalia. The following forms of leukoplakia are distinguished: flat, verrucous, erosive, and leukoplakia of smokers.

Flat leukoplakia is characterized by the formation of clearly marked zones of the mucous membrane opacity, which more closely resemble membranous plaques, impossible to be removed with a spatula. Of the 67 patients, 49(73%) patients were diagnosed flat leukoplakia. Depending on the degree of kera-

tinization, the color of the affected area varied from whitish-yellow to grayish-white.

The surface of leukoplakia is dry and slightly rough, the edges are notched, consolidation in the bottom of keratinization area is not observed.

With the localization of leukoplakia in the lip corners hyperemia can also be noted.

In the sites of buccal leukoplakia wrinkles appear. The bottom of the oral cavity also has an appearance of a grayish, wrinkled shell.

Verrucous leukoplakia, which is manifested in the form of an elevated milky-colored plaque or rough, grayish-white areas that extend 2–3 cm beyond the surface of the mouth mucosa, most frequently develops against the background of flat leukoplakia.

Erosive leukoplakia with erosions and cracks of various shapes and sizes is a concomitant lesion encountered in leukoplakia. This form of the disease is accompanied by pain. Verrucous leukoplakia was observed in 15(22.4%) cases.

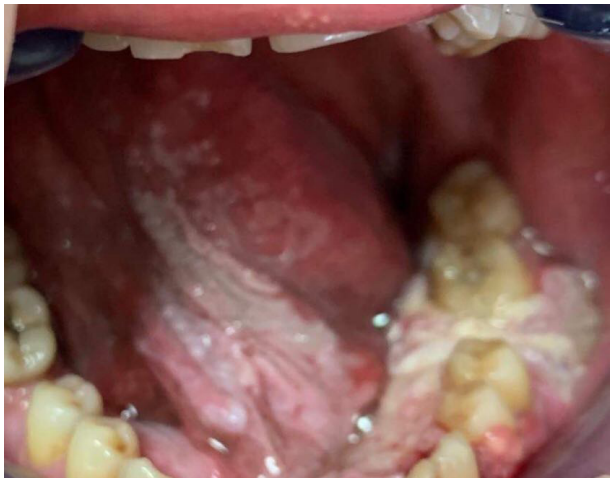

Figure 3.

The slide shows squamous cell cancer of the protective epithelium of the mandibular alveolar process resulting from malignization of leukoplakia. The diagnosis was confirmed only after excisional biopsy had been performed. Noteworthy, the patient had been inadequately treated in dental clinic for three months due to incorrect diagnosis.

In smokers with leukoplakia (Tuppeiner leukoplakia), areas of keratinization are grayish and whitish in the soft and hard palate. Against this background, there are red dots that are the narrowed openings of the excretory ducts of salivary glands. In severe forms of disease, nodes were observed in the areas of keratinization in 2(28.7%) cases.

Leukoplakia as a symptom was detected in 7(10.4%) cases of various chronic diseases, of which a diagnosis was made: systemic lupus erythematosus –2(30%) cases; AIDS-1(14%) case; TB –1(14%) case; hepatitis C-3(43%) cases. For the confirmation of diagnosis, all patients underwent cytologic examination. Of the 67 patients, leukoplakia was documented in 56(81.4%); in situ carcinoma in 6(9.8%) cases; lichen planus in 2(28.7%) cases; systemic lupus erythematosus in 1(13.3%) case.

Leukoplakia has a chronic course. Elimination or significant attenuation of an irritating factor, as well as sanitation of the oral cavity (in a broad sense), inhibits the disease progression, which, with proper conservative treatment leads to the regression of disease At the first stage, 67 patients (out of 67) underwent a course of conservative treatment. Along with the conservative treatment, an explanatory conversation was conducted with each patient about the role and importance of oral cavity sanitation; the patients were given the recommendations regarding this procedure, which contained important information about oral galvanosis caused by silver amalgam and other metal fillings.

To eradicate hyperkeratosis in flat leukoplakia, keratolytic agents were used in the form of applications; electrophoresis was used in erosive and ulcerative forms.

In the first place, to restore the integrity of the epithelial layer, the treatment of ulcerative-necrotic lesions was carried out using proteolytic enzymes, anti-inflammatory and keratoplastic drugs. In the case of ineffective conservative treatment, cryodestruction was carried out.

During cryodestruction, exposure to low temperature causes homo- or heterogeneous nucleation, accompanied by intracellular and extracellular ice formation. As a result, intracellular crystallization

under the influence of ice causes a rupture of the cell membrane;. Protein denaturation and toxic effect of electrolytes due to their high concentration, vascular stasis and the development of microinfarction, temperature – all these are the causes of immediate death of the cells that fall into the cryodestruction zone.

Of 67 patients, cryolysis as a method of treatment was applied in 12(19.7%) cases. After a course of cryodestruction, patients received further recommendations, such as: irrigation of the oral cavity with cold distilled olive oil, or using other vegetable oil products that facilitate epithelialization.

Recurrences after cryodestruction were noted in 1(8.8%) case out of 12.

The rest of the patients who underwent prophylactic medical examinations and monitoring did not experience any recurrence or progression of the disease.

According to international data, the percentage of malignant leukoplakia varies from 15 to 75. Of 67 patients, malignization of leukoplakia was observed in 8(13.1%) patients, 3(38.7%) patients had concomitant hepatitis C; there was one (12.5%) case of acute renal failure and in 2(26%) patients hemoblastosis was revealed.

Thus, when making the diagnosis of leukoplakia, the probability of malignization of the verrucous form (15–75%) should be considered, as well as its occurrence at the background of flat leukoplakia. It is important to perform the sanitation of the oral cavity before treatment, and timely provide restoration of dental crowns and tooth alignment using a rational prosthesis. It is vital to permanently ban the systematic use of nicotine and alcohol. It should be remembered that the tobacco combustion products contain more than 1000 toxic substances that adversely affect not only the oral mucosa, but also the entire organism. Treatment should be directed towards the normalization of gastrointestinal pathologies, vitamin dificiency, endocrine diseases, various infectious diseases and blood disorders. The dentist must explain to the patient the importance of oral hygiene and the role of chemical, mechanical and thermal factors in the development of leukoplakia. Proper, timely diagnosis and adequate treatment (cryodestruction after unsuccessful conservative therapy), makes it possible to avoid a high risk of leukoplakia malignization (transformation of leukoplakia into cancer).

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BUSINESS PROCESS REENGINEERING METHODOLOGY FOR MEDICAL ORGANIZATION ACTIVITIES DEVELOPEMENT

Abstract. The article describes the methodology of business processes reengineering at medical organizations. The basic principles, approaches and algorithm of reengineering are shown.

Keywords: business-process reeengineering, medical organization, process approach.

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МЕТОДОЛОГИЯ BUSINESS PROCESS REENGINEERING В ОПТИМИЗАЦИИ ДЕЯТЕЛЬНОСТИ МЕДИЦИНСКОЙ ОРГАНИЗАЦИИ

Аннотация. В статье описана методология реинжиниринга бизнес-процессов в медицинской организации. Показаны основные принципы, подходы и алгоритм проведения реинжиниринга.

Ключевые слова: реинжиниринг бизнес-процессов, медицинская организация, процессный подход.

Актуальность

На сегодняшний день тема организации и проектирования бизнес-процессов является достаточно важной и актуальной в любой сфере, в том числе и в сфере оказания медицинских услуг. Проектирование бизнес-процессов – важный шаг к успешному менеджменту в организации [1]. Медицинская клиника, как и любое другое учреждение, нуждается в проектировании и совершенствовании внутренних бизнес-процессов. Проектирование бизнес-процесса планирования и контроля для медицинской организации может определить самые рациональные и обоснованные направления развития клиники, минимизировать риски, повысить конкурентоспособность [2].

Понятие бизнес-процесс появилось в начале 90-х гг. И вот как определял его классик реинжиниринга М. Хаммер: «бизнес-процесс есть организованный комплекс взаимосвязанных действий, которые в совокупности дают ценный для клиента результат» [2].

Бизнес-процессы играют одновременно и роль стандартов оценки качества медицинской помощи, которая оказывается определенному потребителю медицинских услуг, а также роль регламента основных показателей медицинской помощи. В настоящий момент дальнейший рост и развитие лечебно-профилактической сферы невозможно без внедрения и применения медико-экономических стандартов и бизнес-процессов [2; 3].

Материалы и методы

Цели руководителя медицинской организации при применении технологии процессного управления:

- Рост качества медицинских услуг;
- Повышение доходов организации с помощью методологии управления по целям, в частности, за счет диверсификации;
- Уменьшение затрат;
- Рост удовлетворенности пациентов качеством оказанных медицинских услуг;
- Повышение конкурентоспособности, выход на лидирующие позиции на рынке медицинских услуг [3].

За основу методологической базы лучше всего использовать реинжиниринг бизнес-процессов. Классическая технология описания бизнес-процессов медицинской организации включает в себя восемь этапов:

1) определение организационной структуры;

2) определение направлений деятельности;

3) создание и построение дерева бизнес-процессов;

4) выбор и оценка бизнес-процесса для анализа, описания и оптимизации;

5) описание основных бизнес-процессов;

6) разработка руководящих документов;

7) определение ключевых показателей эффективности;

8) проведение внутреннего и внешнего аудита [4].

Таким образом, процессно-ориентированная система управления (реинжиниринг бизнес-процессов) будет способствовать росту результативности и эффективности деятельности организации, а также позволит медицинскому учреждению разрешить ключевые проблемы управленческой деятельности.

Результативность отражается в реализации целей учреждения. Она показывает уровень достижения стратегии. Эффективность системы проявляется в оценке применения ресурсов учреждения в процессе воплощения в жизнь стратегии. Необходимо, чтобы система ключевых показателей оценки эффективности бизнес-процессов медицинского учреждения обладала комплексным характером. При этом требуется, чтобы главные составные элементы оказывали непосредственное воздействие друг на друга и находились в постоянной связи. Все эти особенности хорошо подходят для создания системы менеджмента качества (СМК) в учреждении [5–7].

Можно сделать вывод о том, что процессный подход и процессно-ориентированная система управления и, в том числе, реинжиниринг бизнес-процессов будет способствовать росту результативности и эффективности деятельности учреждения, а также позволит лечебно-профилактическим учреждениям разрешить ключевые проблемы их управленческой деятельности. Реинжиниринг, основанный на существующем процессе (бизнес-процесс «as-is»). На этом, крайне важном, этапе осуществляется сбор информации об основном бизнес-процессе. Далее реализуется анализ и оценка основного бизнес-процесса, происходит сбор информации по качественным, количественным и относительным показателям бизнес-процесса [6].

В последнее время возросла роль проектирования и реинжиниринга бизнес-процессов в организациях, включая лечебно-профилактическую сферу.

Анализ литературы показал, что:

1. Бизнес-процессы и процессно-ориентированный подход есть основа эффективного управления предприятием в любой сфере, в том числе и в медицинской отрасли. Для эффективного управления бизнес-процессы необходимо правильно организовывать и проектировать;

2. Информация все в большей мере становится важнейшим ресурсом повышения эффективности деятельности любой организации. Без разработки и внедрения новейших информационных технологий, которые основываются на комплексном, системном подходе к вопросам проектирования,

невозможно обеспечить своевременное и качественное выполнение функций по планированию и контролю в современных организациях;

3. За последнее время возрос уровень потребительских ожиданий и конкуренции, одновременно появилось множество возможностей повышения эффективности работы медицинских учреждений с помощью использования современных информационных технологий;

4. Отсутствие правильно спроектированного процесса финансового планирования и контроля приводит к проблемам:

– длительный и детальный анализ несущественных операций и показателей;

– разработка документации «вручную» [4–6].

К основным принципам эффективного изменения бизнес-процессов относятся:

1) проектирование и совершенствование бизнес-процессов осуществляется без учета предыдущего опыта;

2) реинжиниринг – это отчасти творческий процесс;

4) радикальные изменения осуществляются на основе и с помощью применения современных информационных технологий.

Уже на этапе подготовки к реинжинирингу выявляется основной бизнес-процесс. Для этого проводится SWOT-анализ, который позволяет оценить сильные и слабые стороны внутренней среды учреждения, а также угрозы и возможности со стороны внешней среды. Такой анализ позволяет руководителю медицинского учреждения понять, как с помощью сильных сторон и возможностей ликвидировать слабые стороны и угрозы, либо свести их к минимуму. Таким образом и определяется, какой именно процесс будет в дальнейшем совершенствоваться. Также на этапе подготовки определяется организационная структура, а также персонал, задействованный в реинжиниринге бизнес-процесса. Создается регламентирующий документ и система мотивации для исполнителей.

Следующий этап: реинжиниринг «как есть», тут: осуществляется сбор информации об основном бизнес-процессе, проводится его анализ и оценка, описываются качественные, количественные, и относительные показатели основного бизнес-процесса. Затем осуществляется его моделирование и выявление проблемных мест бизнес-процесса и поиск вариантов повышения эффективности этих самых проблемных мест.

Затем следует этап: бизнес-процесс «как должно быть». На этом этапе определяют, как внедрить новый процесс с учетом существующего процесса, обучения и т.п. Рассчитывают и получают прогнозные показатели модели. На основе моделирования и полученных показателей проводится анализ целесообразности реинжиниринга бизнес-процесса. Далее, при положительном решении начинется внедрение изменений. Предложения, разработанные на предыдущих этапах и согласованные с лицами, принимающими решения, внедряются, модифицируется бизнес-процесс. Это заключительный этап [5–7].

Заключение

Проектирование и реинжиниринг бизнес-процессов являются эффективным решением для любого медицинского учреждения. Это поможет повысить и контролировать в том числе и финансовую устойчивость учреждения.

Правильный подход к разработке и проектированию рассматриваемого бизнес-процесса позволит получить не только описание и детализацию самого процесса, но и улучшить его, оптимизировать, обратив внимание на проблемы, существующие в организации процесса. Улучшение и совершенствование процесса – это шаг к успешному будущему учреждения любой сферы и любого масштаба.

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HOMEOSTASIS OF LIPOPEROXIDES IN CHILDREN WITH BRONCHIAL ASTHMA AND CONCOMITANT ENT-PATHOLOGY

Abstract. In children with bronchial asthma and concomitant ENT-pathology, the homeostasis of lipoperoxides is most pronounced at the level of the alveolar lining of the lung tissue compared with blood serum. Premorbid background aggravates lipid peroxidation and leads to destruction of cell membranes. Exhaled breath condensate as a diagnostic method for bronchopulmonary pathology is simple and non-invasive, it's especially important in pediatrics.

Keywords: bronchial asthma, concomitant ENT-pathology, lipid peroxidation, antiradical activity, blood serum, exhaled breath condensate.

The climate of the northern latitudes contributes to the development of acute bronchopulmonary pathology and further progression of the recurrent forms, potentiating changes in lipid metabolism, free-radical reactions and also intense functioning of the child respiratory apparatus.

In clinical practice the influence of concomitant chronic diseases of the upper respiratory tract on the quantitative constants of peroxide homeostasis in bronchial asthma are of particular interest. The respiratory system impairment is defined both by independent role of lungs in the pathological process and the secondary premorbid background which increases the disease, worsening outcome and making difficult therapeutic prognosis.

We analyzed the effect of chronic recurrent upper respiratory tract pathology on the dynamics of the system parameters «lipid peroxidation-antioxidants» in children with bronchial asthma at the level of the alveolar-capillary membrane and organism [3, 54–56; 6, 26–28]. In our research we used modern methodological approaches to the study of lipid metabolism and their peroxidation in the pulmonary surfactant system, namely exhaled breath condensate [7, 79–82; 8, 13–15; 9, 102–107].

The aim was to study the parameters of the peroxide status both in expiration and blood serum in

children with bronchial asthma and concomitant ENT-pathology.

Materials and methods. The study included 28 children aged from 7 to 10 years (no significant differences in age groups were noted). Among them there were 13 patients with ENT-pathology: chronic tonsillitis – 10.7%, adenoid vegetations – 14.3%, chronic rhinitis – 21.4%. The children were divided into two subgroups: subgroup A – patients without a burdened otolaryngological history, subgroup B – patients who had a history of ENT-pathology. In the hospital conditions a comprehensive paraclinical examination was carried out. The control group included 15 children, comparable in age, sex and without signs of respiratory system damage, suffering from vegetative-vascular dystonia. In the exhaled breath condensate (EBC) and in the blood serum the following parameters have been studied: total lipids, acyl hydroperoxide lipids (ACHPL), TBA-active products and anti-radical activity (ARA). In all patients the parameters of lipid metabolism in the exhaled breath condensate [8, 13–15] and in blood serum were studied. The condensate was collected by the method of G. I. Sidorenko [4, 65–68], the content of hydroperoxides was determined according to the method described by V. B. Gavrilov, I. A. Volchegorsky [2, 33–36; 5, 127–131], the concentration of TBA-active products – according to L. I. Andreeva [1, 41–43; 10, 647], antioxidant activity (AOA) – according to the method of E. B. Spector [6, 26–28].

Statistical processing of the research results was carried out using a statistical software package Statistica 6.1. For comparison the Mann-Whitney test was used. Student's test values were obtained using some electronic tables. Differences were significant at $p < 0.05$. Correlation analysis was performed using the Spearman correlation coefficient.

Results and discussion. For patients with bronchial asthma a severe inhibition of the generation of antiradical protection factors and their intensive consumption both in the pulmonary surfactant system and in the blood were characteristic. Moreover, a more severe response to a secondary infection that is the pathology of the upper respiratory tract was noted in the surfactants of the lungs. In patients without a burdened otolaryngological history (subgroup A) in exhaled breath condensate the parameters of anti-radical activity were 51.2%, and in subgroup B – 39.4%. We studied similar indicators in the blood serum of children in the subgroup A (without ENT-pathology), which decreased to 71.2%, and in the subgroup B (with ENT-pathology) – to 58.4% respectively. The values of the initial and final metabolites of lipid peroxidation significantly increased in children with asthma. Thus, the figures of hydroperoxides in exhaled air vapor were 163.7% in the subgroup A and 245.1% in the parallel subgroup. The content of similar lipid peroxidation intermediates in the blood serum was 154.2% and 240.6% respectively relative to the control values (Table 1, 2).

Table 1. – Indicators of lipid peroxidation and anti-radical protection in exhaled breath condensate in children with bronchial asthma, depending on the concomitant ENT-pathology (M ± SD)

The examined group	Hydroperoxides, D_{233} per 1 mg of lipids	TBA-active products, μmol/mg of lipids	AOA,%
Healthy (n = 15)	20.12 ± 2.00	4.17 ± 0.46	6.80 ± 0.46
Bronchial asthma without ENT pathology (n = 15)	32.93 ± 4.50*	16.55 ± 1.92*	3.48 ± 0.34*
Bronchial asthma with concomitant ENT pathology (n = 13)	64.13 ± 5.78*	24.11 ± 3.24*	2.83 ± 0.41*

*Note: * – reliable differences compared with healthy; n – the number of observations*

Table 2.– Indicators of lipoperoxidation and antiradical protection in the blood serum of children with bronchial asthma, depending on the concomitant ENT-pathology (M ± SD)

The examined group	Hydroperoxides, D_{233} per 1 mg of lipids	TBA-active products, μmol/mg of lipids	AOA,%
Healthy (n = 15)	0.33 ± 0.01	0.074 ± 0.004	33.52 ± 1.33
Bronchial asthma without ENT pathology (n = 15)	0.52 ± 0.05*	0.167 ± 0.023*	23.86 ± 4.37
Bronchial asthma with concomitant ENT pathology (n = 13)	0.91 ± 0.08**	0.330 ± 0.030**	16.48 ± 3.15*

*Note: * – reliable differences compared with healthy; ** – reliable differences between subgroups; n – the number of observations*

The comparison of the obtained data with the level of TBA-positive material in both biological fluids (expirate and serum) in children with bronchial asthma was 396.9% in the subgroup A (without ENT-pathology) and 418.6% in children with ENT-pathology. In the blood serum the indicators of TBA-active products were 225.7% and 423.1% respectively relative to the control figures. The obtained data proved the fact that chronic respiratory pathology activates lipid peroxidation processes during oxidative stress due to the influence of tissue hypoxia and the allergic component.

The unidirectional nature of changes in the system "lipid peroxidation-antioxidants" and the reliability of correlative relationships in children with chronic bronchopulmonary pathology determine a new level of metabolic processes. In patients without a burdened premorbid background, relationships have been recorded between the numbers of lipid hydroperoxides and antioxidant activity in expiration ($r = + 0.56$; $p < 0.05$). A serum parameter characterizing the onset of peroxidation reactions was associated with a positive average strength due to a similar metabolite of expirate ($r = + 0.61$; $p < 0.05$). The biochemical test characterizing the completion of these reactions in the blood serum had a significant dependence with lipid hydroperoxides also at the level of the whole organism, that is in the serum ($r = + 0.59$; $p < 0.05$). In the parallel subgroup the following correlative relationships were established: negative connections between the values of the initial products of lipid peroxidation and the antiradical activity of the condensate ($r = – 0.50$; $p < 0.05$); the amount of TBA-positive material and the level of hydroperoxides in the pulmonary surfactant system ($r = + 0.89$; $p < 0.001$).

Findings. The results of the study indicate the maximum severity of free radical reactions in expiration compared with serum in children with bronchial asthma and concomitant recurrent diseases of the upper respiratory tract. It is logically to suggest that this biochemical picture both at the level of the whole organism and at the level of the surface-active substances of the lungs is caused by a sharp weakening of the compensatory-adaptive forces of the child as a result of prolonged stress, as well as the tissue hypoxia and the allergic component.

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A STUDY OF EPIDEMIOLOGY SURVEILANCE IMPLEMENTATION OF HIV-AIDS MOBILE VCT ON RISK POPULATION

Abstract. Voluntery Counseling and Testing (VCT), is now widely known internationally as an effective and very important strategy, both for HIV-AIDS prevention and tackling. The purpose of this study is to determine the study of the implementation of VCT inspection measures in the Banda Aceh Port working area. This type of research is an observational descriptive study. The research subjects were the reporting system for VCT-HIV and STI mobile activities, health checks and early detection screening through rapid testing of HIV antibodies, namely by using HIV ½ 3.0 Rapid Test reagent 1, with the target being Ship Crew (ABK), Labor and Unloading Load (TKBM) and the community. Data collection is done by document study. The results of the study shows that there were no patients who are suspected of HIV or HIV Reactive from the physical working area of Banda Aceh with a physical examination and blood was Non Reactive. It is recommended that efforts were made to promote health and provide education about the dangers and ways to prevent HIV AIDS and STIs, especially in the port area and the entrance of other countries.

Keywords: Voluntery Counseling and Testing (VCT), HIV AIDS.

Introduction

Voluntary counseling and detection of HIV or VCT (voluntary counseling and testing) is now widely known internationally as an effective and very important strategy for both HIV-AIDS prevention and services, especially among those at high risk of HIV. 1) AIDS. estimates that there are at least 4.5 million people in the world, and 98% of them are in developing countries. In Indonesia, with approximately 202 million people facing a big problem with HIV AIDS infection. Much progress has been made by programs such as the development of HIV-related service facilities that have penetrated wider areas in Indonesia since 2005; 2) However, the number of cases and people with HIV AIDS (PLWHA) still tends to increase. In fact HIV-AIDS is an incurable disease. However, prevention of transmission can be done in various steps; 3) The use of antiretroviral drugs will increase the positive impact on the level of individual health as well as at the community level, namely increasing the quality of life for PLWHA and decreasing HIV transmission in the community; 4) The number of people living with HIV who know their status faster or earlier; 5) For the diagnosis and finding of those living with HIV, at the beginning of the program a voluntary HIV counseling and testing

(VCT) guideline was then followed by guidelines for HIV counseling and testing at the initiative of health care providers and counseling (TIPK) or Provider Initiated Testing and Counseling (PITC) [6].

Indonesia has become the fifth country in Asia at the highest risk of HIV-AIDS, so it is inevitable that Indonesia will implement an international level agreement followed by national policy. As we know, the fundamental problem faced by people with HIV / AIDS (PLWHA) is not only the disease, but also many people still cannot accept the existence of PLWHA. The stigma against PLWHA is still quite a lot coupled with a judgmental attitude, distancing, ostracizing, discriminating, even to treatment that not only violates human rights but also crimes. For this reason, efforts are needed to prevent stigma and discrimination through counseling, support, care and treatment programs that involve all parties involved so that PLWHA can function socially again.

HIV testing is the most important "entrance" to prevention, care, support and treatment services. After a long time the availability of HIV antibody tests in Indonesia, and with increasing coverage of HIV testing in Indonesia, it is still not enough to reach the public to know their HIV status. HIV testing and counseling (TKHIV) will encourage a person and partner to take steps to prevent transmission of HIV infection. Further HIV testing will provide an opportunity to obtain preventive services including prevention of mother-to-child transmission and is an important component of antiretroviral treatment interventions as a prevention measure such as early treatment for serodiscordant couples, so that increased coverage of HIV testing in partners is very necessary. At the community level, expanding the reach of TKHIV services will "normalize" HIV testing itself and reduce stigma and discrimination related to HIV status and HIV testing [7].

Knowledge of HIV status is also needed to start ARV treatment, but until now there is still a high gap between the estimated number of people with HIV and AIDS (PLWHA) with PLWHA who have reached HIV services. 8) There are still many PLHIV who have not been diagnosed or know that they infected with HIV. They come to health services after symptoms arise and become symptomatic. HIV testing is a prerequisite for establishing a diagnosis, connecting PLWHA with early prevention and care services. With a diagnosis that has been enforced, access to therapy can begin. Therefore ARV therapy services must be available in all referral hospitals at the provincial and district / city levels so that they can be easily accessed by PLWHA in need [9].

Starting in 2006, the main model of HIV testing services was at the client's initiative or known as voluntary HIV testing and counseling. This approach relies solely on the client's activity in seeking HIV testing services in health facilities or community-based HIV testing services. 7) However, the coverage of KTS services is limited because there are still fears of stigma and discrimination and most people do not feel themselves at risk of HIV infection even in the regions or in high prevalence groups. In addition to the need to expand the reach of KTS, there needs to be another approach to increase coverage to achieve universal access to HIV prevention, care, support and treatment. 10 Another approach is through HIV testing at the initiative of health care and counseling providers (TIPK) or provider-initiated HIV testing and counseling (PITC) which is the main approach in health services and will be able to increase coverage of HIV testing, improve access of PLHIV to health services that increase opportunities for HIV prevention services [5].

Method

This type of research uses observational qualitative descriptive research conducted to see first hand the VCT HIV – AIDS control program for the discovery of new HIV cases against risky populations in the Banda Aceh Port work area in 2018. Health and early detection screening through rapid testing of HIV antibodies using reagents 1 HIV ½ 3.0 Rapid Test, with the aim being Ship Crew (ABK), Manpower and Unloading (TKBM) and the community.

The research was carried out at the Banda Aceh Port Health Ministry and 6 working areas. The research was conducted in March – April 2019. The subjects in this study were the epidemiological surveillance system and information system of the VCT mobile HIV-AIDS control program for the discovery of new HIV cases against at-risk populations in the port work area and airports carried out in 2018. Research data were obtained from source of data on reports on the implementation of HIV-AIDS control programs.

Processing and presenting data using data reduction, namely the process of selection, focusing, simplification, and data abstraction. Displacement data, namely looking at a presentation of data, all of which are designed to summarize information on a regular basis so that it is easily seen and understood in a systematically arranged form accompanied by a table as a supporter of data presentation. The analysis technique used is analysis of content or narration, tables and graphs.

Results

Distribution of risky population characteristics

The characteristics of the at-risk population on voluntary counseling and testing for the discovery of HIV-AIDS cases in the 6 working areas of the Banda Aceh port and airport in 2018 based on the report can be seen in the following table:

Table 1.– Distribution of the characteristics of the population at risk based on age

Working Area	Age						Total	
	15–44 year		45–59 year		> 60 year			
	n	*f*	*n*	*f*	*n*	*f*	*n*	*f*
Sultan Iskandar Muda Airport	18	8.95	8	0.8	0	0	26	7.92
Labuhan Haji Sea	28	13.9	20	0.20	7	25.9	55	16.7
Lhok Nga Sea	35	17.4	19	0.19	0	0	54	16.4
Malahayati Sea	37	18.4	11	0.11	2	7.4	50	15.2
Meulaboh Sea	40	19.9	13	0.13	0	0	53	16.1
Singkil Sea	43	21.3	29	0.29	18	0.66	90	27.4
Total	201	61.2	100	30.4	27	8.23	328	100.0

Source: KKP, Banda Aceh 2018

Table 1 shows that the majority of the population carrying out the examination are more 15–44 years old, which is 201(61.2%) and the most in the Singkil sea area 43(21.3%) compared to the other regions.

Table 2.– Distribution Characteristics of risk population by sex

Working Area	Sex			
	Man		Woman	
	n	*f*	*n*	*f*
Sultan Iskandar Muda Airport	15	7.81	11	8.08
Labuhan Haji Sea	43	22.3	12	8.82
Lhok Nga Sea	23	11.9	31	22.7
Malahayati Sea	36	18.7	14	10.2
Meulaboh Sea	52	27.0	1	0.73
Singkil Sea	23	11.9	67	49.2
Total	192	58.5	136	41.4

Based on the results of the study, it was found that the population at risk of VCT examination was more men, ie 192(58.5%) than women as many as 136(41.4%). Voluntary counseling and detection of HIV or VCT (voluntary counseling and testing), provides the following results:

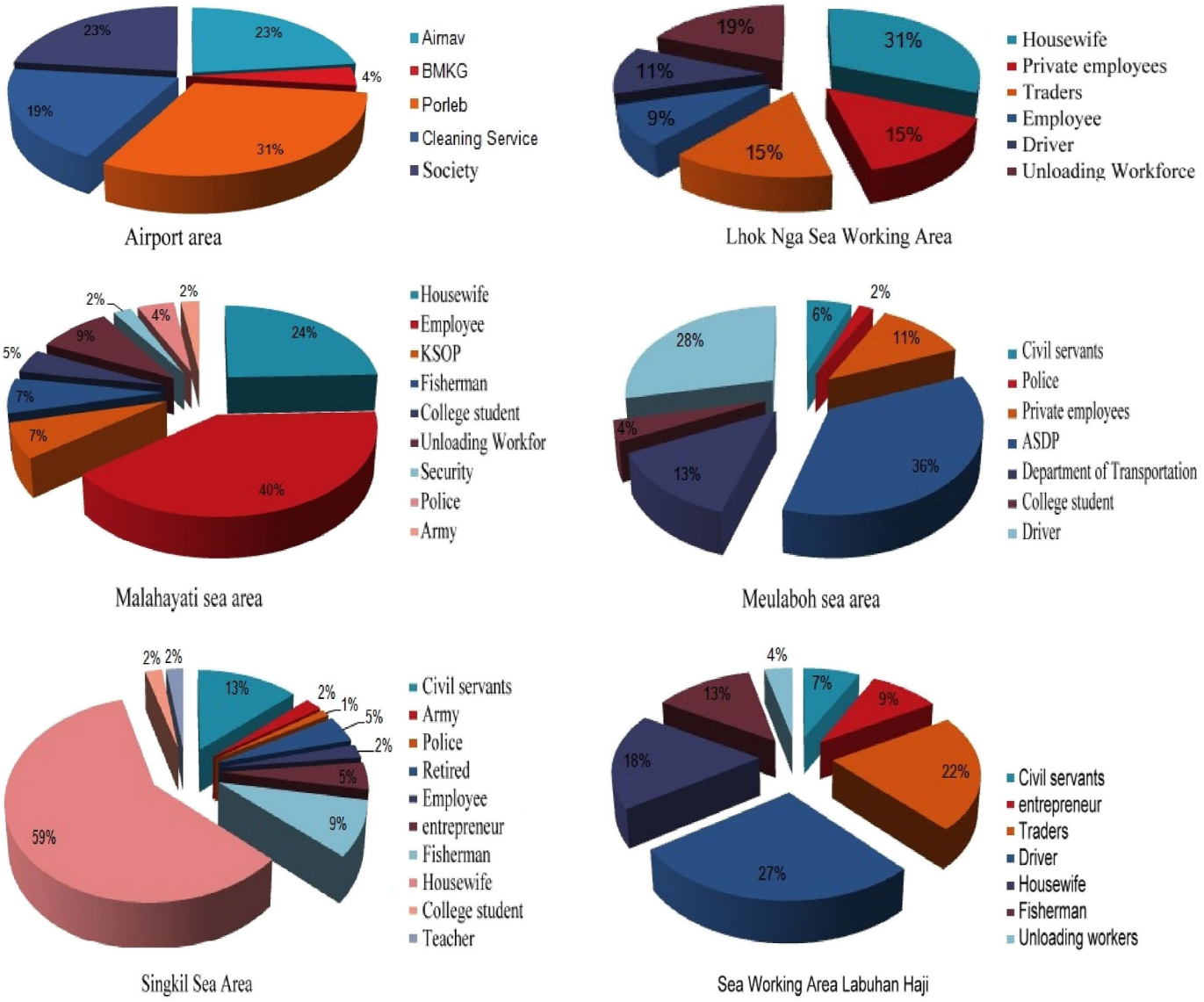

Figure 1. Distribution of characteristics of at-risk populations based on type of work in the airport area

Table 3.– Health examination and early detection screening data in the Port area and Banda Aceh Airport in 2018

Working Area	Risk Population		
	Number of participants	%	Result of Reagen 1 Rapid Test HIV ½ 3.0
Sultan Iskandar Muda Airport	26	7.92	Non Reactive
Labuhan Haji Sea	55	16.7	Non Reactive
Lhok Nga Sea	54	16.4	Non Reactive
Malahayati Sea	50	15.2	Non Reactive
Meulaboh Sea	53	16.1	Non Reactive
Singkil Sea	90	27.4	Non Reactive
Total	328	100.0	Non Reactive

Table 3 showed 328 VCT (voluntary counseling and testing) testing in populations at risk of HIV-AIDS and STIs in the port and airport areas showed that of the 6 most working areas the number of participants in the Singkil Sea was 90(27.4%). Health screening and early detection screening through rapid testing of HIV antibodies, namely using reagent 1 HIV ½ 3.0 Rapid Test, with the aim of being a Ship Crew (ABK), Labor and Dismantling (TKBM) and the community carried out by surveillance officers resulted non reactive.

Discussion

Human Immunodeficiency Virus (HIV) is caused by a virus called HIV, which is a type of virus that is in human blood that can weaken the body's resistance, so that the sufferer is susceptible to other infections, such as tuberculosis, canker sores and prolonged diarrhea. 11) Acquired Immune Deficiency Syndrome (AIDS) is a collection of symptoms of a disease caused by the decline of human immunity by HIV. Based on the most recent data on the transmission of HIV infection in Indonesia, the HIV virus is present in the blood and body fluids of someone who has been infected, even though the person has not shown any complaints or symptoms of the disease. The first is through sexual relations with people who have been infected without using condoms, second is through the use of blood-contaminated syringes containing HIV, which is possible, among others, due to the use of shared syringes among injecting drug users, and third is transmitted from mothers HIV sufferers to children, both during pregnancy, childbirth or during breastfeeding; 12) Other modes of transmission are through blood transfusions containing viruses, puncture devices and other equipment (tattoos, etc.) that have the potential to transmit HIV and the presence of sexually transmitted infections such as syphilis. People who have high risk behaviors for HIV infection are: Women and men who have risky sexual behavior, such as changing partners in unprotected sexual intercourse and having sex with strangers, as well as injecting narcotics, who use syringes together (alternately). 5 Indonesia has become the fifth country in Asia at the highest risk of HIV-AIDS, so it is inevitable that Indonesia will implement an international level agreement followed by national policy. HIV testing is the most important "entrance" to prevention, care, support and treatment services. After a long time the availability of HIV antibody tests in Indonesia, with the increase in coverage of HIV testing in Indonesia, it is still not enough to reach people to find out their HIV status.9 HIV testing and counseling (TKHIV) will encourage individuals and partners to take steps to prevent transmission of HIV infection; 13) Furthermore HIV testing will provide opportunities to obtain preventive services including prevention of mother-to-child transmission and an important component of treatment interventions; 14) ARVs as a preventive measure such as early treatment in serodiscordant couples, so that increased coverage of HIV testing in partners is very necessary; 15) At the community level, expanding the reach of TKHIV services will "normalize" HIV testing itself and reduce stigma and discrimination related to HIV status and HIV testing [12].

The Banda Aceh Port Health Office has the main task of carrying out prevention of the entry and exit of infectious and potential outbreaks of disease, limited health services in the Port / Airport and cross-western work areas and control of environmental health impacts based on legislation and applicable provisions; 16) In carrying out these tasks, described through the roles and functions that must be carried out in the implementation of various programs / activities by not disturbing the smooth flow of international / national traffic both for people, goods and tools [17].

Effective disease observation is needed to determine the endemicity of the disease or to find out early the possibility of cases of HIV-AIDS sufferers. 10 Based on the characteristics in this study are age and gender. Participants in the health examination using the mobile VCT were found to be 15–44 years old as many as 201 participants in 6 banda Aceh KKP

work areas and more than the age of 45–59 years and > 60 years old while the majority were in the Singkil sea working area of 90 people obtained 43(21.3%) participants and ages 45–59 years 29(0.29%) and > 60 years old ie 18(0.66%).

Age associated with the VCT method gets results that the characteristics of participants to carry out early detection examinations aged 45–59 years and > 60 years have a tendency to decrease work productivity. According to Robbins and judge (2008), increasing age means productivity also decreases compared to productive age; 17) Based on research it is known that most populations in the productive age category think that screening with a health check with VCT is very useful for early detection of health conditions so they can remain carry out daily activities. Productive age is a period where someone already has a great curiosity so that they will find out as much information as possible and will behave according to their life experience and knowledge, they will process that information and adapt it to their own knowledge; 18) This is appropriate with the results of research that Indonesia estimated that 75% of people with HIV-AIDS are aged 15–50 years, so that it will reduce productivity in the community.

Based on gender, the proportion of health examinations with VCT more that health check is male gender 192(58.5%) compared to women which is equal to 136(41.4%). This happened because more men were working in the port and airport areas, screening tests with male sex had a risk factor for contracting HIV-AIDS compared to women. The circulation of the HIV-AIDS virus is more focused on populations that have risk factors such as changing sexual partners both heterosexual, bisexual and homosexual or those who are under the influence of drug dependence; 19) Therefore sexuality is a medium of transmission, so the practice of heterosexuals and bisexuals determines the transmission of viruses that are generally male and have a family. They often use the services of sex workers in fulfilling their biological needs as a consequence of the work they do. The types of jobs considered risky are jobs that require high mobility such as truck drivers, mobile workers, traders and seafarers and crew, labor and loading and unloading (TKBM).

The connection of the progress of modernity with the epidemic of AIDS leads us to understand rationally the pyramids of AIDS cases that occur a lot in the young or productive age population. This population group has a strong drive with stimuli of modernity offered in various forms and manifestations [7].

The results of the study with medical examinations and early detection screening through rapid testing of HIV antibodies, namely by using reagent 1 HIV ½ 3.0 Rapid Test, of the 6 working areas of the Banda Aceh CTF were not found to be reactive or positive test results, all population results were non reactive.

If an in-depth analysis of trans-dimensional analysis is conducted between the speed of transmission and the highest incidence of productive population groups, then we will be faced with the problem of regeneration. The phenomenon of death at a young age will break the chain of human reproduction which should occur cyclic through marital ties or family ties. At some point the loss-generation phenomenon emerges. This is where the VCT HIV and IMS mobile activities program finds its significance as an issue that has the impact of HIV and AIDS. The model of socializing knowledge with conventional communication styles requires critical evaluation towards participatory community involvement at all stages of control. Participatory engagement requires the existence of community empowerment capabilities that the surveillance officer must possess for the discovery and early detection and management; 20) Visiting the community, listening to them, and opening social dialogues and providing them with ample opportunities to define their own problems and solve them in their own way to avoid the risk of HIV AIDS transmission [21].

Conclusion

The results of the research that have been carried out show that the proportion of the population at

greater risk for productive age and male sex is because the VCT HIV-AIDS examination is conducted with the aim of Ship Crew (ABK), Labor and Unloading (TKBM) as well as the community conducted by surveillance officers the results are Non Reactive. It is expected that the executors of the HIV-AIDS and STI control programs can provide education on HIV-AIDS and VCT regularly. To the population in the area of the Port and Airport work area, given the high mobility where they dominate and work, they can understand about HIV-AIDS and the impact of transmission and want to do a VCT examination.

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Section 3. Pharmaceutical Sciences

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STUDY OF EMBRYOTOXIC, TERATOGEN ACTIONS OF THE DRUG "BAKAGIN" FROM THE PAROTID SECRETES CENTRAL ASIAN GREEN TOAD *BUFO VIRIDIS LAUR* AND ITS EFFECT TO THE REPRODUCTIVE FUNCTION OF RATS

Abstract. The sum of bufadienolides, named as "Bakagin" obtained from the venom of the Central Asian green toad *Bufo viridis Laur*. The effect of the preparate to the embryotoxic, teratogenic activities and influence on the reproductive function was studied in laboratory rats. Obtained results show that, "Bakagin" when injected by intraperitoneally, in doses of 0.046 and 0.093 mg/kg, has not cause embryotoxic and teratogenic activities. A study of "Bakagin" on to reproductive function in white rats showed that in the studied doses it has not negative affect to the reproductive function of white outbred rats.

Keywords: Embryotoxicity, teratogenicity, bufadienolides, bakagin, reproductive function, persecuted females, pre-implantation, post-implantation, prenatal, fecundity of females, embryos.

In previous studies we identified bufadienolide composition of "Bakagin", from the Central Asian green toad *Bufo viridis Laur* venom. In that work by chromatographic methods six individual bufadienolides were isolated, and their chemical and conformational structures determined using NMR and X-ray analysis. In a result bufadienolides identified as: arenobufagin (3β,11α,14-trihydroxy-12-oxo-5β,14β-bufa-20,22-dienolide), gamabufotalin (3β,11α,14-trihydroxy-5β,14β-bufa-20,22-dienolide), telocinobufagin (3β,5β,14β-trihydroxy-20,22-dienolid) marinobufagin (3β,5β-dihydroxy-14,15β-epoxybufa-20,22-dienolid) bufarenogin (3β,12β,14β- trihydroxybufa-20,22-dienolide) and bufalin (3β,14β-dihydroxy-20,22-dienolide) [1; 2].

It is known that when using medicines it is necessary to take in to account about its possible impact on the mother's organism, on the natural physiological barrier – placenta and direct impact to the embryo. Embryotoxic action can be appear in increased levels of fetal mortality, delayed ossification of the skeleton, changing in body mass and cranyo caudal size of the fetus, an increasing in perinatal pathology and etc. [3].

Approximately 1% of fetal developmental abnormalities in pregnant women cause uncontrolled

and not correct use of drugs. Therefore in modern medicine more attention is paid to study the effects of drugs on the intrauterine development of a child and on a pregnant woman herself at different stages of pregnancy. In the pre-clinic evaluation on safety of new drugs, it is necessary to know their effect to the embryogenesis of laboratory animals [4].

Purpose of this work is study of embryotoxic, teratogen effects of "Bakagin" and its influence on the reproductive function of laboratory rats.

Experimental

Investigation of embryotoxic, teratogen effects of "Bakagin"

Experiments were carried out on white outbred rats (180 ± 20g), animals were divided into 3 groups of 10 male and 20 female. Experimental animals were kept and feeding by standard conditions [5]. During 48 days, the males were intra-peritoneal injected with Bakagin at a daily therapeutic dose: 1-group – 0.046 mg/kg; 2-group – 0.093 mg/kg; 3-group – physiological solution, as a control. At the end of this period, the female rats were placed in a ratio of 2:1 to the males. During the week, pregnant females were isolated (the presence of sperms in a vaginal smear) and they were daily injected with drug in the same doses.

At 7, 17 and 20 days after pregnancy, females were killed by dislocation of cervical vertebrae and dissected. As indicators of embryotoxic action, against to control were determined pre – and post-implantation embryonic mortality, morphological (anatomical) malformations, a general retardation of fetal development.

Pre-implantation mortality was determined by difference between numbers of yellow bodies in ovaries and implantation sites in uterus. Post-implantation mortality is determined by difference between numbers of implantation and live fetuses.

Teratogenic effect was determined by proportion of anomalous fetuses at external observation. For that 20-day yields of each litter weighted and their cranyo caudal dimensions were measured. After external examination, yields of each litter were fixed in Buen's solution and used to study of internal organs. To study of skeleton state other yields were fixed in 96% ethanol.

Due to the fact that abnormalities in fetuses development can appear in a later period, part of pregnant females from each group were kept in separate cells for natural childbirth, followed by monitoring of offspring development in the postnatal period (generation was investigated during 1 month).

Obtained results were statically processed by standard methods, using Microsoft Excel program: determination of average value (M) and average error (m).

Investigation of "Bakagin" on to reproductive function of white rats

Investigation of "Bakagin" on to reproductive function of white rats was carried out on 24 male and 60 female of white outbred rats (160–180g).

"Bakagin" was intra peritoneal injected into females for 15 days at doses of 0.046 and 0.093 mg/kg of body weight (the group of "hounded females"). Then the animals were mated with intact males. Females were planted to males in a 2:1 ratio for 10 days period. During the study general physical condition and behaviour of animals were monitored. Fertilization was recorded using vaginal smears. In the third week, part of the pregnant females were killed by dislocation of the cervical vertebrae and dissected. State of the reproductive organs of females was studied, in the uterus number of yellow bodies, in the ovaries implants live and dead fetuses were counted. Based on the data obtained, indicators of pre-implant and post-implantation mortality were determined and the fertility index – ratio of the number of pregnant females to the seated females was calculated. In each group of females, a part of pregnant rats were left before the birth and during one month offspring development – the general physical condition, behaviour and rats death was observed.

In males ("group of hounded males"), "Bakagin" was injected by intra peritoneal in a dose of 0.046

and 0.093 mg/kg of body weight for 48 days. After end of injection of the drug to the males, intact females were planted in a ratio of 1:2 for 10 days. A status of reproductive function of males was estimated by the results by study of reproductive organs of females paired with males who received the drug of "Bakagin".

Results and discussion

Results of investigation embryotoxic, teratogen actions of the drug "Bakagin"

Results obtained showed that in female white rats who received "Bakagin" in doses of 0.046 and 0.093 mg/kg, all parameters of embryo-lethality do not have significant differences with those in the females in control group (see Table 1).

Table 1.– Effect of Bakagin on pregnancy and fetal development

Indicators	Group of animals		
	Control	0.046 mg/kg	0.093 mg/kg
Number of females in the experience	20	20	20
Fecundity of females	16	17	16
Number of yellow bodies per 1 female	8.63 ± 0.37	8.53 ± 0.36	8.25 ± 0.40
Number of dead and resorbed yields	4.0	5.0	4.0
Death of embryos,%			
Pre-implantation	2.90	3.44	3.03
Post-implantation	3.62	4.13	3.78
Overall embryo survival,%	93.5	92.4	93.2
Mass of embryos, g	2.53 ± 0.12	2.51 ± 0.17	2.67 ± 0.50
Size of embryos, mm	25.8 ± 0.27	26.8 ± 0.29	26.3 ± 0.14

Indicators of pre-implantation mortality in control and studied variants are 2.90, 3.44 and 3.03%, and post-implantation mortality – 3.62, 4.13 and 3.78%, respectively. The mass of yields in control and studied groups after injection of Bakagin in doses of 0.046 mg/kg, 0.093 mg/kg is 2.53 ± 0.12, 2.51 ± 0.17 and 2.67 ± 0.50 g, respectively. They do not have significant differences and cranyo-caudal dimensions: 25.8 ± 0.27, 26.8 ± 2.94 and 26.3 ± 0.14 mm, respectively. All indicators of embryo toxicity remain at the control level. During external examination of yields of each litter development of visible external anomalies are not observed.

Statistical difference in survival and death of fetuses before implantation and after implantation in the studied groups were not found.

A daily examination of pregnant females after injection of Bakagin did not reveal a significant difference in their common condition, neatness and revealed no significant differences by increase of body mass, compared to control group of pregnant female rats.

In the study of the teratogenic effect of "Bakagin" on the basis of macro anatomical analysis of internal organs and embryo skeleton anomalies, no significant deviations compared to control were detected (see Tables 2 and 3).

Table 2.– Results of macroscopic study of embryos by influence of "Bakagin"

Indicators	Group of animals		
	Control	0.046 mg/kg	0.093 mg/kg
1	*2*	*3*	*4*
Number of investigated embryos	60	60	60
Hemorrhage,%			
Subcutaneous	–	–	–
Facial skull	2	2	2

1	*2*	*3*	*4*
In the chest cavity	–	–	–
Into the abdominal cavity	3	3	3
Anomalies of brain development,%			
Hemorrhage	–	–	–
Expansion of brain ventricles	–	–	–
Spinal hemorrhage	–	–	–

Table 3.– State skeleton of rats yields by action of Bakagin

Indicators	**Group of animals**		
	Control	**0,046 мг/кг**	**0,093 мг/кг**
Number of yields, investigated by Dauson	50	50	50
Number of ribs			
Right	13.00	13.00	13.00
Left	13.00	13.00	13.00
Number of embryos with anomaly development			
External anomalies	–	–	–
Internal anomalies	–	–	–

Thus, based on obtained results, it is possible to say that "Bakagin" at intra peritoneal injection in doses of 0.046 and 0.093 mg/kg, has not embryotoxic and teratogenic properties.

Results of studies of "Bakagin" on the reproductive function of white rats

Studies have shown that injection of "Bakagin" and did not affect to the accouchement time. So, in rats receiving the drug, and control, this period was 20–21 days. During drug injection, the state and behaviour of experimental rats did not difference against to control. In all experimental groups, the body weight of pregnant rats injected with Bakagin increased by an average of 34.8 and 35.5% relative to the outcome. The same increase in body weight of pregnant rats was observed in the control of 37.4%.

Indicators of the reproductive function of white female rats after intra peritoneal injection of Bakagin in doses of 0.046 and 0.093 mg/kg did not difference against to control animals. The data obtained are shown in the (Table 4).

Table 4.– Effects of "Bakagin" on the fertility of rats in the group of "baited females"

Indicators	**Groups**		
	Control ♀ **– intact** ♂ **– intact**	**0.046 mg/kg** ♀ **– hunted** ♂ **– intact**	**0.093 mg/kg** ♀ **– hunted** ♂ **– intact**
Number of females hooked with males	20	20	20
Number of fertilized females	17	18	17
Number of pregnant females	17	16	17
Fertility Index,%	85.0	90.0	85.0

The results are shown in Table 4 shows that the fertility index of the females of this group remained at the level of the fertility index of the control group. Thus, analysis of obtained results

allows concluding, that fecundity of females in experimental groups is equivalent against to control values.

In the third week of pregnancy number of yellow bodies, their number per 1 female, number of implantation sites and their number per 1 female, number of live fetuses and their number per 1 female were determined. These indicators of female reproduction did not statistically significantly different against to control (see Table 5).

Table 5.– Action of "Bakagin" on the reproductive function of female rats (group "baited females")

Indicators	Groups		
	Control ♀ – intact ♂ – intact	**0.046 mg/kg ♀ – hunted ♂ – intact**	**0.093 mg/kg ♀ – hunted ♂ – intact**
Number of pregnant females	8.0	8.0	8.0
Number of yellow bodies per 1 female	70/8.75	68/8.50	69/8.6
Number of implantation sites per 1 female	67/8.37	66/8.25	65/8.12
Number of live yields per 1 female	65/8.12	64/8.0	65/8.12

Thus, the analysis of obtained data allows concluding that reproductive indicators of females in the experimental group of "hounded females" remain at the level, against to control group. This result indicates that "Bakagin" in used does has not negative affect to the reproductivity of females.

Results of the experimental group of "hounded males" by fertility show that the fertility index of females in these experimental groups does not difference against to control. Results on the fertility of female rats in the "hounded males" groups are given in (Table 6).

Table 6.– Effects of "Bakagin" on the fertility of male rats in the group "baited males"

Indicators	Groups		
	Control ♀ – intact ♂ – intact	**0.046 mg/kg ♀ – hunted ♂ – intact**	**0.093 mg/kg ♀ – hunted ♂ – intact**
Number of females hooked with males	20	20	20
Number of fertilized females	18	17	18
Number of pregnant females	8	8	8
Fertility Index,%	90.0	85.0	90.0

The obtained experimental data show that the fertility index of animals – females of these experimental groups, does not statistically significantly difference against to control. This data indicates that Bakagin in used doses does not negative affect to the fertility of male rats.

For investigation the effect of "Bakagin" to other reproductive indicators of rats, males from the group of "hounded males" took pregnant rats in the third week, the part of pregnant animals was opened and the number of yellow bodies was counted, their number per 1 female, the number of implantation sites and their number per 1 female, the number of live fruits and their number per 1 female.

The results of the reproductive performance of female rats in the "hounded males" groups are given in the (Table 7).

As can be seen from the obtained data, reproductive performance of female rats in the "baited males" groups did not difference against to control.

Left to give birth to females of all experimental groups, the process of childbirth and care for the

offspring were unremarkable. The average number of fetuses per female, the ratio of rats by sex, the level of death of new born rats did not change in the litters of all experimental groups. The timing of the out-off the auricle, the appearance of the primary hairline, the incision of the incisors, opening of eyes, lowering of testes and opening of vagina in the litters of both the experimental and control groups were similar. The results of physiological developments of the offspring of rats by influence of "Bakagin" in the early postnatal period are given in (Table 8).

Table 7.– Effects of Bakagin on the reproductive ability of rats of the "persecuted males" group

Indicators	**Groups**		
	Control ♀ **– intact** ♂ **– intact**	**0.046 mg/kg** ♀ **– hunted** ♂ **– intact**	**0.093 mg/kg** ♀ **– hunted** ♂ **– intact**
Number of pregnant females	8.0	8.0	8.0
Number of yellow bodies	68/8.5	67/8.4	68/ 8.6
Number of implantation sites	66/8.2	65/8.1	65/8.1
Number of live yields	65	64	64

Таблица 8.– Results of physiological developments of the offspring of rats by influence of "Bakagin" in early postnatal period

Indicators	**Groups**		
	Control ♀ **– intact** ♂ **– intact**	**0.046 mg/kg** ♀ **– hunted** ♂ **– intact**	**0.093 mg/kg** ♀**- hunted** ♂ **– intact**
Number of females in experiment	10	10	10
Amount of yields	60	60	60
Death of rats in the period of feeding (number)	3	2	2
Auricle Day	3.3 ± 0.08	3.5 ± 0.01	3.6 ± 0.05
Primary Hair Day	5.6 ± 0.14	5.5 ± 0.11	5.4 ± 0.12
Teething Day	8.7 ± 0.12	8.8 ± 0.10	8.7 ± 0.10
Eye opening day	14.6 ± 0.13	15.2 ± 0.13	14.7 ± 0.17
Day of the lowering of the testes	26.0 ± 0.32	26.1 ± 0.15	26.4 ± 0.14
Vagina opening day	31.0 ± 0.21	31.5 ± 0.14	31.5 ± 0.16
Mass of rats, g			
4 day	8.49 ± 0.20	8.84 ± 0.50	8.80 ± 0.11
7 day	12.2 ± 0.10	11.6 ± 0.15	11.4 ± 0.32
14 day	21.4 ± 0.09	21.7 ± 0.14	21.9 ± 0.23
21 day	30.4 ± 0.23	30.2 ± 0.16	30.5 ± 0.16
Death of females during the feeding period	0 ± 0	0 ± 0	0 ± 0

Thus, based on obtained results, it can be assumed that "Bakagin" in the studied doses does not negative affect to the reproductive function of white outbred rats.

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CHEMICAL CONSTITUENTS FROM THE ROOTS OF *CEPHALARIA GIGANTEA*

Abstract. Iridoid and secoiridoid glycosides – swertiamarin, cantleyoside, loganic acid and also triterpene saponin dipsacoside B were isolated from the roots of Caucasian endemic plant – *Cephalaria gigantea.* The structure of these compounds was determined by all spectroscopic means mainly by NMR and MS techniques. All isolated compounds are reported for the first time from ***Cephalaria gigantea*** roots. Iridoids are used as chemosystematic markers for plants of the Dipsacaceae family.

Keywords: Triterpene saponin, iridoid, NMR, MS.

The roots of ***Cephalaria gigantea (Ledeb.***) Bobr. (fam. Dipsacaceae) an endemic plant of Caucasus growing in Georgia, are well-known in traditional medicine as sedative and anti-inflammatory remedies [1], The main constituents of the roots are triterpene saponins, alkaloids, flavonoids, and phenolcarboxylic acids. Previous works reported the identification by about 17 individual components: saponins, alkaloids and phenolic compounds [2–8]. Antifungal, antiprotozoal, antiseizure and cytotoxic

activities of major monodesmosides and root extract have been evaluated [8–12]. HPLC analysis method of the raw material and the purified extract of Cephalaria have been proposed [13–14].

The present paper describes isolation and structure elucidation of three iridoid and secoiridoid glycosides: swertiamarin [15], cantleyoside [16] and loganic acid [17; 18], also, one triterpene saponin dipsacoside B [19]. The structural determination of the obtained compounds were performed on the bases of 2D-NMR experiments (gs-COSY, gs-HMQC, gs-HMBC and gs-HSQC-TOCSY) and mass spectrometry (MALDI-TOF, ESI-HR-MS) and confirmed by comparison with the previously reported data.

All isolated compounds: iridoid and secoiridoid glycosides and dipsacoside B are reported for the first time from ***Cephalaria gigantea*** roots. These components are used as chemosystematic markers for plants of the Dipsacaceae family.

Experimental

General experimental procedures

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-500 spectrometer in CD3OD solutions.

TMS was used as an internal standard. Standard Bruker pulse sequences were used for two-dimensional experiments (gs-COSY, gs-HMQC, gs-HMBC and gs-HSQC-TOCSY). High-resolution Mass Spectra (HR-MS) were obtained an Applied Biosistems MALDI-TOF Voyager Spec. The experiments were performed on a Jeol JMS-700 (Jeol LTD, Akishima, Tokyo, Japan) double focusing mass spectrometer, equipped with an electrospray ionization (ESI) source operating under positive ion mode. Melting points were determine don a BUCHI Melting Point B-540 apparatus. Optical rotations were measured with a Perkin-Elmer model 341 Orot Polarimeter.

Flash Column chromatography was carried out on polyamide MN SC6 Macherey Nagel (70 μm), using a step gradient of H_2O-MeOH of 90:10, 50:50 and 0:100. Low-pressure liquid chromatography was carried out on ChromatoSPAC Prep 100 (Jobin Yvon) with Lichroprep C-18 Merck (15–25 μm, 50 × 4cm), using a step gradient of H_2O-MeOH (100:0, 90:10, 80:20, 70:30, 65:35, 60:40, 50:50 and 0:100, 1 litre for each). For fraction purification was used Column chromatography – silica gel 60 (Merck, 0.040–0.063 mm), with an applied pressure of 300 mbar. TLC analyses were performed on pre-coated silica gel plates (Kiesegel 60 F254 and RP-18 F254, Merck), using the following solvent systems: CH_2CL_2 -MeOH-H_2O (50:16:3, 50:25:5 and 30:13:3), n-BuOH-HOAc-H2O (4:1:5). Spots were detected by spraying the plates with phosphoric acid naphtoresorcinol and H_2SO_4 followed by heating at 110 °C.

Plant material

The roots of ***Cephalaria gigantea*** was collected in Imereti region of Georgia (Octomber 2017) and dried in the shade. A voucher specimen is kept in the department of Pharmacobotany, Institute of Pharmacochemistry, Tbilisi, Georgia (roots No. 98351).

Extraction and Isolation

Air-dried and powdered roots of ***Cephalaria gigantea*** (500 g) were extracted by percolation at room temperature with MeOH (3 L for 24 h), the obtained solution was concentrated under vacuum. . After evaporation of solvent, the dry extract (20 g) was submitted to flash column chromatography on polyamide MN SC6, using a step gradient of H_2O-MeOH 90:10, 50:50 and 0:100, to give enriched fraction 1, 2, 3. Obtained enriched fraction 1 (2 g) was further purified by low-pressure liquid chromatography (LPLC) with C-18 (15–25 μm, 50 × 4cm) and a step gradient of H_2O-MeOH (100:0, 90:10, 80:20, 70:30, 65:35, 60:40, 50:50 and 0:100, 1 litre for each), allowed us to obtain swertiamarin (87 mg), cantleyoside (280 mg) and loganic acid (38 mg). Enriched fraction 2(1g) was fractionated by silica gel column chromatography using CH_2Cl_2 – MeOH-H_2O (50:16:3) to obtain dipsacoside B (65mg).

Chemical elucidation of the obtained compounds were performed by spectroscopic analysis including 2D-NMR and HR-MS data.

Spectroscopic data

Swertiamarin. $C_{16}H_{22}O_{10}$, yellow amorphous powder. ^{1}H NMR (400.13 MHz, CD_3OD, δ, ppm, J/Hz): 7.65 (1H, s, H-3), 5.70 (1H, s, H-1), 5.46 (1H, dt, J=17.0, 9.5, H-9), 5.38 (1H, dd, J=17.0, 2.0, H-10), 5.31(1H, dt, J= 9.8, 2.0, H-10), 4.78 (1H, ddd, J=13.0, 10.8, 2.4, H-7), 4.66 (1H, d, J=7.9, H-1'), 4.36(1H, br dd, J=10.8, 4.8, H-7), 3.92 (1H, dd, J=12.0, 1.4, H-6'), 3.68 (1H, dd, J=12.0, 5.8, H-6'), 3.39 (1H, t, J=9.0, H-3'), 3.34 (1H, m, H-5'), 3.30 (1H, t, J=9.0, H-4'), 3.21 (1H, dd, J=8.9, 7.8, H-2'), 2.94 (1H, d, J=9.4, H-8), 1.93 (1H, td, J=13.9, 5.1, H-6), 1.76 (1H, br.d, J=13.9, H-6).^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 168.0 (C-11), 154.78 (C-3), 133.84 (C-8), 121.18 (C-10), 108.88 (C-4), 100.23 (C-1'), 99.09 (C-1), 78.53 (C-5'), 77.80 (C-3'), 74.43 (C-2'), 71.41 (C-4'), 65.95 (C-7), 64.27 (C-5), 62.57 (C-6'), 51, 94 (C-9), 33.73 (C-6).

Cantleyoside. $C_{33}H_{46}O_{19}$, white amorphous powder. ^{1}H NMR (400.13 MHz, CD_3OD, δ, ppm, J/Hz): 9.40 (1H, s, H-7''), 7.55 (1H, d, J=1.4, H-3''), 7.44 (1H, br.s, H-3), 5.53 (1H, d, J=4.7, H-1''), 5.29 (1H, d, J=4.9, H-1), 5.28 (1H, dd, J=17.2, 1.0, 2.4, H-10''), 5.25 (1H, dd, J=10.3, 1.0, H-10''), 5.20 (1H, t, J=5.0, H-7), 4.71 (1H, d, J=7.8, H-1'''), 4.68 (1H, d, J=7.9, H-1'), 3.92 (2H, dd, J=11.9, 1.8, H-6' and 6'''), 3.71 (3H, s, OCH_3), 3.68 (2H, dd, J=11.9, 6.0, H-6' and 6'''), 3.48 (1H, q, J=6.0, H-5''), 3.39 (2H, t, J=8.9, H-3' and 3'''), 3.28 (4H, m, H-4', 5', 4''' and 5'''), 3.21 (2H, dd, J=8.9, 7.8, H-2' and 2 '''), 3.10 (1H, q, J=8.0, H-5), 2.77 (1H, m, H-9''), 2.74 (1H, m, H-6''), 2.55 (1H, dd, J=17.5, 6.3, H-6''), 2.29 (1H, dd, J=14.5, 7.5, H-6), 2.14(1H, m, H-8 and 8''), 2.07 (1H, td, J=8.7, 5.0, H-9), 1.75 (1H, ddd, J=14.5, 7.7, 5.0, H-6), 1.07 (1H, d, J= 6.8, H-10). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 203.13 (C-7''), 169.35 (C-11), 167.97 (C-11''), 153.90 (C-3''), 152.61 (C-3), 134.94 (C-8''), 120.54 (C-10''), 113.11 (C-4), 110.26 (C-4''), 100.20 (C-1'''), 100.03 (C-1'), 97.57 (C-1), 97.44 (C-1''), 78.42[a] (C-5'), 78.38[a] (C-7), 78.34(C-5'''), 77.98 (C-3' and 3'''), 74.71[b] (C-2'), 74.63[b] (C-2'''), 71.59[c] (C-4'''), 71.55[c] (C-4'), 62.77 (C-6' and 6'''), 51.76 (OCH_3), 47.09 (C-9), 45.63 (C-6''), 45.37 (C-9''), 41.08 (C-8), 32.69 (C-5), 27.78 (C-5''), 13.85 (C-10).

Loganic acid. $C_{16}H_{24}O_{10}$, white amorphous powder. ^{1}H NMR (400.13 MHz, CD_3OD, δ, ppm, J/Hz): 7.20 (1H, s, H-3), 5.20 (1H, d, J=4.2, H-1), 4.66 (1H, d, J=7.9, H-1'), 4.05 (1H, br.t, J=4.2, H-7), 3.90 (1H, d, J= 11.5, H-6'), 3.68 (1H, dd, J=11.5, 5.0, H-6'), 3.39 (1H, t, J=9.0, H-3'), 3.33 (2H, m, H-4', H-5'), 3.21 (1H, dd, J=8.9, 7.8, H-2'), 3.13 (1H, br.q, J=7.7, H-5), 2.24 (1H, dd, J=7.8, 3.7 H-6), 1.99 (1H, td, J=9.0, 4.3, H-9), 1.89 (1H, m, H-8), 1.70 (1H, ddd, J=13.7, 7.7, 4.2, H-6), 1.10 (3H, d, J=6.9, H-10). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): 99.88 (C-1'), 97.21 (C-1), 78.29 (C-5'), 78.01 (C-3'), 75.25 (C-7), 74.80 (C-2'), 71.62 (C-4'), 62.75 (C-6'), 46.83 (C-9), 42.74 (C-6), 42.09 (C-8), 32.93 (C-5), 13.54 (C-10), C-3, C-4 and C-11 no observed.

Dipsacoside B. $C_{53}H_{86}O_{22}$, white amorphous powder. ^{1}H NMR (400.13 MHz, CD_3OD, δ, ppm, J/Hz): Aglycone: 5.41 (1H, t, J=2.9, H-12), 4.16 (1H, m, H-23), 4.29 (1H, m, H-3), 3.75 (1H, m, H-23), 3.18 (1H, dd, J=13.0, 3.3, H-18), 2.31 (1H, m, H-15), 2.21 (1H, m, H-2), 2.01 (1H, m, H-16), 1.99 (1H, m, H-2), 1.93 (1H, m, H-11), 1.92 (1H, m, H-16), 1.40 (1H, m, H-6), 1.91 (1H, m, H-22), 1.77 (1H, m, H-22), 1.76 (1H, m, H-9), 1.73 (1H, m, H-5), 1.72 (1H, m, H-19), 1.70 (1H, m, H-6), 1.60 (1H, m, H-7), 1.55 (1H, m, H-1), 1.31 (1H, m, H-21), 1.22 (1H, m, H-19), 1.17 (3H, s, H-27), 1.14 (3H, s, H-26), 1.10 (3H, m, H-21), 1.09 (3H, s, H-24), 1.09 (1H, m, H-15), 1.06 (1H, m, H-1), 0.98 (3H, s, H-25), 0.87 (3H, s, H-30), 0.86 (3H, s, H-29). Sugars: 28-O-Glc1: 6.29 (1H, d, J=8.1, H-1), 4.74 (1H, m, H-6), 4.39 (1H, m, H-6), 4.37 (1H, m, H-4), 4.25 (1H, m, H-3), 4.15 (1H, m, H-2), 4.13 (1H, m, H-5). Glc2: 5.06 (1H, d, J=7.8, H-1), 4.51 (1H, dd, J=12.1, 2.4, H-6), 4.38 (1H, m, H-6), 4.24 (1H, m, H-4), 4.22 (1H, m, H-3), 4.03 (1H, t, J=8.4, H-2), 3.91 (1H, m, H-5). 3-O-Ara: 5.12 (1H, d, J=6.4, H-1), 4.60 (1H, dd, J=8.6, 8.0, H-2), 4.28 (1H, m, H-5),

4.20 (1H, m, H-4), 4.13 (1H, m, H-3), 3.72 (1H, m, H-5). Rha: 6.28 (1H, d, J=1.3, H-1), 4.76 (1H, m, H-2), 4.71 (1H, m, H-5), 4.67 (1H, dd, J=9.2, 3.5, H-3), 4.32 (1H, m, H-4), 1.65 (3H, d, J=6.2, H-6). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ, ppm): Aglycone: 176.90 (C-28), 144.40 (C-13), 123.30 (C-12), 81.40 (C-3), 64.30 (C-23), 48.50 (C-9), 48.10 (C-5), 47.40 (C-17), 46.50 (C-19), 43.80 (C-4), 42.50 (C-14), 42.00 (C-18), 40.20 (C-8), 39.40 (C-1), 37.20 (C-10), 34.30 (C-21), 33.40 (C-29), 33.10 (C-7), 32.90 (C-22), 31.10 (C-20), 28.70 (C-15), 26.60 (C-2), 26.40 (C-27), 24.20 (C-11), 24.00 (C-30), 23.70 (C-16), 18.60 (C-6), 17.90 (C-26), 16.50 (C-25), 14.30 (C-24). Sugars: 28-O-Glc1: 96.00 (C-1), 79.10 (C-3), 78.30 (C-5),

74.30 (C-2), 71.30 (C-4), 69.70 (C-6). Glc2: 105.70 (C-1), 78.80 (C-5 and 3), 75.50 (C-2), 71.80 (C-4), 63.00 (C-6). 3-O-Ara: 104.70 (C-1), 76.20 (C-2), 75.10 (C-3), 69.70 (C-4), 66.00 (C-5). Rha: 102. 10 (C-1), 74.50 (C-4), 72.90 (C-3), 70.10 (C-5), 18.90 (C-6).

Iridoids and secoiridoids characterize the family Dipsacaceae and could be used as a chemotaxonomic marker of the family [20].

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DETERMINATION OF QUANTITATIVE CRITERIA OF RELIABILITY IN THE EARLY DIAGNOSIS OF PRE-PATHOLOGICAL STATE

Abstract. The authors propose an innovative approach to the issues of early diagnostics of pathological states based on determining quantitative parameters of reliability – criteria of stability and reactivity, which manifest themselves in the interaction of the patient's erythrocyte membrane systems with a chaotropic agent – dosed exposure to ultrasound.

Keywords: organizational resource, reliability potential, variability, stability, reactivity, quantitative kinetic parameters, ultrasonic effect, express-analyzers.

In the modern world there is ongoing analysis of complex systems and their properties. The concept of "reliability" was previously applied to technical systems. Now the reliability of biosystems characterizes the organizational potential, combining the criteria of structural stability and functional reactivity [1; 2].

M. Khazin and M. Elizarov [3; 4] introduced the concept of organizational resource as a **composition** of system asymmetry and coherence. The condition for organizational balance is a certain equilibrium between the active and passive components of the order, allowing their mutual overflow [3]. Moreover, one component without the other cannot give a full effect. Passive consistency is an uncomplaining herd, dead matter, and unorganized activity – the Brownian movement – continuous losses from endless strife. Obviously, the degree of order of the socio-economic system, a kind of its organizational potential, will be zero in the absence of either of the two components.

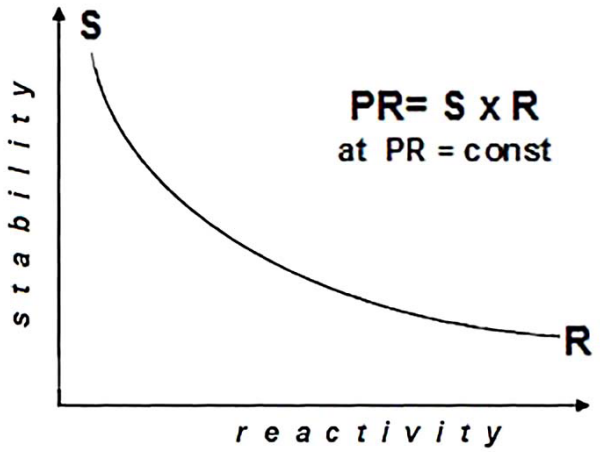

Figure 1. Scheme of interdependencies between reliability potential, stability and reactivity

Let the organizational resource is a constant. Then the relationship between the variables (asymmetry and coherence) becomes hyperbolic, which

can be easily visualized using a visual graphic model in the form of a distribution field, where systemic asymmetry(A) is taken as the horizontal axis and system coherence (C) is taken as the ordinate [3–4].

R = C × A at R = const; R – organizational resource

But the criteria of asymmetry and coherence are difficult to measure and apply into practice. It is better with the category of reliability [2].

If we consider the category of reliability, the relationship between its variables – stability and reactivity – also has a hyperbolic character **(Fig. 1)**: **RELIABILITY = Stability × Reactivity** at the permanency of the reliability resource **RP = S × R** at **RP = const RP – reliability potential**

The third chapter of the review [2] "Stability and reactivity – the structural and functional criteria of the biological reliability of a plant" emphasizes: "The physicochemical mechanisms of biological reliability of higher plants consist in the development of two opposite criteria: on the one hand, the structural stability of molecular organization of cell membranes, on the other hand, high reactivity and sensitivity of membrane structures to phytopathogens as chaotropic agents. In conclusion, the authors came to the conclusion: "Physical and chemical studies of the dynamic plant-parasite host system allowed us to declare a postulate on the presence of dynamic equilibrium of two asymmetric functions in the membrane and cell, to offer a two-compartmental model of membrane processes and possible mechanisms of reactivity of membrane structures".

Transformed from the review [2], the scheme of inter-relation of the categories of biological reliability and variability with the criteria of stability and reactivity [5] gives a broader understanding of the characteris-tics of living systems (Fig. 2). From this scheme, the occurrence of the reactivity phenomenon for living systems only is quite obvious. For the inanimate (lifeless) – stable (rocks, hard rocks, crystals, etc.), the area in the coordinates STABILITY – PASSIVITY is given. For unstable inanimate (lifeless) systems (volcanoes, thunderstorms, lightning, tornadoes, typhoons, nuclear processes, etc.), the range in the coordinates INSTABILITY – PASSIVITY is given.

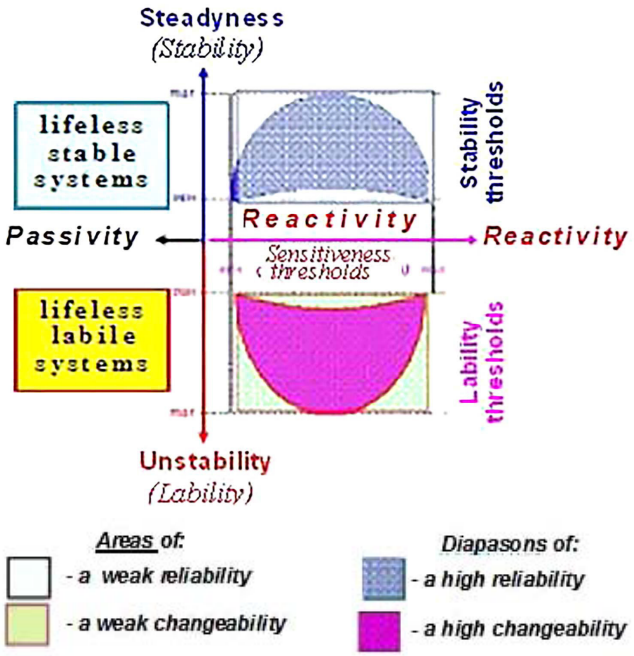

Figure 2. Scheme of interrelation of categories of biological reliability and variability with criteria of stability and reactivity

For living systems, the optimal ratio of sustainability and reactivity criteria (in the interthresholds value space) determines the range of high reliability of the biological properties of the system of higher plants – the area in the coordinates STABILITY-REACTIVITY. The optimal ratio of criteria for reactivity and lability (instability) can determine the range of opti-mal variability that ensures the viability and adaptive evolution of lower plants and microorganisms – in the area with coordinates LABILITY- REACTIVITY [5].

As Mikhail Leonidovich writes: "… **the time has come for important revelations that relate to the most mysterious and inexplicable aspect of the world perception – a way of knowing reality"** [4].

The article proposes not a vulgar understanding of the principle of unity of opposites [4], but a clear idea of the balance of two different orthogo-

nal functions of living systems: structural stability and functional reactivity; then the **composition** of their indicators determines the potential reliability of a system, biological or social. Moreover, among the variation in the indicators, a "window of opportunity" [3] is revealed over the range of sustainability criteria (ΔS) and reactivity criteria (ΔR), which are characteristic of a reliable system **(Fig. 3).** Exceeding the resistance index above the threshold leads to ossification, system necrosis, and excess of the reactivity index above the optimal range leads to chaos and death of the system.

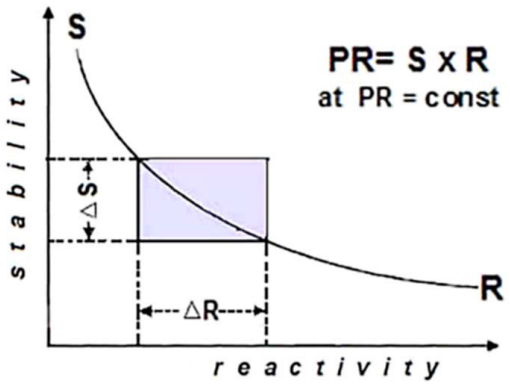

Figure 3. "Opportunities win-dow" for a system with high reliability potential (R) and optimal ranges of stability ΔS and reactivity ΔR

Therefore, not only the "anti-entropic principle" [6] is important, but also the balance, even harmony between the entropy and anti-entropy functions, since the main goal of our existence is not reduced simply to a decrease in entropy at any accessible (personal, social, global) level, but in reducing the reasonable balance of these 2 oppositely directed processes. The process of creativity itself is an entropy process, because violates the established order, but its result flows in the case of successful work in the anti-entropic, informational potential. Famous hooligan poets, burning in the "furnace of entropic processes", carved out a fire of inspiration in the throes of the creation of their masterworks – Yesenin, Mayakovsky, Khlebnikov, Blok [5].

Reactivity as a function of the entropy compartment, and sustainability as a structural characteristic of the anti-entropy compartment are equally important components of the reliability potential of a biosystem.

"PRACTICE – CRITERIA OF TRUTH". Sustainability and reactivity indicators are measurable and reproducible in practice. Here are some examples:

Example 1. **Kinetic study of the immune response in a skin-allergic inflammation reaction of delayed-type to the application of DNCB, a non-specific chaotropic agent, where resistance and reactivity indicators are clearly distinguished** [7].

Example 2. **Method for determining the reliability of PLANT LIFE SUPPORT [8].**

Kinetic analysis of the fungus Verticillium Dahliae Kl. after-effects for different varieties of cotton showed the ability to predict the reliability of immunity by the speed of the response reaction, which corresponds to the criterion of reactivity, and the degree of its deceleration, which corresponds to the criterion of stability [5]. Analysis of the plant response to non-specific effects allowed developing a method for determining the reliability of plant life support [8]. The use of a conductometric method for recording the release of ions will allow automating the process.

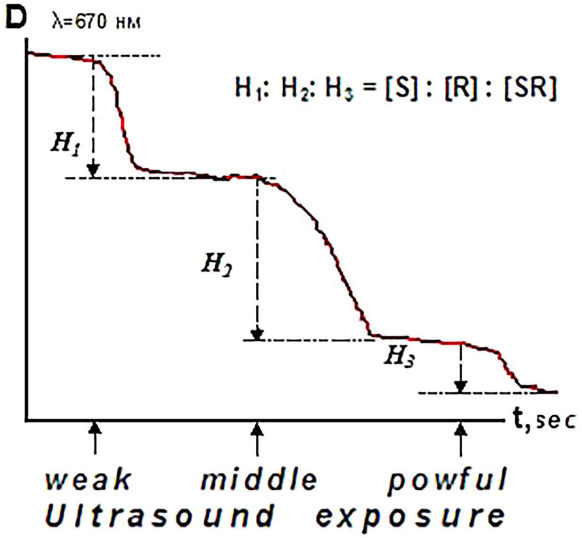

Figure 4. Kinetics of decay of blood erythro-cytes under 3-step-graded ultrasound exposure

Example 3. **Kinetic analysis of the ultrasound resistance of red blood cells in the diagnosis of pre-pathological states of the organism.**

Method 1. Express diagnosis of pre-pathological states.

It is well known that pathology is accompanied by increased stiffness, adhesion and deformation of red blood cells, as shown by microscopy and the study of the rate of erythrocyte outflow through a series of membrane filters. These methods are used in laboratories of scientific research institutes and are not available for automation. We have proposed a method of differentiation of erythrocytes by ultrasound resistance.

Analysis of the ultrasound resistance of a patient's erythrocyte sample is carried out by measuring the optical density at a wavelength of λ = 670 nm with registration of the erythrocyte decay kinetics in the process of phased enhancement of ultrasound exposure. The kinetics of red blood cells decay has a gradual character depending on the time and power of ultrasound exposure and the following picture (Fig. 4): (fractions of erythrocytes: **sensitive – S; resistant – R; super rigid – SR) H1 : H2: H3 = [S] : :[R] : [SR];**
in the norm: [S]: [R]: [SR] = [40 ± 10%]: [50 ± ± 10%]: [10 ± 4%]. The hemoglobin content in the sample is determined by the sum of the broken red blood cells: $\mathbf{D_0 = H_1 + H_2 + H_3}$

Deviations in the direction of increasing the sensitive fraction (S) indicates the presence of allergic and somatic diseases; deviations in the direction of increasing super-resistant (SR) erythrocytes indicates the development of pre-pathological processes and a high degree of immunodeficiency. A particularly pronounced excess of the share of SR-erythrocytes was observed in patients with stage III and IV of cancer. The threshold of pathological resistance of erythrocytes is the excess of the share of SR-erythrocytes by 20 ± 2%, above which pathology obtains the character of irreversibility (Fig. 4).

Then the characteristic of the entropic compartment of reactivity is the content of the sensitive red blood cell fraction [**S**], and the characteristic of the anti-entropic stability compartment is the content of the super rigid erythrocytes fraction [**SR**].

Method 2. Express diagnostics of quantitative parameters of the reliability of the life support of erythrocytes' membrane system.

The method allows to record the dynamics of the erythrocytes decay in standard, kinetic conditions of an experimentally developed medium by measuring the optical density at a wavelength of λ = 670 nm during exposure to ultrasound in a certain mode and power of exposure (Fig. 5). From the obtained erythrocyte decay curve, it's possible to calculate mathematically 6 quantita-tive parameters: reactivity criteria – pool (**A**) with reactivity constant $\mathbf{k_1}$, stability criteria – pool (**B**) with constant $\mathbf{k_2}$, relaxation time of compartments (τ) and erythrocyte reliability potential (viability) (Ψ). **The reproducibility of the results is provided by the optimal medium (pH, t, osmosis, mixing) and the kinetic area of measurement, in which the calculated parameters haven't depended on rate of mixing of erythrocytes in the sample.**

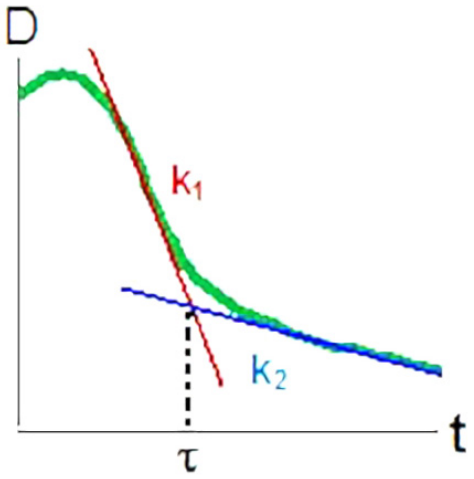

Figure 5. Erythrocyte decay kinetics under standard ultrasound expo-sure conditions for determining quantitative reliability parameters

Optimal ratios of the parameters correspond to a high degree of life support reliability, deviations of the parameter values in any direction – increase or decrease – indicate reversible or pathological shifts in the state of reactivity and stability compartments of the subcellular structures of human erythrocytes. Considering the undoubted progress of IT technolo-

gies in processing and calculating the kinetic parameters of Big Data with statistical accuracy of deviations at least 3 times the experience of measuring a patient's blood sample, one can hope that the primary changes in the functional parameters of the cell membrane systems will be fixed much earlier than the degeneration of the genetic apparatus and the appearance of 1 pathologically perverted cell at least.

Experiments have shown that even a year after surgery (resection of the mammary gland), the content of CP-erythrocytes was recorded slightly higher than normal, after then it was encouraged the patient to continue treatment aimed at harmonizing the parameters and functions of the organism. Thus, the express analysis using the simplified method 1 can be used to monitor the effectiveness of medical procedures and treatment strategies even without the participation of a physician, using an automatic analyzer.

Both methods are available to fully automate the process with the issuance of calculated data without the participation of the "human" factor. Express analyzers of the reliability parameters of the vital supply of human erythrocytes (and animals can also be given in veterinary clinics) require the collection of a minimal amount of capillary blood of 20 μl and 5 min of time for analyzing, processing and issuing kinetic data of express analysis. Automatic express analyzers of the reliability of life support and sowing qualities of seeds (based on registration of electrical conductivity (conductometry) – can significantly increase the efficiency and productivity of the seed and breeding stations in agriculture.

We are confident that the horizons of research and measurements of entropy and anti-entropy parameters and functions in the future are boundless. Progress in science will provide a breakthrough in agriculture, the economy, and most importantly – in health care, when express analyzers of capillary blood come to every clinic to predict and prevent any pathological abnormalities in advance.

Nobel laureate **Luc Montagnier**, the discoverer of human immunodeficiency virus, while in Moscow, said that very soon people will come to doctors not to treat diseases, but to prevent old age [9].

Luc Montagnier directly links aging with a decrease in immunity: "If we want to prevent the development of diseases, we need to remove the imbalance between oxidative molecules and antioxidants. For this, vitamins C, E, enzymes, microelements can be used. Unfortunately, when oxidative stress is strong, the amino acids-antioxidants that our body produces is not enough, and in old age their production decreases even more".

Montagnier believes that in the future, any person will be able to regularly undergo special tests, in time to learn about susceptibility to certain diseases. Knowing the weak link of the body, doctors will be able to prevent possible diseases, protecting them from reaching the irreversibility phase [9].

According to **Sukhonos S. I.** [10], any country that wants to break out of the ring of third-row, not to be a raw materials appendage or "gas station", should develop the creation of an innovative product, and any serious innovation should be turned into a good of global demand.

A full-fledged innovation industry was created in the USSR: from theoretical studies in the USSR Academy of Sciences to the inculcation of new products into production. This industry has worked successfully and has provided our priority in many areas, including nuclear energy, space and weapons. If in the future we create a similar Soviet innovation system, but for inquiries from the world market, this may lead the country to a breakthrough [10].

The innovation process has several stages, each of which must be crowned with full completeness: **1) the birth of an idea; 2) testing the idea with the help of an experiment; 3) creating an experimental model, a prototype of the future product of mass production; 4) creating experienced industrial production, in which all the nuances of the production of a new product are worked out; 5) the creation of serial production; 6) leading of a new product to the world market; 7) warranty**

and post-warranty services (for equipment). The more complex the product, the longer and more expensive this chain, but its stages are the same for any innovation. The point can be put only after a new idea, embodied on the most modern technological lines, occupies its rightful niche in the world commodity segment.

A lot of ideas are born, but there's no practical implementation of a world scale, because there is no experience of creating an innovative sector of the economy, working primarily for export [10].

World practice shows that innovative developments make a profit of up to 1000%. In addition, the country can offer invaluable capital – the Creator Man, who is able to create **new information**.

This fact is the key to the future success of innovation. **"… there is hope that it will be in this sector that a new sum of technologies will be created, which will increase the efficiency of the entire life activity of people on the planet by orders of magnitude, which will save it from the threat of a new world war and from the global resource crisis in general. And how can one assess the economic efficiency of the salvation of mankind? "** – the author asks [10].

The intention of the authors of the article is to attract a "system customer", possibly from China or USA, since these countries have the financial power to trigger the innovation process in the Republic of Uzbekistan, the "pearl" of the Silk Road, whose young people are able to maintain the ancient traditions and cultural values of the East and at the same time be open to innovation.

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