CHAPTER 15

PARAPHARMACEUTICALS OF PLANT ORIGIN – PAST AND FUTURE

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INTRODUCTION

The use of plants for the treatment of numerous human ailments began in ancient times. Hippocrates was convinced that plants should be used in their natural state, without any transformations. The ancient Roman physician Galen advised to grind plants, make extracts and tinctures from them in alcohol, vinegar, which are widely used in our time. Despite the rapid development of chemistry and the growth of the number of new, increasingly effective synthetic drugs, antibiotics, medicinal plants continue to occupy a significant place in the arsenal of therapeutic agents.

Prevention and treatment of purulent-septic infections continues to be one of the complex and urgent problems of modern medicine. The widespread use of antibacterial drugs not only did not justify the hopes placed on them, but also created a number of new problems that require urgent solutions. This is, first of all, the high rate of acquisition of antibiotic resistance by pyogenic microflora. The basis of this process is the uncontrolled and often insufficiently substantiated use of antibiotics in clinical practice.

Undesirable and at the same time common consequences of antibiotic therapy include allergic reactions and direct toxic effects of antibacterial drugs on the macroorganism, which develop in connection with the organotropic pharmacodynamic action. Therefore, many synthetic antimicrobial agents have not been introduced into clinical practice, and some of the existing ones have a rather limited application.

Thus, there is every reason to search for new sources of antimicrobial agents, one of which may be plant extracts. The peculiarity of extracts from medicinal plants is that their biologically active substances are in a certain ratio, which contributes to the optimal effect on the human body. Some components of plant extracts are similar in chemical structure to physiologically active substances of the body (hormones, vitamins, enzymes, etc.). Therefore, such natural medicines

are more actively included in the biochemical processes of the human body than synthetic drugs that are foreign to the body. Unlike traditional antibacterial drugs, most antibiotics of plant origin, in addition to antimicrobial action, have a pronounced positive effect on the macroorganism [1] [2].

Phytoncides were called bactericidal, fungicidal and protistocidal substances produced by plants, which are one of the factors of their immunity and play a role in the relationships of organisms in biocenoses. A large number of volatile phytoncides are released into the atmosphere by deciduous and especially coniferous trees – several kilograms per day per 1 ha of forest. Even in the first years of research, it was established that the presence of phytoncides is not characteristic of any specific group of plants, but of the entire plant world. Any phytoncide has antibiotic properties, but not every antibiotic is identical to the phytoncide of a particular plant.

An ecological approach to the emergence of phytoncides and preparations from them (antibiotics) made it possible to explain a number of questions, for example, why penicillin is less toxic to the human body than streptomycin. From a biological point of view, treatment of humans with antibiotics is the addition of plant properties to the immunological capabilities of the human body, which determine its immunity. Therefore, phytoncides are not a random phenomenon, they are an evolutionarily developed property of plants.

The different approach to naming the antimicrobial properties of phytoncides and plant extracts is due to the fact that during any extraction, various changes in the composition and structure of substances found in plants are possible, and therefore the extracts may not always contain natural products of the plant organism. Nevertheless, extraction is a way to obtain stable antimicrobial drugs and select antibiotic producers. Therefore, plants are a promising source for obtaining antimicrobial agents. In this regard, the availability of a sufficient amount of medicinal plant raw materials for their manufacture is of great importance. Ukraine, and in particular the Carpathian region and the Carpathians, due to its natural and climatic conditions, is one of the regions of Europe rich in environmentally friendly medicinal plants.

The effect of biologically active substances of plant origin on conditionally pathogenic Gram-positive and Gram-negative microorganisms remains insufficiently studied to date. Literature data indicate the study of the action of these substances on a wide range of species of various bacteria, including opportunistic pathogens. But in the vast majority of these studies, collection

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[1] Основи імунології: функції та розлади імунної системи: посібник: пер. 6-го англ. вид. / Абул К. Аббас, Ендрю Г. Ліхтман, Шив Піллай: наук. ред. пер. з англ. Валентина Чоп'яка. Київ: ВМВ «Медицина». 2020. 328 с.

[2] Мамчур Ф. І. Довідник з фітотерапії. Київ: Здоров'я. 1984. 264 с.

strains of the listed bacteria were used. They have been cultivated for decades in laboratory conditions, without contact with the human body, and therefore are characterized by a weakened pathogenic potential.

The study of the influence of biologically active substances of plant origin on opportunistic microorganisms isolated from clinical material, primarily their hospital strains, which are characterized by increased virulence, as well as polyantibiotic resistance, is of both theoretical and practical importance. In particular, I conducted studies of plant extracts (alcohol: 70% and 90%, acetone), as well as officinal tinctures against various strains of staphylococcus [3] [4].

The purpose of this work is to search for biologically active substances of plant origin with antibiotic properties against staphylococcus, the infection of which is characterized by a variety of ─ from the most severe, generalized forms to mild: sepsis, pneumonia, meningitis, abscesses of internal organs, enterocolitis, endocarditis, gynecological diseases, staphylococcal infection with scarlet fever syndrome, purulent-inflammatory diseases of the skin and soft tissues, etc. These searches are carried out among plants of the Carpathian region, promising for the creation of new domestic antimicrobial drugs.

1. Classification of parapharmaceuticals

Parapharmaceuticals (from Latin para – near, pharmaceutics – medicines) are medicinal plants, algae, mushrooms. These are, as a rule, products containing minor food components: bioflavonoids, organic acids, glycosides, biogenic amines, regulatory oligopeptides, polysaccharides, oligosaccharides, etc. The action of parapharmaceuticals is implemented in the following areas: activation of systems involved in the development of adaptive compensatory-adaptive reactions of the body; regulation: within physiological limits of the functional activity of individual organs and systems; activity of the nervous system, including higher nervous activity; microbiocenosis of the gastrointestinal tract. These properties of parapharmaceuticals allow the human body to adapt to changed, extreme conditions, and provide additional, auxiliary therapy for various diseases, which qualitatively expands the possibilities of the main treatment methods.

Differentiation of parapharmaceuticals from medicines occurs according to the following criteria: therapeutic dose, if the dietary supplements present in the preparation do not exceed the therapeutic dose, then it is classified as parapharmaceuticals. Expected effectiveness. When using parapharmaceuticals – 8-12 weeks, no side effects [5].

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[3] П'яткін К.Д., Кривошеїн Ю.С. Мікробіологія. Київ: Вища школа. 1992. 360 с.

[4] Товстуха Є. С. Фітотерапія. Київ: Здоров'я. 2000. 340 с.

[5] Шапіро А.В. Визначення чутливості мікроорганізмів до антибіотиків методами серійних розведень та є

Depending on the biotechnological method of their manufacture, parapharmaceuticals are divided into several groups of dietary supplements containing products: plant synthesis, animal synthesis, microbiological synthesis (eubiotics), beekeeping, natural chemical synthesis. In the vast majority of cases, parapharmaceuticals are safe to use. Although when using parapharmaceuticals, the phenomena of individual intolerance to their individual components are not excluded, which, however, is also characteristic of some food products and even more so for medicines. Thus, parapharmaceuticals, without replacing medicines, significantly improve the quality of preventive and therapeutic measures.

Relatively recently, a little more than half a century ago, a new problem arose in science − the problem of antibiotics, the development of which has already yielded exceptionally valuable results for medical practice. The first producers of antibiotics were discovered among lower plants, fungi, actinomycetes and bacteria, and higher plants remained without attention for a long time. Only after B. P. Tokin raised the question of the antitoxin properties of vapors from propagated parts of fresh plants, thus creating the problem of phytoncides, higher plants attracted attention, and among them the search for producers of antimicrobial substances began.

The presence of antimicrobial substances is characteristic of many plants. In most families, antimicrobial drugs are obtained only from single species, but there are families in which there are significantly more species that can be a source of obtaining these substances. For example, most antimicrobial drugs are obtained from plants of the Asteraceae family, followed by Rosaceae, Liliaceae, etc. Plant species belonging to the same family may contain different antimicrobial substances, and even the same plant may contain several different substances [6] [7].

The most common antimicrobial substances of higher plants, the most extensive in this direction are the works of Osborne, who studied 2300 species of plants and found antibacterial activity in only 160 species belonging to 63 genera. Antimicrobial substances were most often found in buttercups, the antibacterial activity of which could depend on the presence of protoanemonin in them. Then came the liliaceae, which include onions and garlic, rich in allicin or compounds close to it. The most sensitive to antibacterial substances of plant origin were Gram-positive microorganisms, less sensitive − Gram-negative. Antimicrobial substances are represented in plants by a wide variety of compounds. The most common, that is, those that occur most often, will be presented below.

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[6] Іванов С. В., Сімахіна Г. О., Науменко Н. В. Технологія оздоровчих харчових продуктів: підруч. Київ: НУХТ, 2015. 402 с.

[7] Гігієна харчування з основами нутриціології: Підручник у 2-х кн. Аністратенко, Т.М. Білко, О.В. Благодарова та ін.; За ред. проф. В.І. Ципріяна. Київ: Медицина. 2017. 578 с.

Essential oils of different plants are not individual chemical substances. They include carbohydrates (aliphatic and aromatic), mono- and polycyclic terpenes and sesquiterpenes, alcohols, their esters, aldehydes, phenols and phenolic esters, ketones, organic acids, sometimes lactones, etc. Nevertheless, each essential oil has its own characteristics. Literature data indicate that almost all essential oils have more or less pronounced bacteriostatic properties. In particular, the most active essential oils against staphylococci were: Ol. Acorus calami (dilution 1:5000), Ol. Artemisia absinthii (1:1000), Ol. Carum carvi (1:2000), Ol. Cinnamonii (1:8000), Ol. Eucalypti (1:4000), Ol. Ferula sp. (1:1500), Ol. Thymus polessicus (1:10000 – 1:25000), Ol. Valerianae nitidae (1:2500 – 1:5000), Ol. Cannabis sativa (1:50000 – 1:100000) and others.

It is possible that the use of antimicrobial substances also takes place in the food industry, since many spices contain antibacterially active essential oils (ginger, nutmeg, cinnamon, marjoram, laurel, allspice, cloves, coriander, anise...). Balsams and resins are also not individual substances, but mixtures. Balsams with antibacterial properties include the Peruvian, Copaiba, Toluan balsams and styrax, known since ancient times. Resins (resin acids) with antimicrobial properties include resins from Balsamea Myrrha and Styrax benzoin, which contains benzoic and cinnamic acids [8].

Organic acids are found in large quantities in higher plants. Antimicrobial properties are possessed by haulmugrovy and hydnokarpov, as well as usnic and gallic acids. Tannins, in particular tannin and gallic acid, have been used as antiseptics since ancient times. Many literary sources indicate that the antimicrobial properties of a number of plants are due to the presence of tannins in them, in particular, such plants are thick-leaved badan, lingonberry, common yarrow, snakeroot, erect cinquefoil, scumpia, etc. Thus, tannin exhibits a bactericidal effect in a dilution of 1:1000 – 1:5000, bacteriostatic − 1:20000 – 1:100000; pyrogallol in 1:2000 and 1:20000; hydroquinone in 1:500 and 1: 1000-2000; pyrocatechin in 1: 3500, respectively.

Of the proteins, only one has been described as an antibiotic – purothionine, which is isolated from unbleached wheat flour. It is toxic not only to bacteria, but also to animals, and also inhibits the reproduction of Gram-positive bacteria. Alkaloids and glucosides exhibit the most pronounced antimicrobial effect among all plant substances. In particular, piptanin, isoamodendrin, anabasin, hatinin, glaucine, delphonin, taspin, spherophysin, harmine, etc. have a pronounced effect on staphylococci [9].

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[8] Фізіологія харчування: підручник / Павлоцька Л.Ф., Дуденко Л.В., Левітін Є.Я., Цихановська І. В., Москаленко О. В., Алнксандров О. В, Іллюха М. Г., Шовгопол Г. Ш. Суми: Університетська книга. 2017. 473 с.

[9] Нутриціологія: навч.посібник / під ред. Н.В.Дуденко. Харків: Світ книг. 2013. 560 с.

2. Raw materials for herbal parapharmaceuticals and methods of its extraction

A fairly large number of extracts from medicinal plants collected in the Ivano-Frankivsk, Lviv and Zakarpattia regions were studied. Extracts were prepared from plants and their various parts (leaves, stems, flowers, roots, bark) using various solvents: alcohol (40%, 70%, 90%), acetone. In some cases, the extracts were evaporated to a certain density; in other cases, the plants were processed in the usual way for the isolation of alkaloids. The active substance was precipitated, separated from the liquid, dried, and then the dilutions necessary for research were prepared from it.

2.1.1. Culture media, equipment. To determine the sensitivity of bacteria to antibiotics, the following media are used:

№1. 1000 ml of Hottinger broth, containing 120-140 mg of amine nitrogen, 15 g of agar, 3 g of sodium phosphate dibasic;

№2. 1000 ml of meat peptone broth (1:2), 15 g of agar, 3 g of sodium phosphate dibasic;

№3. AGV (dry powder is diluted according to the instructions on the label).

To conduct screening studies, culture media are prepared according to a certain principle. A sterile Petri dish is evenly filled with a dense culture medium with a volume of 30 ml. Then, wells of the same capacity are cut in it. A suspension of one culture is sown on the dish, and then plant extracts are added alternately to the wells.

For sowing the cultures under study on a dense nutrient medium with antibiotics, replicator stamps are used for 25 or 50 cultures.

The volume of bacterial suspension or other liquid left by the replicator stamp pin on the imprint of the nutrient medium is 0.001 − 0.002 ml.

The replicator stamp ensures standardization of results, reduces the number of errors and reduces the time spent on sowing and the consumption of nutrient media compared to other methods of sowing.

A stencil for 25 or 50 zones is used for sowing, labeling cultures and recording results. This is a piece of paper with a shape and size equal to the bottom of a Petri dish. This is how the replicator pins moistened with ink are imprinted. The places are numbered from 1 to 25 or 50. Instead of a replicator stamp, you can use a Pasteur pipette.

To perform the method, you will need a thermostat at 37 degrees Celsius, a household refrigerator at +3 … −5 degrees Celsius, stands that do not deteriorate during sterilization, bacteriological cups with a diameter of 9.5 cm, bacteriological test tubes, precipitation test tubes, Pasteur and measuring pipettes,

analytical scales, anatomical tweezers, a water bath, 0.5% NaCl solution, 10% gelatin solution, distilled water [10].

2.1.2. Preparation of nutrient media with antibiotics. When determining the clinical resistance index of a bacterium, 1 ml of nutrient media should contain a concentration equal to ¼ of the working (recommended for practical use) concentration of the antibiotic. The lower concentration of the antibiotic in the nutrient media compared to the working one was selected on the basis of special studies that showed that after the introduction of the antibiotic into the biotope, its concentration rapidly decreases.

To prepare media with antibiotics, depending on the volume of work, a certain measured amount of nutrient media (15, 30, 45, 60, 90 ml) is prepared in test tubes or volumetric flasks. For antibiotics produced by industry in dry form (powder), aliquots of the drug are added to the medium, for liquid forms – certain specified volumes of saturated or diluted solutions. If it is necessary to dilute the original solutions, sterile distilled water is used. The melted nutrient medium after the introduction of the antibiotic is thoroughly mixed and poured into 1-2 or more cups. On the bottom of sterile cups prepared for pouring agar, mark the "top" (draw a straight line at a distance of 1 cm from the edge), indicate the name and concentration of the antibiotic, and the batch number. Ready-made cups with antibiotics can be stored in the refrigerator for a week. Before sowing, the cups must be dried in a thermostat for 30-40 minutes.

When determining the MIC (minimum inhibitory concentration), the method of serial dilutions of drugs in a dense nutrient medium is used. For this, a series of nutrient media with different concentrations of antibiotics is prepared. The interval between concentrations can be double. Depending on the activity of the antibiotic, a range of concentrations is selected − from the minimum, at which all strains of a certain species grow, to the maximum, which suppresses the growth of all strains of this species.

2.1.3. Selection and preparation of cultures for research. In research for the purpose of selecting drugs, strains from patients with suppuration of wounds of mucous membranes, skin, subcutaneous tissue are used. Pure cultures of bacteria are taken for research. In closed processes, 2-3 cultures of each species that have etiological significance are studied from one pathological material; from open (associated with cavities or the external environment) pathological processes, in which the bacterial population is more heterogeneous, the sample should be larger − 5-10 cultures.

If one culture is studied, the error in determining sensitivity can reach 50%. With a large consumption of antibiotic and nutrient medium, the error

[10] Барбаш В.А, Дейкун І.М. Хімія рослинних полімерів. Київ: Каравела. 2018. 440 с.

does not increase, since the same species and isolated from the same material can be mixed and tested in one sample (on one plate with nutrient medium, 25-50 cultures can be tested for sensitivity to antibiotics) [11].

The cultures under study are grown in a thermostat for 18-20 hours on slanted nutrient media. The growth of the cultures is washed off with warm sterile NaCl solution with 0.1% gelatin solution and standardized to 850 million. bacteria per ml (bacterial standard No. 10). Cultures of the same species and from the same material are studied separately or a mixture is prepared from them in equal volumes, so that 1 ml of the mixture has the same density (850 million/ml) [12]

2.1.4. Technique of sowing the cultures under study on a medium with antibiotics. Before sowing, the cultures under study are assigned stencil numbers, which are entered in the research protocol. There are 2 options that give identical results. Sowing with a replicator stamp. The cultures under study are introduced into the wells of the replicator stamp bases with a Pasteur pipette. The order of introducing the cultures must correspond to the numbers assigned to them according to the stencil.

The replicator stamp pins are immersed in the wells and an imprint is made with them (for this, the pins are slightly pressed to the surface of the medium and kept for 10 s) on the antibiotic medium: one cup for each antibiotic when determining clinical and biological resistance indicators, and on a series of cups with each antibiotic when determining the MIC. For a standard seed dose, the pins are immersed in the wells with the culture before each replica. In the serial method, the culture is carried out from a lower concentration to a higher one. At the same time, a control culture is made on a nutrient medium without an antibiotic.

Culture with a Pasteur pipette. On the background of a stencil for 25 strains, small depressions are made with the open end of a sterile precipitation tube into the nutrient medium with an antibiotic – standardizing the culture zones. For culture with a pipette, the initial culture (850 million/ml) is diluted with a 0.5% NaCl solution 2 times (to a density of 425 million/ml). One drop of the suspension of the studied cultures is added to the culture zones with a Pasteur pipette. The roller made with a test tube prevents the drop from spreading. A separate pipette is taken for each culture [13].

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[11] Harkenthal M, Reichling J, Geiss HK, Saller R. Comparative study on the in vitro antibacterial activity of Australian tea tree oil, cajuput oil, niaouli oil, manuka oil, kanuka oil, and eucalyptus oil. Pharmazie 1999 Jun;54(6):460 p.

[12] Digrak M, Ilcim A, Hakki Alma M.Antimicrobial activities of several parts of Pinus brutia, Juniperus oxycedrus, Abies cilicia, Cedrus libani and Pinus nigra. Phytother Res 1999 Nov;13(7): P. 584-587.

[13] Adeniyi BA, Fong HH, Pezzuto JM, Luyengi L, Odelola HA. Antibacterial activity of diospyrin, isodiospyrin and bisisodiospyrin from the root of Diospyros piscatoria (Gurke) (Ebenaceae). Phytother Res 2000 Mar;14(2): P. 112-117.

The cultures are kept on the laboratory table until the cultures are absorbed, after which they are placed in a thermostat at a temperature of 37°C until the next day. The results are recorded based on the presence or absence of bacterial growth in the inoculation zones against the background of a stencil with culture numbers and in accordance with the control culture. A culture that did not grow on a medium with an antibiotic is evaluated as sensitive to a given concentration, and a culture that grew on a medium with an antibiotic (even individual colonies) is evaluated as resistant.

2.1.5. Characteristics of microorganisms of the genus Staphylococcus as an object of study. Staphylococci, like other bacteria, belong to the kingdom of Prokaryotes (Prokariotae); Division Firmicutes – Gram-positive organisms, shaped like cocci, multiply by binary fission; Class Firmibacteria; Group Gram-positive cocci; Family Micrococcaceae – these are cocci that divide in more than one plane, non-spore-forming; Genus Staphylococcus (Staphylococcus) – found on the skin, skin glands, mucous membranes of warm-blooded animals. Species: Staphylococcus aureus – causes furunculosis, postoperative complications, sepsis; Staphylococcus epidermidis; 3.Staphylococcus haemolyticus; Staphylococcus hominis;

Staphylococcus is a large group of microorganisms that differ in their characteristics. The division into pathogenic and non-pathogenic strains is rather conditional. Non-pathogenic staphylococcus, which has weakly expressed potentially pathogenic properties, under certain conditions can cause staphylococcal diseases, especially in newborns, premature babies and infants. With a decrease in the general immunobiological reactivity of the body, against the background of acute respiratory viral or other diseases, non-pathogenic staphylococcus can exhibit pathogenic properties and be the cause of the development of diseases by the autoimmune mechanism [14].

In most cases, diseases are caused by pathogenic strains of Staphylococcus aureus. In laboratory conditions, blood, milk-salt or bile-salt agar is used to cultivate staphylococcus. Depending on the characteristics of the pigment produced, colonies develop: golden, white, cream, lemon-yellow. In the broth, staphylococcus forms a uniform turbidity, and then a flake-like loose sediment at the bottom of the test tube.

Staphylococcus is able to ferment lactose, glucose, sucrose, mannose, xylene, fructose, glycerol without gas formation: to ferment milk. It does not ferment raffinose, dulcitol, inulin, does not break down starch. Staphylococcus

[14] Bortolotti, P., Delpierre, C., Le Guern, R., Kipnis, E., Lebuffe, G., Lenne, X., ... & El Amrani, M. High incidence of postoperative infections after pancreaticoduodenectomy: A need for perioperative anti-infectious strategies. Infectious Disease. 2021. AJOC MGM. 51(5): P. 456-463. doi: 10.1016/j.idnow. 2021.01.001. Epub 2021 Jan 9.

secretes hydrogen sulfide, does not form indole, reduces nitrates and nitrites. Staphylococcus stains Gram-positive. In smears from pure culture, their cluster-like arrangement is typical. One of the signs of pathogenicity of staphylococcus is its ability to be lysed by specific phages.

Due to the widespread invasion of antibiotics, as well as sulfonamide drugs, antibiotic-resistant strains of staphylococcus have appeared that have pathogenic properties. Therefore, staphylococcal infection can be considered as one of the forms of the disease that is the cause of epidemic outbreaks among newborns. The fight against staphylococcal diseases is complicated by the widespread distribution of staphylococcus among the population and in the human environment. Epidemiologically dangerous are especially those carriers in whom the same phage type of staphylococcus is constantly and for a long time detected [15].

Staphylococcus refers to quite unpretentious microorganisms, easily adapts to environmental conditions, relatively quickly acquires resistance to antibiotics and other therapeutic agents, while maintaining its virulent properties. It has been established that under the influence of antibiotic treatment, the vegetative form of staphylococcus can transition to the L-form, which has the ability to persist in the body and reverse to the original pathogenic form when the overall immunobiological reactivity of the body decreases or due to the addition of other diseases. Staphylococcus multiplies in a wide range of temperatures (from 10 to 43 °C) in aerobic and anaerobic conditions on all simple nutrient media. Staphylococcus is most resistant to the action of various physical and chemical factors, tolerates drying, cooling, high temperatures, and is less resistant to chemical disinfectants.

The source of infection is children and adults with various diseases of staphylococcal etiology, as well as healthy carriers. Epidemiological danger is posed by children and adults with acute and chronic diseases of the upper respiratory tract, oral cavity and lungs (tonsillitis, pharyngitis, rhinitis, adenoiditis, sinusitis, periodontitis, tracheitis, tracheobronchitis, pneumonia), purulent diseases of the skin and subcutaneous tissue (pyoderma, furunculosis, phlegmon, subcutaneous abscesses) and others.

Staphylococcus does not spread independently in nature. Infection of external environmental objects depends exclusively on contact with the source of infection. Depending on the localization of the focus, staphylococcus

[15] Alemu, B. K., Azeze, G. G., Wu, L., Lau, S. L., Wang, C. C., & Wang, Y. Effects of maternal probiotic supplementation on breast milk microbiome and infant gut microbiome and health: a systematic review and meta-analysis of randomized controlled trials. American journal of obstetrics & gynecology MFM. 2023. 5(11). P. 301-323. AJOC MGM. doi: 10.1016/j.ajogmf.2023.101148. Epub 2023 Sep 1.

can be released into the external environment with sputum, mucus from the upper respiratory tract, breast milk, amniotic fluid, urine, vapors, secretions of inflammatory elements of the skin, subcutaneous tissue, middle ear, etc.

Staphylococcal diseases in children can occur as a result of exogenous and endogenous infection. Infection occurs in the following ways: airborne (when talking, coughing, sneezing); airborne (in a room with insufficient ventilation, poor cleaning quality); contact (direct contact with a patient or a carrier of bacteria, through dishes, toys, underwear ...); alimentary (infection of food products, breast milk with staphylococcus); intrauterine infection (a disease of pregnant women, then penetration occurs through amniotic fluid entering through the skin, mucous membranes of the mouth, digestive canal, airways, in case of violation of the integrity of the placenta − hematogenously); autoinfection route (transition of staphylococcus carriage into the disease) [16].

Immunity after suffering staphylococcal diseases is unstable. In the mechanism of development of immunity, both the formation of antimicrobial antibodies and antitoxic antibodies are important. In the mechanism of development of diseases caused by staphylococcus, the most important is the state of reactivity of the child's body and the biological features of the pathogen, capable of producing toxins, enzymes and other biologically active substances.

The main products of the vital activity of Staphylococcus aureus are toxins, which, depending on the characteristics of the action on tissues and systems of the body, have received the following names: necrotoxin (causes necrosis, suppuration in tissues, as well as vascular thrombosis); fibrinolysin (contributes to the separation of emboli from blood clots, which are complete foci of infections); lethal toxin (destructively affects individual tissue elements, causes deep reflex disorders); dermonecrotoxin (inflammatory seals on the skin, accompanied by necrosis); staphylolysins or hemolysins (destroy erythrocytes); enterotoxin (causes gastroenterocolitis). In addition to the toxic effect of staphylococcus, it causes sensitization of the body due to the presence of an allergic component in staphylococcal toxin, it also has a denaturing effect on tissues that acquire autoantigenic properties.

Of the enzymes secreted by staphylococcus in the process of its vital activity, the following are of greatest importance: fibrinolysin (separates emboli from blood clots), hyaluronidase (has a destructive effect on mucopolysaccharide – hyaluronic acid, the basis of connective tissue), coagulase (coagulates blood plasma, participates in the formation of the primary inflammatory focus), lecithinase (is important for the reproduction of staphylococcus, as well as the

[16] Mingot-Ascencao, J. M. Search and selection of probiotics that improve mucositis symptoms in oncologic patients. A systematic review. Nutrients. 2021. 11(10). P. 2322. https://doi.org/10.3390/.

ability to increase the permeability of the cell wall), penicillinase (reduces the therapeutic effect of penicillin and ampicillin) [17].

The modern diet is dominated by simple carbohydrates, trans fats, sodium chloride, and there is insufficient consumption of fiber, omega-3 fatty acids, etc. An unbalanced diet, together with lifestyle factors such as low physical activity, smoking, and alcohol abuse, has led to a sharp increase in diseases called "diseases of civilization." These include atherosclerosis (which has recently become much younger and is already quite common in children), type 2 diabetes (which is defined as a threat to the continued existence of humanity), arterial hypertension, osteoporosis, and other chronic non-communicable diseases. Staphylococcus is also able to produce other biologically active substances. Thus, in the mechanism of the disease, an important role belongs to staphylococcal anticoagulant, which prevents normal blood clotting; staphylococcal hemagglutinin (affects erythrocyte agglutination). Antiphagin formed by staphylococcus, which has the ability to delay phagocytosis, plays a role in the development of the disease[18]. The following points are important in the pathogenesis of various clinical variants of staphylococcal diseases:

1) the mass of infection with Staphylococcus aureus;

2) localization, activity and long course of the primary focus, which determines the possibility of hematogenous spread of staphylococcus in the body;

3) the state of immunobiological reactivity, which determines the severity of the body's reaction to the invasion of staphylococcus.

The main clinical forms, taking into account the role of all the above factors, as well as clinical data, it is appropriate to distinguish the following types of staphylococcal infection [19]:

1) Staphylococcal sepsis: acute, prolonged, chronic. This is a general infectious process in which microbes and their toxins constantly or periodically enter the blood (or lymphatic channels) from the local (primary) focus, are carried with the blood flow and settle in the tissues of various organs and systems.

2) Focal infection, which occurs with persistent staphylococcemia, but without clinical signs of sepsis. Foci of staphylococcal infection are found in

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[17] Li J., Jia H., Cai X., Zhong H., Feng Q., Sunagawa S., et al. An integrated catalog of reference genes in the human gut microbiome. Nat Biotechnol 2014. 32. P. 834–841. doi: 10.1038/nbt.2942. Epub 2014 Jul 6. PubMed PMID: 24997786.

[18] Iqbal S., Quigley E.M. Progress in our understanding of the gut microbiome: implications for the clinician. Curr Gastroenterol Rep 2016. 18. P. 49. doi: 10.1007/s11894-016-0524-y. PubMed PMID: 27448618.

[19] Hill C., Guarner F., Reid G., Gibson G.R., Merenstein D.J., Pot B., et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 2014. 11. P. 506–514. doi: 10.1038/nrgastro.2014.66. Epub 2014 Jun 10. PubMed PMID: 24912386.

the lungs, kidneys, gallbladder, tonsils, lymph nodes, paranasal sinuses, and middle ear. This group of diseases includes: pneumonia, sinusitis and rhinitis, mesotympanitis, cholecystoangiocholitis, pyelonephritis, tonsillitis, which are often accompanied by allergic neurodermatitis, bacterial eczema.

3) Focal infection accompanied by transient staphylococcemia. It is observed in acute or aggravated diseases of staphylococcal etiology: acute pneumonia, tonsillogenic intoxication, pyelonephritis, enteritis, enterocolitis, acute mesotympanitis.

4) Focal staphylococcal infection without staphylococcemia. It is characterized by moderately pronounced signs of chronic intoxication. Staphylococcus is localized in the tonsils, middle ear, nasal passages, larynx and trachea, bronchi, paranasal sinuses, gallbladder, affected areas of the skin, mucous membranes. This includes chronic tonsillitis, adenoiditis, recurrent otitis, laryngotracheitis, bronchitis, rhinitis, sinusitis, minor forms of staphylococcal diseases.

5) Staphylococcus carriage. There are no symptoms of intoxication. Staphylococcus aureus is often found on the unchanged mucous membrane of the nasal passages and pharynx. It is observed in 30-50% of cases in healthy people. The most common antimicrobial substances of higher plants are the works of Osborne, who studied 2300 species of plants, and found antibacterial activity in only 160 species belonging to 63 genera.

Antimicrobial substances were most often found in buttercups, the antibacterial activity of which could depend on the presence of protoanemonin in them. Then came the liliaceae, which include onions and garlic, rich in allicin or compounds close to it. The most sensitive to antibacterial substances of plant origin were Gram-positive microorganisms, less sensitive − Gram-negative. Antimicrobial substances are represented in plants by a wide variety of compounds. The most common, that is, those that occur most often, will be presented below [20].

Essential oils of different plants are not individual chemical substances. They include carbohydrates (aliphatic and aromatic), mono- and polycyclic terpenes and sesquiterpenes, alcohols, their esters, aldehydes, phenols and phenolic esters, ketones, organic acids, sometimes lactones, etc. Nevertheless, each essential oil has its own characteristics. Literature data indicate that almost all essential oils have more or less pronounced bacteriostatic properties. In particular, the most active essential oils against staphylococci were: Ol. Acorus calami (dilution 1:5000), Ol. Artemisia absinthii (1:1000), Ol. Carum carvi (1:2000), Ol. Cinnamonii (1:8000), Ol. Eucalypti (1:4000), Ol. Ferula sp.

[20] Floch M.H., Walker W.A., Sanders M.E., Nieuwdorp M., Kim A.S., Brenner D.A., et al. Recommendations for probiotic use. 2015 update: proceedings and consensus opinion. J Clin Gastroenterol 2015.49. P. 69–73. doi: 10.1097/MCG.0000000000000420. PubMed PMID: 26447969.

(1:1500), Ol. Thymus polessicus (1:10000 – 1:25000), Ol. Valerianae nitidae (1:2500 – 1:5000), Ol. Cannabis sativa (1:50000 – 1:100000) and others [21].

It is possible that the use of antimicrobial substances also takes place in the food industry, since many spices contain antibacterially active essential oils (ginger, nutmeg, cinnamon, marjoram, laurel, allspice, cloves, coriander, anise...). Balsams and resins are also not individual substances, but mixtures. Balsams with antibacterial properties include the Peruvian, Copaiba, Toluan balsams and styrax, known since ancient times. Resins (resin acids) with antimicrobial properties include resins from Balsamea Myrrha and Styrax benzoin, which contains benzoic and cinnamic acids.

Organic acids are found in large quantities in higher plants. Antimicrobial properties are possessed by haulmugrovy and hydnokarpov, as well as usnic and gallic acids. Tannins, in particular tannin and gallic acid, have been used as antiseptics since ancient times. Many literary sources indicate that the antimicrobial properties of a number of plants are due to the presence of tannins in them, in particular, such plants are thick-leaved badan, lingonberry, common yarrow, snakeroot, erect cinquefoil, scumpia, etc [22].

Thus, tannin exhibits a bactericidal effect in a dilution of 1:1000 – 1:5000, bacteriostatic − 1:20000 – 1:100000; pyrogallol in 1:2000 and 1:20000; hydroquinone in 1:500 and 1: 1000-2000; pyrocatechin in 1: 3500, respectively. Of the proteins, only one has been described as an antibiotic – purothionine, which is isolated from unbleached wheat flour. It is toxic not only to bacteria, but also to animals, and also inhibits the reproduction of Gram-positive bacteria. Alkaloids and glucosides exhibit the most pronounced antimicrobial effect among all plant substances. In particular, piptanin, isoamodendrin, anabasin, hatinin, glaucine, delphonin, taspin, spherophysin, harmine, etc. have a pronounced effect on staphylococci.

3. Antimicrobial substances from plants of certain families and their effect on bacteria of the genus Staphylococcus

From plants of the conifer family (Coniferales), the following antibiotics are found: pinosylvin (isolated from Pinus silvestris wood), inhibits the growth of Staphylococcus aureus at a dilution of 1:10,000-20,000; thujaplicin (wood of Thuja plicata and Thuja ocidentalis) at a dilution of 1:32,000; aqueous and alcoholic extracts from juniper berries inhibit the growth of

[21] Bäckhed F., Fraser C., Ringel Y., Sanders M.E., Sartor R.B., Sherman P.M., et al. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. Cell Host Microbe 2012. 12. P. 611–622.

[22] Lau C.S., Chamberlain R.S. Probiotics are effective at preventing Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Int J Gen Med. 2016. Feb 22 9. P. 27–37.

Staphylococcus. From the family of cereals (Gramineae), antibacterial activity against Staphylococcus was demonstrated by extracts of corn leaves, as well as substances isolated from wheat, one of which resembles a fatty acid, acting at a dilution of 1:250,000; another of a protein nature − purothionine, at 1:20,000.

Puhiin from the Cyperaceae family, as well as an extract of the flowering plant Tillandsia usneoides from the Bromeliaceae family, inhibit the growth of Staphylococcus aureus. Plants of the Liliaceae family are known for such an antibiotic as allicin, which has a broad spectrum of action, its bacteriostatic concentration relative to staphylococcus is 1:45,000-125,000. Its derivatives have a similar effect. From Allium sativum, sativin and defenzoate were isolated, which at a dilution of 1:1,000-1,600 inhibit the growth of St. aureus and St. albus, as well as alizarin, which is detrimental at a dilution of 1:50,000. From Allium odorum, odorin was isolated, which has an antibacterial effect on Staphylococcus aureus. Methylenebutyrolactone isolated from Erythronium americanum and essential oil of wild garlic juice (Allium ursinum) act on staphylococcus at a dilution of 1:2000 [23].

From oak (Quercus tinctoria) of the beech family (Fagaceae), the flavone pigment quercetin was isolated, which is active at dilutions of 1:10000-13000. From hops of the hemp family (Cannabiaceae), humulone and lupulone were isolated, which are active on staphylococcus at a dilution of 1:30000-50000 and 1:400000-650000, respectively. Cansatin isolated from hemp (Cannabis sativa) inhibits the growth of St. aureus at a dilution of 1:10000-40000. The alkaloid substance that affected the growth of St. aureus in a 1:50000 dilution from water pepper (Polygonum hydropiper) from the buckwheat family (Polygonaceae) [24].

The effect of a very large number of plant extracts from different families on bacteria of the genus Staphylococcus has been studied. Thus, the antimicrobial activity of flavonoids and their mixtures isolated from some species of flowering plants was reported. They found that some isoflavones (osain, genistein) and flavones (quercetin, diosmetin) have antibacterial activity against spore cultures and staphylococci. Later, they conducted studies of decoctions, alcohol extracts and individual fractions containing various biologically active compounds, including polyphenolic ones.

The greatest activity against all studied crops was shown by a decoction of the aerial part of Centaurea orientalis, Vicia truncatula, Alcea angulata, Malva neglecta, Scutellaria polyodon; inflorescences or flowers of Hibiscus syriacus,

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[23] Haznedaroglu M.Z., Karabay N.U., Zeybek U. Antibacterial activity of Salvia tomentosa essential oil. Fitoterapia 2001. Nov 72(7). P. 829−831.

[24] Hossain M.M., Paul N., Sohrab M.H., Rahman E., Rashid M.A. Antibacterial activity of Vitex trifolia. Fitoterapia 2001. Aug 72(6). P. 695−697.

Forsythia intermedia, Mimosa biuncifera; from the fruits of Feijoa selloviana, Maclura pomifera; from the bark of the stems and leaves of Forsythia intermedia [25].

It turned out that in some cases the antibacterial effect can be enhanced by the presence of flavonoids and phenolic acids. For example, Ocnothera species contain hyperoside, which is easily hydrolyzed during the processing of raw materials with water or alcohol with the release of quercetin. It is active against staphylococci and spore cultures. It is also known about the high antibacterial activity of the isoflavone osain, which is contained in the fruits of Maclura pomifera. It turned out that alcoholic extracts from fruits also inhibit the growth of staphylococci and some bacilli [26]

Regarding Staphylococcus aureus and other microorganisms, it turned out that all the plants studied contained antibacterial substances. In most cases, the most active were phenolic and acidic fractions. However, in marsh marigolds and celandine, the most active were the fractions of basic and neutral substances. In sage and mountain ash, substances with sodium bicarbonate were isolated, which inhibited the reproduction of Staphylococcus aureus in a dilution of 1:200,000-250,000. Extremely high antibacterial activity (1:2,500,000-5,000,000) was found in acidic substances of St. John's wort. Yarrow, lingonberry, marsh marigolds showed quite high antimicrobial activity [27] [28].

The antibacterial activity of the vast majority of the studied substances decreased in the presence of 10% blood serum. The latest data on this issue will be presented below: Centipeda minima (Asteraceae). Sesquiterpene lactones: 6-0-methylacrylylplenolin, 6-0-isobutyroylplenolin, 6-0-apgeloylplenolin. Used in Nepalese medicine for sinusitis. Active against Bacillus subtilis and Staphylococcus aureus. Avena sativa L.s. Cultivated oat (Poaceae). In vitro: stimulates the release of IL-1, induces the production of IL-2, IFN-4 and secretion of IL-4 dose-dependently in the culture of splenocytes of mice. Increases the nonspecific resistance of animals to infection with Staphylococcus aureus. Chromolaena moritziana (Asteraceae). Dichloromethane and aqueous extract of leaves, ethyl acetate extract of flowers. Used in Venezuela as an anti-inflammatory and cleansing agent for the treatment of skin diseases. Active

[25] Lis-Balchin M., Buchbauer G., Ribisch K., Wenger M.T. Comparative antibacterial effects of novel Pelargonium essential oils and solvent extracts. Lett Appl Microbiol 2008. Sep 27(3). P. 135−141.

[26] Mandal S.C., Nandy A., Pal M., Saha B.P. Evaluation of antibacterial activity of Asparagus racemosus willd. root. Phytother Res 2000. Mar 14(2). P. 118.

[27] Saeed M.A., Sabir A.W. Antibacterial activity of Caesalpinia bonducella seeds. Fitoterapia 2001. Nov 72(7). P. 807−809.

[28] Shrimali M., Jain D.C., Darokar M.P., Sharma R.P. Antibacterial activity of Ailanthus excelsa (Roxb). Phytother Res 2001. Mar 15(2). P. 165−169.

against Staphylococcus aureus. Flavonoids have been identified: kaempferal, 3-0-kaempferal rutinose, rutin, isoquercetin, triterpene L-amyrin [29].

Mutisia acuminata (Asteraceae). Methanolic and aqueous extracts. Active against Staphylococcus aureus, Bacillus subtilis (Catalano S). Ephedra transitoria (Ephedraceae). Quinoline alkaloid transtorine from the aerial part − 4-quinoline-2carboxylic acid. Inhibits the growth of Enterobacter cloacae, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus. Eutrema wasabi , Wasabia japonica (Cruciferae). The ether extract of the stems − 6-methylsulfinylhexyl isothiocyanate and its analogues. Active against Escherichia coli, Staphylococcus aureus. Entada abyssinica, Terminalia spinosa, Ximenia caffra, Azadirachta indica, Harrisonia abyssinica, Spilanthes mauritiana (Fabaceae, Combretaceae Olacaceae, Meliaceae, Asteraceae). Extracts of the bark of the trunk, young branches, roots, leaves have antibacterial activity against staphylococci. MIC_{50} − 0.13-8 mg / ml; MIC_{90} − 0.5->8 mg / ml; MBC_{50} and MBC_{90} − 0.5-8 mg / ml [30].

Micromeria nervosa, Inula viscose, Ruscus aculeatus, Phagnalon rupestre, Ziziphus spina-christi (Asteraceae, Rhamnaceae). Alcoholic and aqueous extracts are active against Staphylococcus aureus, Esherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris, Candida albicans. Allium sativum (Alliaceae). Turbidimetric method established antimicrobial activity of garlic against all tested microorganisms that can be transmitted through food: Staphylococcus aureus, Streptococcus typhi, Esherichia coli and others. Thus, garlic is recommended for extending the shelf life of semi-finished products. Piper gibbilimbum. Alkeninphenols, gibbilimbole are cytotoxic for nasopharyngeal carcinoma cells. All exhibit antibacterial activity against Staphylococcus epidermidis and Bacillus cereus.

Melaleuca. Essential oil has antimicrobial activity against Staphylococcus aureus, Escherichia coli (Fasagali Jt). Commiphora tenuis Vollensa (Ethiopia). The essential oil of the bark exudate contains in the monoterpenoid fraction α-pinene (60.8%), β-pinene (8.8%), sabinene (6.3%), α-thuene (8.8%), mononene (5.5%) 3-carene (3.7%), β-myrcene (1.8), β-elemene (1.1%) α, β, γ-identified sesquiterpene components. The main triterpene component is omenolic acid acetate and 3 more triterpenes (oman-12-ene group). It has antibacterial activity against Staphylococcus aureus, Protey mirabilis, Escherichia coli (MIC 0.5-1%) (Asres K).

Viscum capense (Loranthaceae). Inhibits the growth of Staphylococcus aureus. Pelargonium sp. (Geraniaceae). Essential oil from the leaves is a promising

[29] Пасальський Б.К. Хімія харчових продуктів: НП. Київ. Держ.торг.-екон.ун-т, 2000. 196 с.

[30] Ластухін Ю.О. Хімія природних органічних сполук. Навчальний посібник: Л: Нац. ун-т «Львівська політехніка»; Інтелект-Захід, 2005. 560 с.

antibacterial agent for cosmetology. It has a pronounced antibacterial activity against Staphylococcus aureus, Staphylococcus epidermidis. The activity of the methanol extract and the extract with petroleum ether is greater than the oil obtained by steam distillation (Lis-Balchin M). Caffeae Beverage. The acid extract is highly active against Staphylococcus aureus and Streptococcus mutens 9102.

Anethum lavlolens, Acorus gramineus (Umbelliferale, Araceae). The hexane fraction of methanol extracts significantly reduces the manifestation of antibioticresistance of multi-resistant Staphylococcus aureus (when tested against ampicillin and chloramphenicol). The active substance is carvone isolated from Anethum lavlolens. The active substance from Acorus gramineus is a liquid mixture containing phenylmethyl ester of benzoic acid (benzyl benzoate). They at a concentration of 20-50 μg/ml reduce antibiotic resistance when co-incubated with 100 and 50 μg/ml Amk and Lev, respectively.

Alichrysum trilineatum (Asteraceae). Pinocymbrin balcony has antimicrobial activity against Staphylococcus aureus. Lycoperricon esculentum, Tomato (Solanaceae). Oil extract of fruit pulp has a wide spectrum of antimicrobial activity against gram-positive and gram-negative microorganisms and fungi of the genus Candidis (Enterobacter, Streptococcus, Staphylococcus, Klebsiella, Esherichia − clinical strains. Antimicrobial activity is associated with a complex of organic acids (oxalic, citric, tartaric, etc.). Cryptostegia grandiflora (Asclepiadaceae). Leaf extract has pronounced activity against St. aureus NCIM-2492, E. coli NCIM-2345, Bac. subtilis NCIM-2349, Bac. coagulans NCIM-2323. Paulownia tomentosa. Butanol extract of branches has antibacterial activity against St. aureus (sg 511,285,503), Str. pyogenes (A 308, A 77), Str. Faecium MD 8v. The most active is campneoside (MIS-150 μg/ml). It has been established that the methoxy group in its molecule plays an important role in the manifestation of antibacterial activity.

Wedelia trilobata – ethyl acetate extract is active against Bac. subtilis, Myc. smegmatis, St aureus, St. epidermidis, Pr. vulgaris, Ps. aeruginosa, Salmonella grav C, S. paratyphi, Sh. Sonnei. Hypericum perforatum (Hypericaceae). Hyperforin (triterpene) is active against multidrug-resistant St. aureus and gram-negative bacteria (Schempg CM). Mitracarpus scaber. The alcohol extract of the aerial part of benzo-γ-soquinoline-5,10-dione is maximally active, exhibits well-defined antimicrobial activity, including against AIDS-associated microorganisms (Bac. subtilis, C. albicans, Cript. neoformans, M. avium, St. aureus). Camellia sinensis. The components of the extract reverse the methicillin-resistant staphylococci. The morphological changes are based on selective inhibition of penicillin-binding proteins.

Baccharis dracunculifolia The leaf secret, which serves as a source of bee glue − propolis, has antibacterial activity against St. aureus, C. albicans. Buddleja

cordaba Verbascoside. By studying the kinetics of killing and incorporation of labeled precursors, a lethal effect on St. auricus was established. It is based on the effect on protein synthesis and a decrease in the incorporation of leydin in. Byrsonima crassifolia – ethyl acetate extract of the roots is maximally active against Pl. pneum, Ps. aerugin, S. typhi, Sh. flexneri, St. aureus, St. epidermidis, Str. pneumonica, M. luteus.

Senecio graveolens (Asteraceae). The essential oil contains valeric aldehydes: α-pinene, α-phellandrene, α-terpinene, P-cymene, sabinene, γ-terpinene, terpinolene, 1-methyl-4-isopropylbenzene, ter-pinen-4-ol, piperpenone, α-β-eusemol. It has antimicrobial activity against M. Luteus ATCC 9341, St. aureus, as well as clinical isolates of C. Albicans.MIC – M. Luteus 8.73*10-2 mg/ml; MIC – St. aureus $10.91*10^{-2}$ mg/m; MIC – C. Albic. $2.3*10^{-2}$ mg/ml.

Dios pyros mespiformis (Ebenaceae). Crude extracts have a wider spectrum of activity against gram-positive and gram-negative microorganisms, some strains of fungi. The maximum activity is in the chloroform extract of the roots, some of the studied extracts are sensitive to strains of St. aureus and strains of Ps. aeruginosa. Clove (Alliaceae). The extract has bactericidal activity: after 1 h. exposure kills 93% of Staph. epidermidis; 93% killing of S. tiphi is achieved after 3 h; complete killing of Candida is achieved after 5 h. with clove and after 1 h. with garlic.

Piper betle Leaf extract (ethyl acetate, ethanol) has a pronounced antimicrobial activity (disk method) against St. aureus, Str. pneumonica, Kl. aerogenes. Combretum erythrothyllum Antimicrobial activity against St. aureus, Ent. faecalis, E. coli, Ps. aeruginosa. Psidium guajava. Aqueous leaf extract exhibits antimicrobial activity against St. aureus (9 different strains) − in wells, disk method and turbidimetric. Complete inhibition of growth of all strains − 6.5 mg / ml. Eysenhardtia texana Flavanones from the aerial part are active against St. Aureus. Hypericum papuanum. Petroleum ether extract of the aerial part has antibacterial activity against Bac. cereus, St. epiderm, Microc. luteus. Sophora flavescens. Significant antibacterial activity against gram-positive bacteria − St. aureus, Bac. Subtilis, St. epidermidis, Propionibacterium acne. Mikania micrantha 2 sesquiterpenoids − micanolides are used in Jamaican folk medicine, active against St. aureus and C. albicans. So, as can be seen from a large number of studies by scientists from different countries of the world, plants deserve great attention regarding antimicrobial activity. That is why it is very important to reveal their various properties that are still unknown to us.

The presence of antibiotic properties in 40%, 70%, 90% ethanolic and acetone extracts of plants common in the Ciskarpattia and Carpathian regions was tested on clinical strains of aureus, epidermal, hemolytic and other coagulase-negative staphylococci. For comparison, a number of tinctures

and antiseptic preparations that are already widely used in medicine were studied [31] [32].

Significant inhibition of the growth of St. aureus and St. epidermidis was observed only under the influence of biologically active substances of Grindelia raschepirena (n/h), Biota orientalis (leaves and fruits) and Siversia montane. At the same time, the zones of growth inhibition of St. epidermidis were larger compared to Staphylococcus aureus. The sensitivity of Staphylococcus aureus strains to the studied drugs was individual and did not depend on the level of their antibiotic resistance. The antibiotic-sensitive strain of Staphylococcus epidermidis was characterized by higher sensitivity to extracts of mugwort, black dropsy, and comfrey than antibiotic-resistant strains [33].

Of the 70% ethanol extracts, the biologically active substances of snake gourd and white willow showed the greatest activity. The sensitivity of strains of both types of staphylococci was similar. The strain of Staphylococcus aureus, sensitive to antibiotics, also showed weak sensitivity to some other extracts, in particular, hemlock, orange-red, and soft marigold. The antibiotic-resistant strain of St. epidermidis showed individual sensitivity to hemlock. Resistant strains did not show special sensitivity to 70% ethanol extracts. In this case, strains of epidermal Staphylococcus aureus were less sensitive to antimicrobial substances of plant origin than strains of aureus, which is not entirely characteristic of it, since in other studies Staphylococcus epidermidis shows greater sensitivity.

Strains of different types of staphylococci throughout the study period showed different sensitivity both to plant extracts and to drugs. Among the pharmaceutical preparations, peppermint tincture showed the greatest activity, it had the best effect on strains of golden and epidermal staphylococci. Strains of Staphylococcus hominis and Staphylococcus haemolyticus turned out to be quite resistant to the action of biologically active substances of plant origin. Perhaps this is due to the fact that they were mainly clinical, therefore they acquired high resistance upon contact with the human body [34] [35] [36].

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[36] Ерін Ловелл Веріндер Сила трав. 2025. Київ: Сварог. 288 с.

CONCLUSIONS

They have been talked about for 30 years, but the debate has not subsided yet, and opinions are just as opposite and categorical. Opposing views usually arise because people cannot figure out this problem themselves. There is a lot of information, but it depends on who provides it, what goal they are pursuing, and what opinion they want to impose on the consumer. Many people do not trust dietary supplements because they doubt the quality of these products. Many manufacturers today cannot provide this data in full. As a result, the consumer does not know where he can get objective information. Often it is simply inaccessible, since it is found in special journals, little-known methodological developments, and legislative acts. Relatively recently, the situation with dietary supplements in our country has changed seriously. A clearly developed legislative framework regulates all aspects of the development, certification, clinical trials, and distribution of dietary supplements. If you get acquainted with this information, with data on the clinical effects of the use of dietary supplements and their distribution in the world, you may change your attitude towards them. Biologically active additives (BAD) are natural or identical to natural biologically active substances obtained from plant, animal or mineral raw materials, as well as, but much less often, by chemical or microbiological synthesis. They can be included in the composition of food products, beverages, or used independently in various forms, in order to provide the human body with the necessary amount of essential nutrients (complete proteins or individual amino acids and their complexes, polyunsaturated and fatty acids, phospholipids, vitamins, minerals). Biologically active additives appeared in Ukraine relatively recently, about 10 years ago. But today, more than 200 companies producing biologically active additives offer their products to the population of Ukraine. Possessing such an arsenal of dietary supplements, a doctor can introduce them into a diet or rational nutrition to optimize metabolic processes and functions of the human body, taking into account the state of his health. Biologically active additives are divided into 3 main categories: nutraceuticals, parapharmaceuticals and eubiotics. Nutraceuticals − dietary supplements are used to correct the chemical composition of food. Nutraceuticals are indispensable nutrients or their close predecessors. The use of nutraceuticals in the daily diet of sick and healthy people allows: − to easily and quickly eliminate the deficiency of essential nutrients, which are ubiquitously found in the majority of the adult and child population of Ukraine; − to maximally take into account the individual needs of a particular person in their nutrition, which differ significantly not only by age, gender, intensity of physical activity, but also due to genetically determined features of the metabolism of an individual, his biorhythms, environmental conditions of the

region of residence, physiological states (pregnancy, psycho-emotional stress, etc.); − to maximally ensure the changed physiological needs for nutrients of a sick person, bypass the areas of metabolic pathways damaged by the disease, and sometimes − to correct them; − by strengthening the protective elements of cellular enzyme systems, to increase the general, non-specific resistance of the body to the action of adverse environmental factors in the population living in both ecologically clean and ecologically disadvantaged regions; − primarily affect enzyme systems, purposefully change the metabolism of certain substances, in particular, xenobiotics, as well as enhance and accelerate the binding and excretion of foreign and toxic substances from the body. The use of nutraceuticals is an effective means of prevention, as well as additional (and sometimes primary) treatment of patients with widespread chronic vascular diseases, malignant neoplasms, immunodeficiency states, diseases of the gastrointestinal tract, degenerative diseases of the musculoskeletal system.

Parapharmaceuticals − dietary supplements are used for prevention, adjuvant therapy and support of the functional activity of organs and body systems. These are, as a rule, products containing minor food components – bioflavonoids, organic acids, glycosides, biogenic amines, regulatory oligopeptides, polysaccharides, oligosaccharides, etc. They have a wider range of doses than drugs, at which they exert their normalizing or correcting effect on the functions of individual organs and systems of the human body with a significantly lower probability of manifestation, in comparison with drugs, of toxic and side effects. Parapharmaceuticals are most often sources of natural food components, in most cases, do not have nutritional value, however, due to the fact that they are able to gently regulate the functions of individual organs and systems, these food components should also be considered as indispensable nutritional factors. Eubiotics (probiotics) are dietary supplements that contain living microorganisms and normalize the intestinal microflora.

The widespread use of biologically active additives, not only of the nutraceutical but also of the parapharmaceutical series, is an attempt at a new turn in the spiral of human development to once again come into harmony with nature and significantly expand its adaptive abilities in conditions of the constantly increasing impact of technogenic and socio-stressor factors. According to statistics, 70% of the population of developed countries regularly use dietary supplements. And this is not due to a new fashion, aggressive advertising or mass deception of gullible consumers. Dietary supplements could not fail to appear. The main reason for this was the "social order" − the desire of people to live a healthy life. Quitting smoking and strong alcoholic beverages, mass sports enthusiasm – all this was actively stimulated and competently regulated until it became a policy of society. But the main thing is that the population's health

indicators have really increased. For example, population health is regulated at the government level. According to very approximate data, in Ukraine, dietary supplements are still regularly used by no more than 5% of the population. However, for us, the use of these products is much more relevant than for the countries of Western Europe and America. The reasons are clear: unfavorable ecological situation, low standard of living, not always accessible medical care. For low-income people, dietary supplements can become the main way to maintain some minimum "level of health". The main principles of using food BAD: principle of: systematicity and functionality; phasing; adequacy; optimal doses; combination; syndromic principle; biorhythmological principle.

The above principles are closely intertwined and provide an opportunity to more deeply understand the place and role of correcting the chemical composition of diets using dietary supplements in order to optimize the biological action of the nutritional factor in complex therapy. The principle of systematicity and functionality must take into account that in the body there is a close relationship between the state of nutrition and the regulation of tissue catabolism and the work of regulatory systems, primarily the central nervous system. Research results indicate hierarchical connections between the hypothalamic-pituitary system and the endocrine apparatus of the duodenum and the pancreas. It has also been proven that when using certain agents that suppress the excitability of the nervous system, suppression of the functions of the immune system is observed, while stimulants of the nervous system simultaneously contribute to the increase in the function of the immune system.

Such a close relationship between the body's systems requires deep knowledge of the mechanism of action of each of the dietary supplements used in the prevention or treatment of diseases. Thus, the above provides grounds for a broader understanding of the function of diet therapy and, in particular, not only as a carrier of energy, but also as a means of high biological action on various links of metabolic processes. This is especially true of micronutrients of plant origin, which are a component of many biologically active food additives. Skillful use of the latter in order to achieve a balanced diet will contribute to the optimization of preventive and therapeutic measures, and any scientifically unfounded use of them can contribute not only to disappointment, but also to negative consequences.

The daily energy expenditure of a modern person is significantly lower than in the past. Therefore, the structure of nutrition is characterized primarily by a significant decrease in the energy value of the daily diet. Thus, according to calculations using computer modeling, the energy expenditure of an ancient person – a primitive adult hunter – amounted to 5-6 thousand kcal per day. In the early period of the development of cattle breeding and agriculture, the energy

expenditure of an adult person amounted to about 4 thousand kcal. Currently, the energy expenditure of the adult population is approximately 2 thousand kcal. In turn, this leads to the consumption of a reduced volume of food. Such a diet cannot fully satisfy the needs of the human body in micronutrients, which, according to some sources, is about 600 items. Especially if, when compiling food rations, you limit yourself to calculating only the "big four": proteins, fats, carbohydrates and calories. Free access to simplified computer programs, which have become household names for "calorie calculators", contributes to the spread of unbalanced diets among the population in terms of micronutrient composition. Deficiency of nutrients and biologically active components in the diet reduces the body's resistance to harmful environmental influences, causes immunodeficiency states, and disrupts the functions of antioxidant defense systems.

SUMMARY

The characteristic feature of the Ukrainian parapharmaceutical market is the tendency to increase the already wide range of domestic and foreign-produced goods. There is a competitive struggle for the sales market between foreign and domestic manufacturers. The former have significant financial resources to carry out work on promoting products; the latter, as a rule, lose in the competition for potential buyers due to the policy of foreign firms that use aggressive advertising, "non-advertising" means of promotion, various promotions and bonuses. Therefore, in Ukraine, there was a need for state intervention in the issue of regulating prices for the main parapharmaceuticals of foreign and domestic manufacturers. It was found that 60% of specialists supported the issue of the need to revise regulatory documents to regulate prices for parapharmaceutical products; 30% of specialists had a pessimistic view: the development and implementation of regulatory documentation, in their opinion, will not lead to significant changes in the situation that has developed on the country's parapharmaceutical market, and 10% of respondents noted that the documents do not need to be revised at all. Most respondents noted that the financial crisis for some time slowed down the processes of development and modernization of distribution companies due to a decrease in consumer demand and giving preference to medicines. Solving the problem of forming the assortment of parapharmaceuticals remains one of the priority areas of work of distributors and pharmacies. The high level of awareness and culture of the population determines the relevance of the task of further expanding the pharmacy assortment through the arrival of new parapharmaceuticals.

The parapharmaceutical market in Ukraine began to form in 1990–1997, actively developed in 1997–2004, and this process continues to this day.

Currently, its active formation is due to the arrival of new parapharmaceutical products (for hair care, facial skin care, products for athletes, for infant care, etc.). According to consumer data, the range of products that are most often purchased in pharmacies has been established. The main factors in product selection: safety, effectiveness and price. The lack of complete and truthful information among 55% of respondents affects the formation of the stereotype about the medicinal properties of parapharmaceuticals, and only 45% of consumers know that these products are used only for prevention. Pharmacists record that 40% of consumers receive their basic information from medical representatives. The need to divide parapharmaceuticals into two parts (therapeutic and prophylactic and perfumery and cosmetic products) in a pharmacy was identified by the majority (58%) of respondents. 60% of the specialists noted that it is necessary to make adjustments to the regulatory documents regarding the advertising of parapharmaceuticals by manufacturers and distributors.

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