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MODERN CONCEPTS OF BIOLOGICAL ACTIVITY OF BROWN ALGAE PRODUCTS

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СУЧАСНІ УЯВЛЕННЯ ПРО БІОЛОГІЧНУ АКТИВНІСТЬ ПРОДУКТІВ З БУРИХ ВОДОРОСТЕЙ

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Summary/Резюме

Modern industrialization of agricultural production and excessive culinary processing of food products cause the loss of the necessary set of vitamins, microelements, and biologically active substances by the body. Existing and increasing anthropogenic ill-being — radioactive and chemical pollution of the environment, chronic psycho-emotional stress loads in combination with the absence of mechanisms for controlling the level of microelements and vitamins in the human body, require targeted intake of these compounds with food products. The solution to this problem is to use products that support health (FOSHU — Food for specified health use). One of the representatives of this group of products is products from algae, including brown seaweed. The article provides generalized data from available literature (Scopus Web of Science Crossref databases, etc.) on the unique composition of brown algae, the advantages of essential microelements and vitamins, as well as the presence of fucoxanthin, carotenoids, tannins, and analginic acid in high concentrations. The authors summarize the data on the biological effects of these compounds on the regulation and direct flow of vital processes in the bodies of humans and animals. The authors conclude that it is advisable to widely use brown algae products as nonspecific modulators in adverse conditions.

Key words: *brown algae, alginic acid, fucoxanthin, tannins, carotenoids, biological activity, non-specific modulators.*

Сучасна індустріалізація сільськогосподарського виробництва та надмірна кулінарна обробка харчових продуктів зумовлює втрату організмом необхідного набору вітамінів, мікроелементів та біологічно активних речовин. Існуючі та посилювані антропогенні неблагополуччя — радіоактивне та хімічне забруднення навколишнього середовища, хронічні психо-емоційні стресорні навантаження в сукупності з відсутністю в людському організмі механізмів контролю рівня мікроелементів та вітамінів, вимагають цілеспрямованого надходження цих сполук з продуктами. Вирішення цієї проблеми полягає у вико-

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ристанні продуктів, що підтримують здоров'я (FOSHU — Food for specified helth use). Одним із представників цієї групи продуктів є продукти з водоростей, у тому числі бурих морських водоростей. У статті наводяться опубліковані дані доступної літератури (бази даних Scopus Web of Science Crossref та ін) унікального складу бурих водоростей, про переваги есенціальних мікроелементів і вітамінів, а також наявності у високих концентраціях фукоксантину, каротиноїдів, танінів, анальгінової кислоти. Автори підсумовують наведені дані про біологічну дію цих сполук на регуляцію та безпосередній перебіг процесів життєдіяльності в організм людини та тварин. Автори приходять до висновку, що продукти з бурих водоростей доцільно широко використовувати як неспецифічні модулятори в несприятливих умовах.

Ключові слова: *бурі водорості, альгінова кислота, фукоксантин, таніни, каротиноїди, біологічна активність, неспецифічні модулятори.*

Introduction

The modern stage of human population existence is characterized by the growth of external adverse effects, including radioactive contamination and chemical contamination [1, 2], an increase in the share of production processes with harmful working conditions [3, 4], changes in the structure and quality of human nutrition [5].

Active industrialization of land use has led to the fact that plant products have lost a significant part of their nutritional properties due to the loss of the necessary set of macro- and microelements and vitamins [5]. Since humans have no mechanisms to control the level of microelement and vitamin deficiency, deficiency of these compounds is manifested only by symptoms of a specific disease, often incurable [6, 7].

The use of foods in the diet that do not provide the body with the necessary set and quantity of microelements and vitamins creates a nutritional imbalance, which leads to a reduction in life expectancy and an increase in mortality [8]. Excessive cooking, freezing of products for a long period, canning and lyophilization of them, as well as additional chemical ingredients lead to the destruction of vitamins and organic acids and the accumulation of poorly soluble toxins, phosphates and oxalates in the body, which negatively affects the health of an individual and the population as a whole [9]. In addition, it should be noted that changes in the quality of food products and associated changes in the activity of immune mechanisms are accompanied by the development of dysbacteriosis, i.e., changes in the quantitative and qualitative parameters of the normal microbiota of the human digestive tract [10].

This study aimed to analyze and summarize data on assessing the composition of food products from brown algae and their effect on the state of metabolism. It also sought to provide the bodies of humans and animals with essential microelements and vitamins. Such products are necessary to maintain the health of humans and animals and prevent the development of many pathological processes.

In connection with the need to correct the unfavorable impact of modern food products on human health and vital functions, at the end of the 20th century, the concept of products used to maintain human health (FOSHU — Food for specified health use) was formed, according to which food products are considered functional only if their positive impact on any human function is established, in addition to the usual nutritional effects [11, 12, 13].

Organization of special (preventive) nutrition for people working in unfavorable conditions, people leading a sedentary lifestyle, as well as people who have been using low-quality food products for a long time is aimed at enhancing the protective functions of the physiological barriers of the human body (skin; gastrointestinal mucosa; upper respiratory tract mucosa [14, 15], to restore biotransformation processes; remove toxic metabolites from the body, enhance the antitoxic function of the body [16].

The greatest attention in preventive nutrition is paid to products with a detoxifying effect; therefore, in recent years, special attention has been paid to products from seaweeds. This is because they can provide diets with such specific compounds as iodine-containing amino acids, phlorotannins, polysaccharides, and vitamins; in particular, they are characterized by a high content of vitamin E and vitamin B12 [17]. Acidic polysaccharides of brown algae (alginates) intensively bind and remove heavy metal salts from the body and do this better than many drugs used in medical practice [18].

Since in recent decades, the adverse impact of the external environment on humans and the decline in the quality of food products have tended to increase, the problem of compensating for the deficiency of microelements, vitamins, and macroelements in the products used with additives, including those based on algae, arises [19 — 21]. Compelling evidence is provided in favor of the fact that today, algae, including marine ones, are one of the alternative and promising traditional sources (their protein content ranges from 11 % to 32 % of dry weight). The presence of a unique amino acid composition and bioactive compounds makes them valuable for various diets in both preventive and rehabilitative aspects of use protein [22]. In addition, the cultivation and use of seaweed in production requires relatively minimal costs and does not worsen environmental problems.

However, to date, the issue of the influence of these products on the balance and interaction of different functional systems of the body (structural-metabolic-functional continuum) under physiological norms and pathological processes is not fully understood. There has been a significant increase in cardiovascular, gastrointestinal, endocrine, and oncological diseases globally [23 — 27].

One of the main reasons for the observed phenomenon is the increase in adverse environmental impacts on humans, changes in the structure and quality of nutrition, and deterioration in the quality of food products [28]. The latter has led to the cessation of meeting the human body's needs for macro- and microelements, vitamins, and minerals. This requires correction by introducing therapeutic and prophylactic products into the human diet containing the necessary macro- and microelements and vitamins [29]. Recently, researchers have turned their attention to ocean products since the oceans produce many biological compounds. Among all the inhabitants of the oceans, macroalgae and microalgae are the most prolific producers of such compounds [30]. Algae are divided into two types: benthic microalgae, found throughout the ocean, and macroalgae, common in the coastal zone; they are considered a source of the main bioactive macromolecules. Macroalgae, unlike land plants, do not have roots, leaves, or a vascular system and feed through osmosis with the surrounding water. Macroalgae are divided, depending on the pigment they contain, into green (pigment — chlorophyll), brown (pigment — fuchsin), and red (contain the pigments phycocyanin and phycoerythrin). Brown algae are a class of algae known for their olive green to golden brown color, which is due to the presence of large amounts of fucoxanthin and carotenoids in the chromatophores, the content of which exceeds the amount of chlorophyll a and c, which causes their brown color [31]. During the life process, brown algae produce numerous secondary metabolites. When consuming seaweed, these metabolites can make a significant contribution to the regulation of the vital activity of the whole organism [32, 33]. In addition, recently, data have been provided on seaweed products' antimicrobial, antioxidant, anti-inflammatory, and anticancer properties [20]. Depending on the morphology of brown algae, they are divided into:

1. Laminaria — has a sporophyte body (1-3 m) and a support attached to rocks;

2. Dictyota — has a dichotomously divided sporophyte thallus, sporangs that form 4 gametophyte spores.

3. Sargassum — a free-floating or attached form consisting of an attachment, the main body, and lateral parts.

4. Ectocarpus — a filamentous form attached by a prostatic part and a rhizoid.

5. Fucus — a leathery branched brown alga with rudiments on the branches. The

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most important pigments of brown algae are chlorophylls a, c1, c2, в-carotene, lutein, fucoxanthin, dioanthin, and violaxanthin. In addition, laminaran, mannitol, and some oils are determined in the cells of brown algae, and cellulose and alginic acid are found in the walls [34].

Let us consider the biological properties of brown algae components. Tannins are polyphenolic compounds found in marine and terrestrial plants. Phlorotannins are determined in brown algae, which differ from tannins of terrestrial plants in their simpler structure, resulting from the polymerization of phloroglucinol. Numerous studies have shown that phlorotannins improve sleep and have antibacterial, antioxidant, and algicidal effects [35, 36].

Fucoxanthin is a natural pigment of the carotenoid family. In brown algae, it is the most common xanthophyll. It is found in the chloroplasts of brown algae, giving them an olive-green or brown color. According to [37] fucoxanthin stimulates the burning of white adipose tissue by expressing thermogenin. In addition, fucoxanthin has been found to have a wide range of bioapplications, including antioxidant and anti-inflammatory activity [38]. Alginic acid and fucoidan are polysaccharides synthesized in brown algae. Alginates are polysaccharides of –l hyaluronic and 1.4-linked в-D-mannuronic acid. This hydrophilic colloidal polysaccharide is found in the cell wall and cytoplasm. Fucoidan is a sulfated cell wall polysaccharide that has anti-inflammatory and antioxidant activity. This may be due to their high degree of sulfation. In addition, fucus contains significant amounts of essential amino acids — lysine, proline, and glycine, which can be used by the body to create elastic fibers of connective tissue [39]. Data on the antitumor, antiviral, anti-inflammatory, and anticoagulant activity of alginic acid derivatives and fucans are provided [40, 41].

Laminaran is a polysaccharide that constitutes the substrate reserve of brown algae cells, accounting for up to 35 % of the dry mass of the algae. The polysaccharide chains of laminaran consist of в-glucose with random intrachain branches. There are 20 to 50 units of glucose molecules in a chain. It is believed that laminaran has a variety of biological effects [42]. One of the most promising areas of combating the tumor process today is considered to be the activation of apoptosis of neoplasm cells. The ligand (TRJZ), which is part of the kelp, activates the expression of tumor necrosis factor (TNF-б) and leads to the development of cancer cell apoptosis [43, 44]. Since chemotherapeutic agents extracted from natural resources have fewer side effects than classical chemotherapy drugs, their further study is promising [45].

Extracts and compounds isolated from brown algae have antioxidant activity [46], and this activity is higher in brown algae products than in the same products from green and red algae [47]. In addition, brown algae products can chelate metals [48]. Phenolic acids abundant in brown algae (fucols, fuhalols, phlorethols, fucofloetins, and eccols) significantly enhance their antioxidant activity [49], while the antioxidant activity of brown seaweed compounds varies greatly depending on the season [50].

The authors conducted a study to examine the effect of oral administration of brown seaweed products on the body condition of broiler chickens subjected to heat stress (HS) [51]. HS significantly decreased ($p < 0.05$) the average feed intake but increased ($p < 0.05$) the rectal temperature of the bird and increased the level of corticosterone, sodium, chloride, glucose, amylase, and uric acid in the blood plasma. At the same time, serum IgM and IgG content increased ($p < 0.05$), alanine aminotransferase activity increased in plasma, and glutathione reductase and glutathione peroxidase decreased. In general, the use of brown algae products in liquid (addition to drinking water) and solid (addition to feed) increased the albumin level and magnesium concentration in plasma, significantly decreased ($p < 0.05$) the plasma activity of alanine aminotransferase, gamma-glutamyl transferase, and decreased the concentration of lipase and uric acid in broilers subjected to heat stress, respectively, compared with other treatment methods. It should be noted that the weight of immune organs,

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the level of interleukins (IL6, IL10), and the plasma activity of superoxide dismutase did not change in healthy birds or birds with TS. The authors conclude that using a brown algae product improved the growth rates of birds in all groups and reduced the negative effects of heat stress on the body of birds, including by restoring the activity of plasma enzymes. The anti-inflammatory ability of compounds in brown algae is associated with the ability of the compounds in their composition to inhibit LPS-activated macrophages, reduce the activity of 5-lipoxygenase and cyclooxygenase-2, that is, they inhibit the development of recovery reactions and facilitate their course [52].

Inflammatory cells (mast cells, eosinophils) generate signals leading to the release of reactive oxygen species, which induce nuclear factor kappa в; cyclooxygenase -2, nitric oxide synthesis (iNOS); tumor necrosis factor (TNF-б) and interleukin — 1в (1L -1в) [53]. In brown algae, phlorotannins, alginates, and other phenolic compounds strongly inhibit б-amylase and б-glucosidase. Since these enzymes cause post-potential hyperglycemia, their inhibition may prevent the development of diabetes, i.e., brown seaweed products have antidiabetic activity [54, 55].

Data are provided indicating the presence of antimicrobial activity of brown algae products, which is associated with the presence of terpenoids, hydrogen peroxide, bromoether compounds, and volatile fatty acids in them [56]. These compounds, interacting with various enzymes of the microbial body, inhibit their activity, disrupting the microbe's vital processes. In addition, these compounds can cause protein leakage from the microbial cell, increase the production of active forms, and cause a loss of permeability of its membranes; such a loss disrupts the substrate supply of the microbe and leads to its death [57]. Numerous studies have shown that extracts from different brown seaweeds cause the death of Leishmania, Trypanosoma braces, Plasmodium falciparum, etc. [58, 59, 60]. With the general direction of action of extracts from different algae, there is a discrepancy in the strength of the effect of these extracts. In general, we can talk about the presence of antiparasitic activity of brown algae and the possibility of their use in the treatment of relevant nosologies. In the biological effect of brown algae compounds on the body, in addition to the direct effect on the regulation of the activity of functional systems, there is another aspect — the effect of these compounds on the state of the microbiota of the digestive tract. Since the waste products of microbes in the digestive tract have a significant effect on metabolic processes in humans, changes in its quantitative and qualitative parameters can be associated with the development of many diseases [61 — 64]. Restoration of the microbial status of the gastrointestinal tract, which is necessary for the successful treatment of several diseases, is more effectively carried out by non-drug methods [65, 66] One non-drug method may be the intake of brown seaweed products [67].

In the work of Venardou B. and co-authors [68] The antibacterial and prebiotic potential of extracts obtained from two species of seaweeds — Laminaria hyperborea and Laminaria Digitata, was assessed using laboratory modeling of the intestinal microbial community (fecal inoculum) of weaned piglets. A significant increase in the number of Bifidobacterium thermophilum and Lactiplantibacillus plantarum and a significant decrease in the number of Salmonella Typhimurium and Enterotoxigen Escherichia coli were found. The results indicate selective antibacterial and prebiotic activity of the extracts, depending on the type of seaweed, season of extraction and production conditions, and in general, that seaweeds are a promising source of antibacterial and prebiotic food additives for the correction of gastrointestinal dysbacteriosis in piglets during the weaning period.

In the review, the authors summarize numerous in vivo studies reporting the prevention and treatment of metabolic syndrome using seaweed-derived components (MS) by regulating gut microbiota and producing short-chain fatty acids that positively affect glucose and lipid metabolism [69]. An analysis of animal studies showed that these bioactive components mainly modulate the gut microbiota

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by altering the Firmicutes/Bacteroidetes ratio, increasing the relative abundance of beneficial bacteria such as Bacteroides, Akkermansia, Lactobacillus, or decreasing the abundance of harmful bacteria such as Lachnospiraceae, Desulfovibri, Lachnoclostridium. The authors concluded that the restored balance of the gut microbiota affects the host's overall health by improving intestinal barrier functions and reducing inflammation or oxidative stress caused by MS.

In a review article, the authors [70] present data on the biological activity of seaweed products and clinical data indicating the effectiveness of their use in individuals with MS, which is accompanied by an improvement in the state of the cardiovascular system, a decrease in inflammation, an increase in insulin sensitivity, and weight loss. Other researchers have come to similar conclusions that key metabolites obtained from the restored microbiota (short-chain fatty acids, bile acid derivatives, and tryptophan metabolites, etc.) exhibit a corrective effect not only on glucose and lipid metabolism but are also crucial for intestinal homeostasis, affecting intestinal barrier function, immune responses, energy metabolism, and modulation of intestinal inflammation. That is, the authors point to an important role (including those obtained from brown algae) of bioactive compounds and their metabolites in the prevention and treatment of diseases, including inflammatory bowel diseases, colorectal cancer, cardiovascular diseases, obesity, and type 2 diabetes mellitus [71]. In addition to the direct effect on the gastrointestinal microbiota, the intake of brown algae products has a positive effect on immune parameters [72]. The intestine is the largest immune system in the body, and the gut-associated lymphoid tissue is a major component of the intestinal immune system, accounting for 70 % of systemic immune function. Gut-associated lymphoid tissue consists of isolated or aggregated lymphoid follicles that form Peyer's patches, which are considered, among other things, as immune sensors of the intestine. [73]. The functions of Peyer's patches are to induce immune tolerance or protect against pathogens, which results from complex interactions between immune cells in lymphoid follicles and follicle-associated epithelium. Intestinal immune cells include T cells, B cells, innate lymphocytes (ILC1, ILC2, ILC3), and the mononuclear phagocyte system (monocytes, dendritic cells (DC), and macrophages) [74]. These immune cells can secrete relevant pro- and anti-inflammatory cytokines and enzymes to regulate intestinal inflammation and immune responses [75]. Specific secretory immunoglobulins (sIgA) are mainly produced by lymphocytes and plasma cells that are distributed on the intestinal mucosal surface. They are the most abundant immunoglobulins in intestinal secretions, functioning as major factors that stop invading pathogens and thus playing a key role in the intestinal immune system. Fucoidan contained in brown seaweed has bidirectional immunomodulatory and immunosuppressive effects. Pattern recognition receptors (PRRs) that recognize polysaccharides in the intestine include Toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD)-like receptors (NLRs). Specific recognition of polysaccharides by PRRs can trigger signaling pathways that regulate inflammation and immune cytokines, ultimately leading to upregulation of associated gene expression and protein synthesis, thus regulating intestinal immunity to protect against weakened intestinal immune barriers [76].

In a series of experiments, the authors studied the effect of polysaccharides — laminaran and sodium alginate (obtained from brown algae) on the production of putrefactive compounds by human fecal microbiota in a broth containing soy protein [77]. In the second series, the effect of laminaran solution or alginate diet on putrefactive compounds of rats' cecum on a diet containing soy protein was studied. Laminaran inhibited the production of ammonia, phenol, and indole by human fecal microbiota. Both polysaccharides reduced the indole content in the rat cecum. It was found that, unlike sodium alginate, laminaran increases the number of Coprobacter, while Helicobacter decreases in the presence of both polysaccharides. It is known that soy protein is rich in tryptophan, which is

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metabolized by intestinal microbiota into indole, a putative risk factor for colon cancer. The authors established the inhibitory effect of laminaran and alginate on the production of indole and other putrefactive compounds, such as ammonia and phenol, from soy protein by human fecal microbiota in vitro, which indicates a potential corrective effect of these polysaccharides on intestinal microbiota disturbance. In their study, the authors [78] studied the potential therapeutic properties of acetyl esters (AE) obtained from Laminaria when administered to a mouse model of colitis. The use of AE modulated inflammatory responses by upregulating anti-inflammatory cytokines (IL-10 and TGF-в1). It restored the gut microbiota composition, increased the number of Bifidobacterium and Lactobacillus, and enhanced the production of short-chain fatty acids. At the same time, a decrease in CD68 expression and an increase in CD163 expression were observed, indicating a shift towards an anti-inflammatory phenotype of macrophages.

Overall, the obtained results indicate the effectiveness of the use of acetyl ester extract of Laminaria in mice with experimental colitis (significant reduction in the activity of inflammatory reactions, restoration of healthy intestinal microbiota), which justifies its use in clinical studies as a therapeutic agent for the treatment of colitis and improvement of intestinal health. Thus, due to the multi-component composition, including various bioactive compounds, brown algae have mechanisms of various biological effects.

The well-studied multifaceted and multilevel action of brown algae products (different metabolic links, different body systems) raises the question of the integrative effect of brown algae on the body, i.e., the possibility of bringing different functional systems of the body into optimal interaction and maintaining a balance in the activity of these systems. According to modern concepts, the most important condition for the functioning of the human and animal body is the stability of the internal environment, which is called homeostasis [79]. Due to the stability of the internal environment, each structural unit of the body (cell) is in an environment that is relatively constant in its properties — the extracellular fluid. Changing or maintaining its composition constant depends on the combined activity of metabolic and physiological mechanisms [80, 81]. For a functional system to operate effectively, its activity must be provided with energy, and its structural elements must maintain the stability of the constituent structures. Both needs are provided by metabolic activity, which is closely related to the cell organelles since they are the material substrate on which it is realized. Consequently, physiological metabolic activity and the structural constancy of the cell are interconnected things that ensure its vital activity. Within the framework of an integral organism, within the framework of functional systems, such a set of strictly defined indicators, which are in certain ratios, determines the preservation of the integrity and viability of the organism. The set of stereotypically interconnected changes in parameters (physiological, metabolic, structural) in different organs, reflecting interorgan relationships in the functional system, are defined as the functional-metabolic-structural continuum (FMS-continuum) [82 — 85]. It should be noted that changes in the external environment affect the functional activity of organs and systems, and this requires changes in the metabolism and structural characteristics of cells to the needs of these organs and systems [81]. As a result, the FMS continuum can change, and it must be corrected to maintain the vital activity of the organism. Natural nonspecific modulators with mechanisms of influence on different aspects of metabolism, physiology, and structure have such corrective abilities. We have assessed the nonspecific modulating activity of natural medicinal resources in several studies [86 — 90].

Conclusion

The analysis of available literary sources shows us that the physicochemical composition of brown algae products ensures the entry of many essential microelements and biologically active compounds into the human and animal body. Bioactive compounds from brown algae have high regulatory activity in relation to free radical formation, inflammation mechanisms' activity, and cell membrane

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structural and functional characteristics. Thus, brown algae products can be considered one of the non-specific modulators of the body's activity.

Prospects for further research

Brown algae products, as nonspecific modulators, have a positive effect on the body's functional systems, so it is expedient and promising to study their effect on the state of the structural-functional-metabolic continuum in the treatment of various diseases.

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ПАТОФІЗІОЛОГІЧНІ МЕХАНІЗМИ РОЗВИТКУ ДИСВІТАМІНОЗІВ І МІКРОЕЛЕМЕНТОЗІВ ПРИ КОМОРБІДНОСТІ ЦУКРОВОГО ДІАБЕТУ ТА ТУБЕРКУЛЬОЗУ ЛЕГЕНЬ: РОЛЬ ЗАПАЛЬНИХ ПРОЦЕСІВ ТА ОКСИДАТИВНОГО СТРЕСУ У ПАТОГЕНЕЗІ УСКЛАДНЕНЬ

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PATHOPHYSIOLOGICAL MECHANISMS OF THE DEVELOPMENT OF VITAMIN AND MICROELEMENT DEFICIENCIES IN THE COMORBIDITY OF DIABETES AND TUBERCULOSIS: THE ROLE OF INFLAMMATORY PROCESSES AND OXIDATIVE STRESS IN THE PATHOGENESIS OF COMPLICATIONS

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Summary/Резюме

The issue of comorbidity between diabetes mellitus (DM) and pulmonary tuberculosis (TB) is highly relevant due to its high incidence. According to international organizations, the number of DM cases is steadily increasing, posing additional challenges for healthcare systems, as these patients have a higher risk of infectious diseases, particularly TB, which remains a leading cause of infectious mortality. The key pathogenetic mechanism of this comorbidity is oxidative stress, which not only affects the course of both diseases but also leads to vitamin and micronutrient deficiencies. Chronic hyperglycemia in DM stimulates the production of reactive oxygen species, which impair immune responses and create favorable conditions for the manifestation of Mycobacterium tuber-