REVIEW ARTICLES

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THE MODULATION ACTIVITY OF THE SULFATED POLYSACCHARIDES SYNTHESIZED IN CYANOBACTERIA *SPIRULINA PLATENSIS* AND ITS ROLE AS A NEW BIOACTIVE COMPOUND

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Summary
Objective. To conduct a literature review to establish the role of cyanobacterial bioactive compounds - sulfated polysaccharides synthesized in *S. platensis* on the immune disturbances and metabolic disorders in patients with respiratory diseases, including tuberculosis.
Material and methods. A systematic literature review was conducted and the electronic sources published through the PubMed and HINARI collection of health literature were evaluated. Printed material was searched through the Universal Decimal Classification (UDC).
Results. Sulfated polysaccharides are intensively studied as they constitute an important source of biologically active compounds. Original biotechnological models for cultivating the cyanobacterium *Arthrospira (Spirulina) platensis (S. platensis)* were created at the Institute of Microbiology and Biotechnology of the Academy of Sciences of the Republic of Moldova, and the extraction and purification methods of the biologically active compounds with therapeutic effects were improved. The mechanism of action of the bioactive compounds extracted from *S. platensis* are different and selective.
Discussions. The bioactive components extracted from *S. platensis* possess antimicrobial (including antiviral), antitumor, antioxidant, radioprotective and immunostimulating effects with the differentiated level of action.
Conclusions. Further studies are needed to evaluate the mechanisms of action of the bioactive compound extracted from *S. platensis* in other biosystems and experiments.
Keywords: *S. platensis*, sulfated polysaccharides, tuberculosis

Introduction

Medical biotechnology represents an important direction in actual science, which offers new ways to strengthen health and prevent the risks associated with pollution, wrong diets, and exposure to various infectious agents [1, 2]. In recent years, cyanobacterial carbohydrates have been intensively studied as a source of biologically active substances [3-9]. Concomitantly new original biotechnological models of direct cultivation of *Arthrospira (Spirulina) platensis (S. platensis)* were created, and the extraction and purification methods of biologically active compounds with curative effects were improved [10].

Current scientific achievements established new targets for the implementation of biological active medicines in the treatment of autoimmune and inflammatory disorders. In this frame of reference, particularly valuable are the biological active compounds - sulfated polysaccharides (SPS) synthesized in cyanobacteria *S. platensis*, which demonstrated an immune modulating effect, and provided evidence to possess multiple curative actions in healthy and sick organisms [11-13]. SPS represents polyanionic complexes located on the external surface of cell membranes and in the extracellular space. The structural complexity of SPS is based on several molecules: fructose, rhamnose, xylose, mannose, glucose, and galactose, various isomeric forms and types of glycosidic bonds, and the three-dimensional structure [14]. SPS plays a particularly important role in the vital activity of organisms, having the functions of tissue barrier, cell adhesion, protection against pathogens, as well as the reservoir of growth factors [2, 5].

Recent studies demonstrated that the development, evaluation, and testing of new remedies based on SPS synthesized in cyanobacteria *S. platensis* for the modulation of immune disorders in respiratory system diseases, especially in tuberculosis (TB), possess a particular interest [14-16]. The fact is due to the increased prevalence of diseases in the Republic of Moldova (RM) and the associated disability [17, 18]. It was demonstrated that improving the treatment outcomes in patients with TB can be achieved by developing immune-modulating drugs, containing extracted SPS based on the updated knowledge regarding the involvement of different pathogenic disturbances at the molecular level in the evolution of the disease [19]. A particular interest in this aspect is offered to the SPS obtained from the cyanobacterium *S. platensis* created at the Sciences Academy of the R. of Moldova Institute of Microbiology and Biotechnology. The drugs BioR®, BioR^{Cr}, BioR^{Ge}, BioR$^{Zn®}$, ZooBioR® and ZooBioR2 contain the bioactive compounds obtained from the biomass of *S. platensis* and include amino acids, SPS, polyunsaturated fatty acids, macro-, meso- and microelements [2, 5]. For

human use BioR® is distributed in tablets of 5 mg produced by Farmateh LTD, BioR$^{Zn®}$ is supplemented with zinc, BioR^{Ge} - germanium, and BioR^{Cr} with chrome [2]. Despite multiple studies available until now in the open access literature about the role of cyanobacterial bioactive compounds, we could not find detailed studies on the influence of sulfated polysaccharides synthesized in *S. platensis* and immune-modulating drugs based on it on the immune disturbances and metabolic disorders in patients with respiratory diseases. The aim of the study was to conduct a literature review establishing the role of cyanobacterial bioactive compounds - sulfated polysaccharides synthesized in *S. platensis* on the immune disturbances and metabolic disorders in patients with respiratory diseases, and tuberculosis.

Material and methods

Was conducted a systematic literature review and the material for the research constituted the electronic sources published through the PubMed web interface and HINARI collection of health literature. The Universal Decimal Classification (UDC) method was used for searching the printed sources. Bibliographic resources were systematized by subject and content.

Results

The pharmacological activity of S. platensis and its role in the development of new bioactive compounds

Cyanobacteria *S. platensis* represents an important source for obtaining biologically active compounds widely applied in food, cosmetics, pharmacology, agriculture, and zootechnology [2-10]. Recent studies established the curative effects of bioactive compounds synthesized by cyanobacteria *S. platensis* and demonstrated the possibilities of their specific use as therapeutical drugs in various pathologies, infectious and non-communicable diseases establishing the therapeutic mechanisms [2, 16, 28]. Many studies demonstrated that *S. platensis* has several pharmacological properties - antimicrobial (including antiviral and antibacterial), antitumor, antioxidant, and immune-stimulating effects [2, 3, 7, 12, 14-19]. A new property was recently established which is metal protective and consists in the prevention of injury during the poisoning with heavy metals – chromium, cadmium, plumb, iron, and hydrargyrum [20]. The enumerated roles are due to its high content of proteins, polysaccharides, lipids, amino acids, essential fatty acids, minerals, vitamins (ascorbate, carotenoids), glutathione, catechins and other bioactive compounds [2, 5, 10, 13]. The results of some studies demonstrated that *S. platensis* showed favorable effects on carbohydrate and lipid metabolism, immune and digestive systems, and antioxidant capacity in elders and hens in which *S. platensis* was used as a food supplement [8, 20].

There were published studies on the use of *S. platensis* in hepatic steatosis and hepatic carcinoma, which confirmed its anti-oxidant and hepatoprotective properties [2, 15, 21]. It was found that the administration of *S. platensis* before exposure to cyclophosphamide protects the rats from cyclophosphamide-induced nephrotoxicity, due to its antioxidant and anti-apoptotic properties, stimulates the enzymatic hydrolysis of the liver extracellular matrix, restores the indices of protein metabolism, enzymes of carbohydrate metabolism and metabolites, induce 5'-nucleotidase and high level of adenosine activity, a potent endogenous anti-inflammatory enzyme [19]. Plant-based SPS was established to reduce the growth of metastatic neoplasms, and angiogenesis, and induce apoptosis in tumor tissue [5, 12].

SPS synthesized in *S. platensis* demonstrated several important properties - anticoagulant and antithrombotic, antitumor and cancer prevention, hypolipidemic and hypoglycemic, antimicrobial, anti-inflammatory and antioxidant, which makes them promising as a bioactive compound in biomaterials with a wide range of applications [2, 6, 11-16, 20-22]. The anticoagulant properties of SPS in correlation with the improvement of fibrinolytic activity and the inhibition of the proliferation of smooth muscle cells and vascular endothelium are therapeutic remedies used in the prevention of atherosclerosis [22]. *Sodium spirulan*, SPS obtained from *S. platensis*, increases the production of endothelial proteoglycans, proving an efficient anti-thrombotic activity and anti-viral activity [23]. SPS synthesized in *S. platensis* is used to control the drug release in regenerative medicine for the treatment of infected wounds and tissue engineering as well [24]. SPS was studied for clinical application in the development of vaccines and antimicrobial biopolymers [24, 25].

S. platensis contains a high concentration of antioxidants, which ensure the inhibition of oxidative reactions through the mechanisms of reduction of the reactive oxygen species (ROS) and in particular, of the hydroxyl ones, which are the most dangerous [15]. The mechanism through which reduces oxidative stress consists in the increase of the antioxidant enzymes, manifested by the activation of catalase and superoxide dismutase [15]. Also, the antioxidant activity of SPS synthesized in *S. platensis* was proved through the radioprotective effect in oncology for the rapid restoration of the hematopoietic system and reducing the level of ROS formed as a result of radiological treatment [26].

The role of polysaccharides synthesized in S. platensis in the modulation of the immune disturbances in patients with respiratory diseases, including tuberculosis

Data recently published demonstrated that the SPS extracted from *S. platensis* improves the immune reactivity in several ways: a) increases the number of peripheric neutrophils and stimulates their migration and differentiation in macrophages; b) improves the activity of reticulo-endothelial cells of the liver and of splenocytes; c) increases the number of neutrophils and lymphocytes; d) stimulates the production of antibodies, anti-inflammatory interleukins, and e) decreases the synthesis of tumor necrosis factor α and other pro-inflammatory cytokines [16, 18, 27, 28].

In a recent study, the antioxidant, immunomodulatory, and anti-angiogenic effects of *S. platensis* were demonstrated in the induced arthritis model in rats, through the decrease in the plasma concentrations of pro-inflammatory interleukins (COX-2, TNF-α, IL-6) and malondialdehyde. Also, it induced the improvement of the serum level of glutathione

(GSH) compared to the unexposed group of patients [28].

Several studies established antiviral properties of SPS from *S. platensis* associated with the immune-modulation activity. SPS was found to be active against the herpes virus, human cytomegalovirus and human immune deficiency virus [13, 14, 23]. The main mechanism responsible for the antiviral action is the increase of the innate antiviral resistance, by direct activation through the TLR-dependent mechanism of the production of interferons (IFN) type I (IFN-ά and IFN-beta) and indirectly mechanism by the production of type II IFN - IFN-γ [23]. Another anti-viral mechanism of SPS represents the constitution of cell barriers, by inhibiting cellular adhesion by this way protecting the organism against multiple pathogens, including viruses [23]. SPS extracted from *S. platensis* determined an important effect on the immune system by building and activating the receptors on macrophages and leukocytes [12, 16]. In experimental peritonitis, SPS significantly increased the production of IL-1 and IFN-γ by peritoneal macrophages [6].

SPS of cyanobacterial origin represents an important source for the development of effective and harmless bioactive drugs with immune and adaptogenic properties particularly valuable in the treatment of patients with respiratory non-communicable and infectious diseases [2, 5, 10, 15]. It was established that the interaction of SPS extracted from the seaweeds *Laminaria japonica, Laminaria cichorioides, Fucus evanescens* and human Toll-like receptors (TLRs), expressed on the membranes of human embryonic kidney cells, activated the nuclear transcription factor NF-kB by specifically binding to TLR-2 and TLR-4 [27]. The results indicated that the extracted SPS - fucoidans could be efficient drugs in the defense against pathogenic microorganisms belonging to different classes [28].

Zinc is a microelement with a decisive role in the regulation of immune function. Its optimal levels ensure the efficient activity of T-lymphocytes, innate resistance, determines the switching of the antibody synthesis to the production of immune cells, as well, as have hyposensitization and anti-anaphylactic effects [29]. The $BioR^{Zn®}$ demonstrated an enhanced immune response because is a zinc-supplemented drug and could be recommended as an immune-stimulating drug in patients with tuberculosis and adaptogenic in patients with adverse drug reactions to the anti-TB drugs [30].

Important data were published regarding the influence of SPS on immune reactivity in patients with non-communicable respiratory diseases [31, 32]. Was demonstrated that SPS in patients with bronchial asthma modulates airway inflammation by decreasing the concentration of mediators of inflammation (IL-2, TNF-α, TGF-β) and fibrogenesis (connective tissue growth factor), restores the indices of protein metabolism, the level of metabolites and enzymes of carbohydrate metabolism, reduces the level of lipid hydroperoxides, improves thiol-disulfide metabolism. In moderate and severe forms of bronchial asthma [31]. SPS increased the activity of glucose-6-phosphate dehydrogenase, decreased the serum level of pro-inflammatory interleukins IL-6 and TNF-α, and increased the level of anti-inflammatory IL-10 values and maintained TGF-β1 at optimal level [31].

Several studies demonstrated that the mechanisms of action of SPS and derivated immune-modulating drugs in patients with TB consist in the increasing the functional activity of lymphocytes, and increasing the rate of CD4 cells. In patients with bronchial asthma was established that restored the normal values of enzymes - acid phosphatase suppressed the N-acetil-β-glucosaminidase, maintained at the optimal levels the functional activity of β-glucosidase, β-galactosidase and arylsulphatases [33, 34].

Discussions

Our research was focused on the literature review establishing the pharmacological activity of cyanobacterial bioactive compounds and the role in the evaluation of the immune disturbances in patients with respiratory diseases, including tuberculosis. The electronic sources published through the PubMed web interface and HINARI collection of health literature and the printed sources searched using the UDC were systematized by subject and content. An important research outcome was the identification of challenges in achieving high anti-TB treatment success rate which certainly required the development of certain optimal and harmless therapeutic methods targeting the immune and metabolic disturbances [14, 16, 30, 33]. Sciences Academy of the R. of Moldova Institute of Microbiology and Biotechnology developed new industrial and laboratory techniques in biotechnology for the cultivation of biomass of S. platensis and extraction of bioactive compounds: SPS (*calcium spirulan*), amino acids, polyunsaturated fatty acids (linoleic acid), vitamins (ascorbate, carotenoids), glutathione, catechins and macro-, meso- and microelements obtained from the cyanobacterium *S. platensis*. New drugs were developed and registered for the human use – BioR®, $BioR^{Cr}$, $BioR^{Ge}$, $BioR^{Zn®}$, and zootechnologies – ZooBioR® and ZooBioR2 [2, 10]. The scientific publications, to which we had access, demonstrated that the bioactive components extracted from *S. platensis* possess antibacterial, antifungal, antiviral, antitumor, antioxidant, radioprotective, and immunostimulating effects [2-4, 14-16, 18-34]. The biochemical and immunochemical mechanisms of SPS extracted from *S. platensis* and derivative drugs is selective and differentiated and further research in this direction is of undeniable relevance and value.

Conclusions

• The pharmacological activity of cyanobacteria *S. platensis* is extremely wide and the extracted biologically active compounds are applied in food, cosmetics, pharmacology, agriculture, and zootechnology.

• The cultivation of cyanobacteria *S. platensis* in the laboratory and industrial conditions allows the obtaining of biologically active compounds, which showed a wide range of pharmacological properties – antimicrobial, antitumor, antioxidant, radio-protective, and immune-stimulating.

• The mechanisms of action of the bioactive compounds extracted from *S. platensis* are different and selective, and further studies are needed to evaluate them in other biosystems and experiments.

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