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SUBSTANȚE BIOACTIVE CU ACTIVITATE ANTIBACTERIANĂ ANTIVIRALĂ ȘI ANTIFUNGICĂ OBȚINUTE DIN CIANOBACTERII

Valentina BULIMAGA, Liliana ZOSIM, Alina TROFIM, Daniela ELENCIUC,

Moldova State University, Republic of Moldova

Valeriu RUDIC, Greta BALAN,

,,Nicolae Testemitanu” State University of Medicine and Pharmacy, Republic of Moldova

Cianobacteriile și microalgele sunt cunoscute ca potențiali producători de noi substanțe naturale fiind surse valoroase de substanțe bioactive (inclusiv metaboliți) și prezintă un interes din ce în ce mai mare pentru cercetători grație efectelor lor benefice asupra sănătății. Exploatarea tulpinilor de cianobacterii bogate în noi substanțe bioactive valoroase din punct de vedere farmacologic, inclusiv substanțe antimicrobiene (antibacteriene, antifungice și antivirale) este foarte actuală datorită apariției și răspândirii rezistenței agenților patogeni la antibioticele utilizate. Unele studii au raportat rezultate promițătoare privind cianobacteriile ca surse bogate de compuși bioactivi cu activități antibacteriene, antivirale, antifungice, algicide și citotoxice, care deschid perspectiva aplicării lor în scopuri terapeutice. În studiul dat sunt prezintate diverse caracteristici ale cianobacteriilor, inclusiv capacitatea lor de a produce compuși cu activități biologice, inclusiv antimicrobiene, antivirale și antifungice, ceea ce le face candidați potriviți pentru exploatarea lor ca surse naturale de agenți bioactivi.
Cuvinte-cheie: *cianobacterii, alge, substanțe bioactive, activitate antibacteriană, antivirală, antifungică.*

BIOACTIVE SUBSTANCES WITH ANTIBACTERIAL ANTIVIRAL AND ANTIFUNGAL ACTIVITY OBTAINED FROM CYANOBACTERIA

Cyanobacteria and microalgae are recognized as potential producers of new natural substances and represent valuable sources of bioactive substances (including metabolites), which are of increasing interest from researchers for their beneficial health effects. The exploitation of cyanobacterial strains rich in new pharmacologically important bioactive components, including antimicrobial substances (antibacterial, antifungal and antiviral) is very current due to the emergence and spread of resistance of pathogens to the used antibiotics. Some studies have reported promising results regarding cyanobacteria as rich sources of bioactive compounds with antibacterial, antiviral, antifungal, algicidal and cytotoxic activities, which open the prospect of their application for therapeutic purposes. The review presents various characteristics of cyanobacteria, including their ability to produce compounds with biological activities, including antimicrobial, antiviral and antifungal, make them suitable candidates for their exploitation as a natural source of bioactive agents.
Keywords: *cyanobacteria, algae, bioactive substances, activity antibacterial, antiviral, antifungal.*

Introduction

The use of antibiotics in fields such as medicine, agriculture, aquaculture and their production affects the environment in critical ways. This fact in recent decades has led to the emergence of multi-drug resistant (MDR) bacteria, making them one of the substantial problems facing the modern healthcare system. Antibiotic resistance has emerged in numerous species of pathogenic bacteria, some of which may be resistant to most available antimicrobials, creating an ,,antibiotic resistance crisis” [1- 4]. A major collaboration between researchers from different branches of science is needed to deal with this problem. As a result, the World Health Organization (WHO) initiated a global plan in 2015 to investigate and use alternative sources of bioactive substances that many countries follow him by developing numerous scientific research projects with reference to this issue [5].

Cyanobacteria are a group of photoautotrophic microorganisms that inhabit various types of environments (aquatic, terrestrial) and show high adaptability to fluctuating environmental conditions by producing different groups of primary and secondary metabolites, which allow them to easily adapt to new environmental conditions [6-8].

Already at the end of the last century, the research of cyanobacteria for the evaluation of compounds with antimicrobial (antibiotic) activity and other pharmacologically active compounds presented an increased interest for researchers [9-11]. So, for more than 2 decades efforts have been made to promote algae and cyanobacteria as food products as well as producers of chemically unique metabolites with different biological activity. These compounds include toxins, algicides, plant growth regulators, and most importantly, compounds with uses in the food and pharmaceutical industries [12-14].

A group of researchers based on an analysis of 670 papers on more than 90 genera of cyanobacteria found evidence that they produce compounds with potentially beneficial activities, most of which belong to the orders Oscillatoriales, Nostocales, Chroococcales and Synechococcales. The rest of the orders remain insufficiently studied. The various cyanobacterial metabolites possessing beneficial bioactivities belong to 10 different chemical classes (alkaloids, depsipeptides, lipopeptides, macrolides/lactones, peptides, terpenes, polysaccharides, lipids, and others) exhibiting various biological activities. They also produce a wide variety of bioactive compounds such as proteins, lipids, polysaccharides, fatty acids, alkaloids and polyketides, substances with valuable properties such as antifungal, antiviral, antibacterial, algicidal and anti-inflammatory activity. 5 classes of chemical compounds (alkaloids, depsipeptides, lipopeptides, macrolides and peptides) have been highlighted that would exhibit a remarkable set of activities. The compounds with the highest activity were found to be alkaloids, lipopeptides and polyketides [15].

So, cyanobacteria strains are a rich source of natural bioactive substances with pharmacological and biotechnological potential [7]. Due to the current increase in their pharmaceutical value and the prospects of their application for use in medicine or biotechnology, the exploration of unvalorified cyanobacterial taxa constitutes a promising strategy to effectively evaluate the chemical diversity of their bioactive compounds [1, 15-17].

Both cyanobacteria and microalgae have been identified as important producers of secondary metabolites that possess both antibacterial and antiviral activities [16, 18]. Indeed, these organisms produce a wide variety of bioactive secondary metabolites, which are accumulated in the cell or excreted into the surrounding media, usually at the end of the exponential and stationary phase of growth. Many of these metabolites such as free saturated or unsaturated fatty acids exhibit antibacterial activity. Other compounds from microalgae and cyanobacteria exhibit antiproliferative or antifungal properties or are able to inhibit viral infection and/or replication [19, 20].

Cyanobacteria and algae, apart from their nutritional value, possess not only antioxidant but also antimicrobial and antiviral properties [21-23].

Cyanobacteria and microalgae produce a wide variety of lipids with antibiotic activity against the most important pathogens that cause severe infections in humans. Lipids are part of the primary metabolites of microalgae and cyanobacteria and can find application in pharmaceutical, cosmetic, food, etc. Some of the antimicrobial activities of microalgae and cyanobacteria have been linked to unsaturated fatty acids. The first such antimicrobial compound, chlorelin, was isolated from *Chlorella* sp. by Pratt et al. in 1944 and represents a mixture of fatty acids that inhibit the growth of both gram-positive and gram-negative bacteria [24].

In addition, eicosapentaenoic acid (EPA), hexadecatrienoic acid and palmitoleic acid isolated from *Phaeodactylum tricornutum* have been shown to possess antimicrobial activity against methicillin-resistant gram-positive *Staphylococcus aureus* [1]. Fatty acids with antimicrobial properties have also been identified in other organisms [25, 26]. Similarly, unsaturated fatty acids from *Scenedesmus intermedius, Chaetoceros muelleri, Haematococcus pluvialis, Chlorococcum* sp. and *Skeletonema costatum* also have antimicrobial effects on a wide range of gram-positive and gram-negative bacteria. The organic extracts obtained from *Euglena viridis* and *S. costatum* showed inhibitory activity against *Pseudomonas* sp. and *Listeria monocytogenes* [27, 28].

Extracts containing fatty acids obtained from the green microalga *Coccomyxa cubensis* were shown to exhibit inhibition against a diverse range of Gram-positive and Gram-negative bacteria and fungi, with a minimum inhibitory concentration (MIC) of 305 and 106 mg/mL against *E.coli* and *P. mirabilis*, respectively [29]. In addition, liquid extracts of *Fucus vesiculosus*, obtained under pressure, contained long-chain fatty acids that showed inhibitory capacity on *E. coli* (IC50 = 2.24 mg/mL) and *S. aureus* (IC50 = 1.27 mg/mL [30]. Important compounds with antimicrobial and others properties besides unsaturated fatty acids are acrylic acid, halogenated aliphatic compounds, terpenes, sulfur-containing heterocyclic compounds, carbohydrates and phenols [31].

Recently, a group of Spanish researchers after screening about 600 strains of microalgae and cyanobacteria selected three strains of microalgae and one strain of cyanobacteria to evaluate their antibacterial and/or antibiofilm activity [32]. The summary organic extracts were first fractionated by solid phase extraction methods and their minimum inhibitory concentration and biofilm minimum inhibitory concentration on some human pathogens were determined. The use of these lipids in clinical treatments alone or in combination with antibiotics may provide an alternative to current treatments.

Although the previous inventions of the developed vaccines provided acquired immunity, recent efforts to develop antiviral, antibacterial, antifungal drugs are increasing tremendously due to the emergence or (re)emergence of infectious diseases and increasing resistance to antibiotics. Therefore, there is a need to investigate new sources of bioactive substances of natural origin.

Cyanobacteria and algae that have come into the limelight for the various therapeutic properties they possess.

Since 2000, epidemics caused by viruses have affected the health of the population internationally, followed by many deaths. Viral diseases such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), bird flu, swine flu, Ebola, and recently, coronavirus disease 2019 (COVID-19) have further aggravated the situation due to increasing viral resistance and adverse effects of antiviral drugs [33, 34]. As an alternative, lectins (antiviral proteins) isolated from cyanobacteria and marine organismare proposed as antiviral agents . Lectins are monomeric proteins with low molecular weight, usually exhibiting inhibitory specificity for glycoproteins and do not require metal ions for their biological activities [41].

Many lectins inhibit viral replication by interacting with viral glycoproteins envelope. Such antiviral lectins have been identified in bacteria, plants, seaweeds and cyanobacteria. Lectins are proteins that bind to specific carbohydrate structures but have no enzymatic activity. A surprising structural diversity is observed in antiviral lectins derived from prokaryotic species, which include the proteins: actinohivin (AH) [36] microvirin (MVN), lectin (MVL) from *Microcystis viridis* [37], agglutinin from *Oscillatoria agardhii* and scytovirin (SVN) [38,39]. Moreover, lectins derived from prokaryotes have a broad specificity to bind both to the high-mannose oligosaccharide core as well as mannose fragments.

Antiviral action was also shown by sulfated polysaccharide compound calcium Spirulan (Ca-SP) isolated from *Arthrospira platensis* (*Spirulina platensis*)

Sulfated polysaccharide was isolated in 1996 and has shown antiviral activity against a wide range of viruses, including HIV-1, herpes simplex virus type 1 (HSV-1), cytomegalovirus human (HCMV), measles morbillivirus (MeV), mumps virus and influenza virus [40]. Ca-SP interferes at a very early stage of the virus replication process, eg, the adsorption and penetration phases.

Others sulfated polysaccharides from the diatom *Navicula directa* and the green microalga *Chlorella autotrophica* were shown to inhibit the replication and hyaluronidase enzymes of VHSV, ASFV, HSV1 and 2 and influenza A virus[41,42].

Another polysaccharide, called nostoflan, was isolated from *Nostoc flagelliforme* and its molecular weight was estimated to be 211 kDa [43]. Nostoflan possesses strong antiviral activities only against enveloped viruses such as HSV, HCMV and influenza virus A.

Singh et al. evaluated the significance of different metabolites in cyanobacteria, which include phenolic compounds, phytoenes/terpenoids, phytols, sterols, free fatty acids, photoprotective compounds (Microasporin-like amino acids (MAAs), scytonemin, carotenoids, polysaccharides, halogenated compounds, etc.), phytohormones, cyanotoxins, biocides (algalicides, herbicides and insecticides) etc. and analyzed the importance of some metabolites as antibiotic, immunosuppressive, anticancer, antiviral and anti-inflammatory agents. Metabolites obtained from cyanobacteria and algae have several biotechnological, industrial, pharmaceutical and cosmetic uses [17].

In some studies it has been observed that the synthesis of antibacterial compounds is influenced by the cultivation conditions. Fatima et al. evaluated the antibacterial activity of isopropanolic, methanolic and aqueous extracts of cyanobacteria *Synechococcus spp. PCC7942*, exposed to UV-B radiation. The antibacterial activity of *Synechococcus spp. PCC7942* was tested on five potent skin pathogens. The highest antibacterial activity was observed in methanolic extracts obtained from cultures of *Synechococcus spp PCC7942* exposed to UV-B radiation for 24 hours. This antibacterial activity could be due to the presence in the extracts of an increased amount of carotenoids and phycocyanin in the culture subjected to UV-B irradiation stress [44]. In confirmation of the antibacterial activity of phycocyanin, can be mentioned the results reported on the biological activity of C-phycocyanin (C-PC) preparations isolated from various strains of cyanobacteria: *Anabaena oryzae* [45]; *Oscillatoria* sp. [46]; *Spirulina platensis* [47,48], and *Westiellopsis sp*.[49]. According to the data reported by Safari et al. 2017, the antibacterial activity of partially purified C-phycocyanin (C-PC) from *Spirulina platensis* on some pathogenic bacteria was performed using agar disc diffusion and microdilution, determining the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC). The selected bacteria were *Escherichia coli*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Streptococcus iniae* and *Yersinia ruckeri*. The results of C -phycocyanin MIC and MBC were 50–500 and 100–500 μg ml–1, respectively. However, in this case the antibacterial activity of C-PC was lower compared to C-PC from other cyanobacteria and algal pigments (such as astaxanthin). It was determined that C-PC from *S. platensis* also exhibited high potential for antioxidant activity in vitro and could also be used as a natural antioxidant in a variety of foods [47].

Another compound with antibacterial activity proved to be Nostocin A isolated from the cyanobacterium *Nostoc spongiaeforme*, the synthesis and releasing of which occurs under conditions of oxidative stress (higher temperature and light) [50]. Other bioactive substances with an antibacterial effect are the antibacterial diterpenoids from *Nostoc commune*, [17, 51, 52]. Many of the metabolites synthesized by cyanobacteria, such as pigments, carbohydrates, polyphenols, fatty acids, lipids and other cellular compounds have shown significant antimicrobial activity [53].

Rania and Taha (2008) reported that numerous extracts obtained from the biomass of the cyanobacterium *Spirulina platensis* showed antimicrobial activity against both Gram-positive and Gram-negative microorganisms [54]. A variety of cyanobacteria are producing natural products that exhibit antifungal activity [8, 55, 56). The chemical structures of these compounds are variable, including alkaloids, aromatic compounds, polyketides, and various types of peptides. Antifungal peptides have been detected in the cyanobacterium *Tolypotrix byssoidea* [52, 57]. In addition, there are several compounds that exhibit antifungal activity along with other activities. In cyanobacteria there are also natural compounds that exhibit, for example, antifungal and cytotoxic activity against mammalian cells, such as scytophycin and glicolipopeptide hassallidin [10**]**.

Recently, several reviews have been published on the isolation of extracts of bioactive substances from algae and cyanobacteria and the evaluation of their biological activity [8, 58-60].

Ethanolic extracts of the microalgae *Isochrysis galbana* and *Dunaliella salina* were also found to be active against four different bacterial strains with an inhibitory concentration (IC50) of 100 and 80 mg/ml, respectively [61].

Numerous investigations carried out in vitro have allowed that species of cyanobacteria such as *Spirulina platensis*(Gomont), *Anabaena variabilis* (Kutz.), *Nostoc muscorum* (Agardh), *Nostoc linckia* (Bornet), *Oscillatoria acuminata* (Gomont), *Oscillatoria amphigranulata* (Goor), *Oscillatoria* sp., *Nostoc* sp., *Nostoc muscorum*, *Nostoc piscinale*, *Phormidium* sp., *Anabaena flos-aquae*, Lyngbya officinalis NCCU-102, *Gleocapsa gelatinosa* NCCU-430, *Chrococcus* sp. NCCU-207, *Aulosira fertillisma* NCCU-444, An*abaena ambigua* NCCU-160, *Hapalosiphon fontinalis* NCCU-339, *Anabaena* sp. NCCU-09, *Anabaena variabilis* NCCU-441, *Westiellopsis prolifica* NCCU-331, *Scytonema* sp. NCCU-126 and other, can be accepted as species producing bioactive substances with antimicrobial action on human pathogens and other activities [62, 63].

In confirmation, other studies have been undertaken on cyanobacteria isolated from soil to assess their antimicrobial activity. Aqueous, etheric and methanolic extracts of 76 microalgae and cyanobacteria were screened for antimicrobial properties against four pathogenic bacteria and two fungi. Of the total microalgae, 22.4% (17 cyanobacteria) showed antimicrobial effects. The selected cyanobacteria with positive antimicrobial activities were members of the families Stigonemataceae, Nostocaceae, Oscillatoriaceae and Chroococcaceae. The growth of Persian type collection cultures of *Bacillus subtilis* (PTCC) 1204 and *Staphylococcus epidermidis* PTCC 1114 were inhibited by 12 and 14 species of cyanobacteria, respectively. Also, eight species of cyanobacteria inhibited the growth of strain *Escherichia coli* PTCC 1047, and two species inhibited the growth of *Salmonella typhi* PTCC 1108 strain. Fungal activity was also established, of which six species inhibited the growth of *Candida kefyr* ATCC 1140 strain, and one specie of cyanobacteria inhibited the growth of strain *C. albicans* ATCC 14053 [64].

Kumar et al. studied the antibacterial and antifungal activity of methanolic extracts of *Phormidium fragile* on some strains of pathogens (*Staphylococcus a*ureus, *Vibrio cholerae* and *Salmonella typhi*) and the antifungal activity on some strains of fungi (*Aspergillus flavu*s, *Candida albicans* and *Trichoderma viride*). Assays were performed after evaporation of the methanol and concentration of the extract (up to 15%) with the application of 20 µl on the agar by the Muller Hinton agar disk diffusion method. The analyzed extracts of *P.fragile* demonstrated significant antibacterial and antifungal activities, which could be much more effective compared to contemporary antibiotics and fungicides [65]. In another study by Tiwari and Sharma (2013), were demonstrated that the extracts obtained from the cyanobacteria *Anabaena variabilis* and *Synechococcus elongates* showed a significant antibacterial effect against *Enterococcus* sp., *Klebsiella* sp. and *E. Coli* [66].

Malathi et al. (2014), investigated the antibacterial action of methanol, chloroform and aqueous extracts obtained from the biomass of the cyanobacteria *Tolypothrix tenuis*, *Anabaena variabilis* and *Cylindrospermum* sp. on the pathogenic bacteria *B. subtilis* and *P. aeruginosa* and established that the tested extracts showed an antibacterial effect, and the most pronounced antibacterial effect was observed in the case of the chloroform extract [67].

In the research carried out by Silva-Stenico et al. were evaluated the antitumor and antimicrobial activities of intra- and extracellular extracts of cyanobacteria. A total of 411 cyanobacterial strains were tested for antimicrobial activity using a subset of pathogenic bacteria as targets. Antitumor tests in vitro were performed with extracts from 24 strains tested against two murine cancer cell lines (colon carcinoma CT-26 and lung cancer 3LL). The intracellular extracts inhibited 49 and 35% of the growth of Gram-negative and Gram-positive pathogenic bacteria, respectively. In addition, the intracellular methanolic extract of *Cylindrospermopsis raciborskii* CYP011K and *Nostoc* sp. CENA69 showed inhibitory activity against cancer cell lines. The extracellular extract from *Fischerella* sp. CENA213 and *Microcystis aeruginosa* NPJB-1 showed inhibitory activity against 3LL lung cancer cells at 0.8 pg ml-1. These extracts showed very low inhibitory activity on human peripheral blood lymphocytes. The results showed that some cyanobacterial strains are rich sources of natural products with potential for pharmacological and biotechnological applications [68].

The antimicrobial and antifungal potential of successive extracts from some species of cyanobacteria on eight human pathogens (bacterial strains) and 5 fungal strains was evaluated by Egyptian researchers [62]. For this purpose, the aqueous and organic extracts of seven species of cyanobacteria (*Oscillatoria* sp., *Nostoc* sp., *N. muscorum*, *N. piscinale*, *Phormidium* sp., *A. flos-aquae* and *S. platensis*) were used. The chloroform extracts obtained from studied cyanobacterial species showed an extended zone of antibacterial inhibition against pathogenic bacterial strains. Chloroform extracts registered a broad spectrum against Gram-negative bacteria (*E. coli*, *Aeromonas hydrophila*, *Salmonella enterica* S 1180, *Salmonella paratyphi, Klebsiella pneumonia* K 51 and *Vibrio cholera* V116),) and Gram-positive bacteria (*S. aureus* S 1426, *L. monocytogenes* L 49). At the same time, the chloroform extracts also showed antifungal activity against *Aspergillus terreus* F98, while none of the extracts of the seven cyanobacterial strains demonstrated activity against species *Tirchoderma viride* F94. Ethanol extracts from four of the studied cyanobacteria species showed antifungal activity against both yeast strains *C. tropicalis* Y26 and *S. cerevisiae* Y39, and for ethyl acetate extracts from all cyanobacteria species, the antifungal capacity against *S. cerevisiae* was also established [62].

Screening of bioactive substances from 4 species of cyanobacteria (*Lyngbya* sp, *Nostoc* sp, *Phormidum* sp and *Calothrix* sp.) isolated from the South East Coast of India was carried out by Indian researchers. Chloroform cyanobacterial extracts were examined by in vitro analysis to evaluate the antimicrobial effects on four pathogenic bacteria (*S. aureus, P. aeruginosa*, *B. subtilis*, *E. coli*) and two fungal species (*A. niger* and *Penicillium* sp.) using the disk diffusion method. Among the four cyanobacterial extracts, *Lyngbya* sp.extract demonstrated a considerable inhibitory effect on the investigated bacterial and fungal pathogens. The most extensive inhibition zone (10 mm) was observed against the *E. coli* strain and the least inhibition activity against *P. aeruginosa* (7.5 mm). The antimicrobial bioassay of the extracts was examined by determining the minimum inhibitory concentration (MIC) with all pathogenic bacteria and fungi. The MIC results of the tests showed that the extracts had a significant influence on the studied microbial pathogens. [69].

Many species of cyanobacteria produce cytotoxic substances, with antibacterial, antifungal and anticancer effects, they are represented by cyclic peptides microcystins (Microcystis, Anabaena, Planktothrix (Oscillatoria), Nostoc, Hapalosiphon, Anabaenopsis) and nodularin (Nodularia), alkaloids (Anabaena, Planktothrix (Oscillatoria), Aphanizomenon, Lyngbya, Schizothrix, Aphanizomenon, Umekazia, Lyngbya, Cylindrospermopsis) and lipopolysaccharides, present in all extant cyanobacteria [70].

In a more recent study, cyanobacterial strains from Brazilian natural product habitats were analyzed to evaluate the antileukemic and antimicrobial activity of their extracts. Thus the Brazilian cyanobacteria belonging to the orders: Synechococcales, Oscillatoriales, Chroococcales, Chroococcidiopsidales, and Nostocales showed anticancer, antibacterial and antifungal activity. Through mass spectrometric analysis and with a dereplication tool, the toxic compounds known as microcystin, saxitoxin, aeruginosin, hassallidin, nodularin, anabaenopeptin, pseudoaeruginosin and puwainaphycin A were identified in the composition of the cyanobacteria. Unknown chlorinated molecules were also detected in the extracts that would present interest as cytotoxic agents [10].

The antimicrobial capacity of the 50% methanolic extracts obtained from 4 species of algae *Ascophyllum nodosum*, *Chlorella vulgaris, Lithotamnium calcareum* and *Schizochytriu*m spp. and from the cyanobacterium *A.platensis* was also evaluated on porcine *E. coli* O138 [21]. To detect the presence of major virulence factors characterized by PCR, the inhibition effect of diluted extracts at concentrations of 25vol%, 12.5vol%, 6vol%, 3vol% and 1.5vol% on the growth of porcine E. coli O138 was determined by the bacterial growth method by microdilution. All tested extracts showed an increase in inhibition activity at the concentration of 25 vol%.

TYAGI et al. examined some cyanobacteria for the evaluation of their antibacterial and antifungal properties, using their extracts in three different solvents (ethanol, methanol-toluene (3:1) and acetone), on agar solidified nutrient medium by the agar diffusion method. The tested extracts from only five cyanobacteria: *Westiellopsis prolifica* ARM 365, *Hapalosiphon hibernicus* ARM 178, *Nostoc muscorm* ARM 221, *Fischerella* sp. ARM 354 and *Scytonema* sp. have demonstrated antimicrobial activity on the bacteria *P.striata*, *B. subtilis*, *E. coli*, *Bradyrhizobium* sp. and fungi *A. niger*, *A. brassicae* and *F.moniliforme*. The ethanolic extracts from the cyanobacteria *W. prolifica* ARM 365 and *H. hibernicus* ARM 178 showed the highest antibacterial and antifungal activity on the tested bacteria and fungi, the formation of the extended inhibition zone on the solidified agar nutrient medium being highlighted proved to be the most prominent. The ethanolic extracts of *H. hibernicus* ARM 178 and *W. prolifica* ARM 365 inhibited the growth of bacteria *P. striata* more strongly, compared to the growth of *A. niger*. These antimicrobial compounds may have pharmaceutical and bio control applications or agricultural potential [71].

Chloroform, methanol and aqueous extracts were obtained from the cyanobacterium *Dolichospermum affine* isolated from fresh water and tested for their effectiveness against 5 pathogenic bacterial strains (*P.*

aeruginosa (ATCC 27853), *Shigella dysenteriae* (ATCC 11835), *E. coli* (ATCC 25924), *S. aureus* (ATCC 29213) and B. *subtilis* (ATCC 6633). In case of methanolic extracts, the highest antimicrobial activity was observed for *E. coli* (DIZ=13.9±0.05 mm), followed by *B*. subtilis (DIZ=13.6±0.05 mm). Minimal antibacterial effect of chloroform extracts of *D. affine* was observed on *P.aeruginosa* (DIZ=11.7±0.02 mm) and *S. aureus* (DIZ=12.2±0.03 mm). No zone of inhibition was detected for gram-negative bacteria *S. dysenteria*. The aqueous extract showed weak activities against the tested pathogenic bacteria. Therefore, this study revealed that extracts of *D. affine* would be a promising natural resource of new antibiotics and additional research is needed related to the isolation and purification of the fractions of bioactive substances of interest [72].

Gheda and Ismaiel tested ethyl acetate, n-hexane and methanol extracts of six species of cyanobacteria isolated from rice fields in Egypt for their antimicrobial activity, using the disk diffusion method. Methanol extracts of *O.acuminata*, *O.amphigranulata* and *S.platensis* showed the largest zones of inhibition. The minimum inhibitory concentration of the *O. amphigranulata* extract recorded lower values. Both methanolic extracts of *O. acuminata* and *O. amphigranulata* showed high cytotoxicity activity on liver cancer cell lines HepG2, colon cancer cell lines HCT-116 and mammary gland adenocarcinoma cell lines MCF-7. At the same time, the *S. platensis* extract showed a moderate cytotoxicity for all cell lines. The results of gas chromatography/mass spectroscopy analysis revealed that the potential activity (of these cyanobacteria extracts could be attributed to a synergistic effect between their pronounced content of fatty acids, alkaloids, phytol, hydrocarbons, phenolic compounds, especially fatty acids [31].

Recently research relating to screening of antimicrobial compounds isolated from cyanobacteria includes in vitro approaches such as activity assays, as well as in silico approaches using contemporary genome extraction tools, extraction and bioactivity assays of bioactive compounds from cyanobacteria providing more extensive data on the antimicrobial action of bioactive compounds obtained from cyanobacteria. In addition to classical methods of antimicrobial activity assessment this study provides an overview of developments in the area of genome-based screening, using in vivo the PCR technique or in silico - a recent genome extraction method [73]. The summary tools are applicable. not only for cyanobacteria and can also be transferred to other microorganisms.

Conclusions

Based on the analysis of data presented by a series of authors over the last two decades, it has been concluded that a key factor in the fight against the spread of drug-resistant pathogens is the identification of new antibacterial, antiviral, antifungal and anticancer substances produced by cyanobacteria and algae and promoting on the market new treatments with their use.

Numerous researches carried out in vitro have allowed that species of cyanobacteria such as: *Spirulina platensis* (Gomont), *Anabaena* sp., *A. variabilis* (Kutz.), *A.ambigua*, *A.flos-aquae*, *Nostoc* sp., *N. muscorum (*Agardh), *N. linckia* (Bornet), *N.piscinale ,Oscillatoria* sp., *O. acuminata* (Gomont), *O. amphigranulata* (Goor), *Phormidium* sp., *Lyngbya officinalis*, *Gleocapsa gelatinosa*, *Chrococcus* sp, *Aulosira fertillisma*, *Hapalosiphon fontinalis*, *Westiellopsis prolifica*, *Fisherella* sp., *Rivularia mesenterica*, *Dolichospermum affine*, *Scytonema* sp. and other can to be examined as species producing bioactive substances with antimicrobial, antiviral, antifungal action on human pathogens.

The identified compounds with biological activity, produced by cyanobacteria are: alkaloids, depsipeptides, lipopeptides, macrolides/lactones, peptides, terpenes, sulfated polysaccharides (Ca-Spirulan, nostoflan, etc.), C-phycocyanin, lipids (polyunsaturated fatty acids), phenols, pigments, carbohydrates, polyphenols, hydrocarbons, phytoenes/terpenoids, phytols, sterols, phytohormones, cyanotoxins (microcystins, nodularin, alkaloids and lipopolysaccharides), biocides (algicides, herbicides and insecticides) and others compounds.

Therefore, the development of new biotechnologies for obtaining and developing antimicrobial, antiviral, antifungal and antitumor natural products from cyanobacteria and algae is a perspective path in the development of pharmaceuticals worldwide.

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Date desre autori:
Valentina BULIMAGA, doctor în biologie, Universitatea de Stat din Moldova.
ORCID: 0000-0002-5042-2952

Liliana ZOSIM, doctor în biologie,conferențiar cercetător, cercetător științific superior, Universitatea de Stat din Moldova.
ORCID: 0000-0003-0510-8064
E-mail: zosim_liliana@yahoo.fr

Alina TROFIM, dr. **în** biologie, cercetător științific coordonator, Universitatea de Stat din Moldova.
ORCID: 0000-0003-4557-9602

Daniela ELENCIUC, doctor în biologie, șef departament Biologie și Ecologie, Universitatea de Stat din Moldova.
ORCID: 0000-0002-5090-5057

Valeriu RUDIC, doctor habilitat, profesor universitar, acedemician al Academiei de Științe a Moldovei, șef Catedră de Microbiologie, Virusologie și Imunologie, Universitatea de Stat de Medicină și Farmacie „N. Testemițanu”.
ORCID: 0000-0001-8090-3004

Greta BALAN, doctor habilitat, conferenţiar universitar, Catedra de Microbiologie, Virusologie **şi** Imunologie, Universitatea de Stat de Medicină și Farmacie „N. Testemițanu”.
ORCID: 0000-0003-3704-3584

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