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Review

Microalgae as Producers of Biologically Active Compounds with Antibacterial, Antiviral, Antifungal, Antialgal, Antiprotozoal, Antiparasitic and Anticancer Activity

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Abstract

Algae have increasingly gained public importance as a sustainable resource in biomedicine (Lee and Mooney, 2012). In this respect, scientometric studies (Garfield, 2006; Konur, 2020) have a lot to offer to enable the key stakeholders to inform themselves about algal science, technology, and medicine, and the underlying research areas in the fields of algal research, especially in biomedicine (Konur, 2016). The ecological and biological diversity of algae allow the synthesis of a variety of biologically active substances that can offer hope for the treatment of many diseases.

This review aims to emphasize microalgae action against infectious and parasitic diseases, including cancer diseases. The reason to discuss these illnesses together is the way they affect the macroorganism as a host. Therefore, it is crucially important to highlight and to consider the challenging features and activities of microalgae, such as antibacterial, antiviral, antifungal, antialgal, antiprotozoal, antiparasitic and anticancer activities. Studies to date have revealed the enormous ecological role of microalgae and the potential for deriving a variety of metabolites from them to be used for treatment of people, animals and other living beings.

Keywords: microalgae, biologically active compounds, source of medicines

Резюме

Водораслите се сдобиха с нарастваща обществена важност като устойчив ресурс за биомедицината (Lee and Mooney, 2012). В това отношение наукометричните изследвания (Garfield, 2006; Konur, 2020) има какво да предложат, за да може ключовите заинтересовани лица да се информират за науката за водораслите, технология и медицина и прилежащите изследователски области, както и в полето от изследвания на водорасли, особено в биомедицина (Konur, 2016). Екологичното и биологичното разнообразие на водораслите дават възможността да се синтезира многообразие от биологично активни вещества, които могат да бъдат надежда за излекуването на много болести.

Това ревю цели да наблегне на въздействието на микроводораслите срещу заразни и паразитни болести, като също така се включват и раковите заболявания. Причината да се обсъждат тези болести заедно е начинът, по който те засягат макроорганизма като гостоприемник. Затова е от решаващо значение да се изтъкнат и да се разгледат предизвикателните особености и действия на микроводораслите като антибактериално, антивирусно, антигъбно, антиалгиево, антипротозойно, антипаразитно и антираково действие. Проучванията, които са правени досега, разкриват огромната екологична роля на водораслите и възможностите да се добиват от тях разнообразие от метаболити, които да служат за лекуване на хора, животни и други живи същества.

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Introduction

Microalgae are a heterogeneous group of microorganisms which does not represent a separate taxonomic group. They can be found as individual cells, colonies or filaments. This is an ecological group which consists of unicellular algae belonging to a variety of larger groups. They inhabit fresh and brackish waters and marine systems, sometimes rocks and soil. Microalgae are the subject of study of botany, algology and microbiology. Cyanobacteria in particular, which are prokaryotes, are the subject of microbiology, not only of botany and algology. Cyanobacteria, unicellular green algae, unicellular red algae, euglenoids (*Euglenophyta*), *Chrysophyta* and dinoflagellates (*Dinoflagellata*) belong to the ecological group of microalgae. As photosynthetic organisms, microalgae are important to life on Earth. They produce a big part of the atmospheric oxygen and use carbon dioxide to grow photoautotrophically. Their biodiversity is enormous. They are found throughout the entire biosphere. They are able to survive under environmental stresses (Minhas *et al.*, 2016), more specifically heat, cold, drought, salinity, photo-oxidation, anaerobiosis, osmotic pressure and UV exposure (Tandeau-de-Marsac, 1993).

Many algal species possess the ability of creating allelopathy. Allelopathy is a biological phenomenon by which an organism produces one or more biochemicals that influence the germination, growth, survival and reproduction of other organisms. These biochemicals are known as allelochemicals and can have beneficial (positive allelopathy) or detrimental (negative allelopathy) effects on the target organisms and the community. Allelochemicals belong to secondary metabolites. The phenomenon of allelopathy can be used as a biological method for suppressing algal bloom and microbial contamination of the environment (contamination with bacteria, fungi and protozoa). Microalgae produce a large number of biological active compounds (BACs) with biotechnological and clinical applications. Drug resistance of bacteria and other microorganisms is a major problem in the healthcare of people and animals.

Therefore, algae, especially microalgae, are considered to be a source of novel antibacterial substances that researchers hope will not lead to drug resistance. More importantly, their cultivation in large-scale photobioreactors can be controlled and as a result high and ultra-high density culture conditions can be achieved (Richmond, 2004; Gordon and Polle, 2007; Sun *et al.*, 2019; Wang *et al.*, 2019; Jin *et al.*, 2020).

Pursuing this train of thoughts, the mini-review tries to focus on BACs which represent the antimicrobial activity of microalgae in seven aspects: antibacterial, antiviral, antifungal, antialgal, antiprotozoal, antiparasitic, and anticancer activity.

Antibacterial activity

As antibacterial agents, microalgae can suppress the growth of pathogenic bacteria in water and prevent the appearance of bacterial diseases in water inhabitants. It is a very common method to use microalgae in growing water cultures in order to prevent the development of bacterial diseases. The microalgal cultures of *Chlorella minutissima*, *Tetraselmis chui*, *Nannochloropsis* sp., *A. platensis* and *Isochrysis* sp. inhibited the growth of bacteria in the culture (Kokou *et al.*, 2012). In this work it was shown that the growth of strains belonging to the following six bacterial species was inhibited: *Vibrio parahaemolyticus, V. anguillarum, V. splendidus, V. scophthalmi, V. alginolyticus* and *V. lentus*.

It is believed that the first antibacterial compound (chlorellin) was isolated from the microalga *Chlorella* sp. (Pratt *et al.*, 1944). It presented inhibitory activity against Gram-positive and Gram-nrgative bacteria.

Some microalgae species exert antimicrobial activity in many different ways. *Fischerella ambigua* isolated from a soil sample produces parsiguine, which has antibacterial and antifungal activity (Ghasemi *et al.*, 2004). Parsiguine has activity against *Staphylococcus epidermidis* PTCC 1114 and *Candida krusei* ATCC 44507.

The marine diatom *Phaeodactylum tricornutum* possesses antibacterial substances against many bacterial species (Desbois *et al.*, 2009). The main isolated and identified active substance is eicosapentaenoic acid (EPA). Highly susceptible to EPA in this study are the multidrug-resistant *S. aureus* (MRSA) strains 16a and 252, other strains of the same species, *S. epidermidis*, *Bacillus weihenstephanensis,* and *B. cereus*. Susceptible to EPA are also *V.* (*Listonella*) *anguillarum* (a fish pathogen which causes deadly haemorrhagic septicaemic disease), *Micrococcus luteus*, *Photobacterium* sp., *Planococcus citaeus*. Eicosapentaenoic acid is toxic for grazers (Jüttner, 2001). Hexadecatrienoic acid isolated from *P. tricornutum* shows activity against *S. aureus* (Amaro *et al.*, 2011).

Ethanol extracts from *Haematococcus pluvialis* in its red stage possess antimicrobial activity against *E. coli* and *S. aureus.* The reason for that action most probably is the presence of the short-chain fatty acids butanoic and methyl lactic acids

(Santoyo *et al.*, 2009).

Polyunsaturated aldehydes have a special place among algal bioactive substances. They are synthesized by diatoms, e.g. *Skeletonema marinoi* (Vidoudez *et al.*, 2008) (formerly *Skeletonema costatum*) (Sarno *et al.*, 2005), *Pseudonitzschia delicatissima* and *Thalassiosira rotula* (Miralto *et al.*, 1999). An example of this is decadienal (probably derived from arachidonic acid), which demonstrates a strong activity against important human pathogens like MRSA and *Haemophilus influenza,* as well as against *E. coli* and *Pseudomonas aeruginosa*, and *S. aureus* and *S. epidermidis*. Moreover, it decreases the growth of diverse marine bacteria, such as the Gram- *Aeromonas hydrophila*, *V. anguillarum, Alteromonas haloplankti, Photobacterium phosphoreum* and *Psychrobacter immobilis*, and the Gram-positive *P. citreus* and *M. luteus* (Smith *et al.*, 2010).

The extracellular metabolites from *S. costatum* in the middle steady-state growth phase have shown an effect against *Listeria monocytogenes* (Terekhova *et al.*, 2009). Naviner and coworkers detected antibacterial activity in organic extract of *S. costatum* against many species of *Vibrio* (Naviner *et al.*, 1999). In their study, this extract inhibited the growth of *V. mytili* T, *Vibrio* sp. S322 (Japanese oyster larvae pathogen), *Vibrio* sp. VRP (clam larvae pathogen), and *V. anguillarum*.

Strains of *Chroococcus dispersus*, *C. vulgaris* and *Chlamydomonas reinhardtii* showed significant activity against the bacteria *S. aureus, S. epidermidis, B. subtilis, E. coli* and *Salmonella typhi* (Ghasemi *et al.*, 2007). In this study, strains of *C. dispersus* also inhibited the growth of *P. aeruginosa*.

A study of Das and coworkers ascertained that organic extracts from *Euglena viridis* inhibit the growth of *P. aeruginosa*, *P. putida*, *P. fluorescence*, *A. hydrophyla*, *Edwardsiella tarda*, *V. alginolyticus*, *V. anguillarum*, *V. fluvialis*, *V. parahaemolyticus*, *V. harveyi* and *E. coli* (Das *et al.*, 2005).

It should be noted that the methods for metabolite extraction from microalgae are very well developed (Cuellar-Bermudez *et al*., 2014; Alassali *et al*., 2016; Stirk *et al.*, 2020). Moreover, current literature offers methods and strategies (in books, review and papers) for identification, isolation and extraction of many various secondary metabolites from microalgae.

Antiviral activity

A number of viral diseases have emerged (and re-emerged) in recent years. Although several antiviral drugs have been specifically developed, drug-resistant mutations are constantly occuring. That is why microalgae have attracted special attention as potential suppliers of antiviral substances (Borowitzka, 1995).

The viral infection is divided into three stages:

Stage I, which consists of adsorption and invasion of cells;

Stage II, or eclipse phase, during which the cell is forced to synthesize multiple copies of the virus;

Stage III, or maturity and release of virus particles (Amaro *et al.*, 2011). For example, the anti-HSV activity of the antiviral compound acyclovir manifests itself at stage II (Elion *et al.*, 1977; Schaeffer *et al.*, 1978; Elion, 1982), but the anti-HSV factor from *Dunaliella* spp. inactivates the viral function at stage I (Ohta *et al.*, 1998). The antiviral activity was expressed during HSV adsorption and invasion of the cells (Ohta *et al*., 1998). The extract of *Dunaliella primolecta* had the highest anti HSV-1 activity. Using chromatographic techniques, three *substances* were purified from *D. primolecta,* which showed anti-HSV effect. The substances were identified as pheophorbide-like compounds using NMR and MS analyses.

The sulfated polysaccharide from the cell wall of the red microalga *Porphyridium* sp. has impressive antiviral activity against *Herpes simplex* virus types 1 and 2 (HSV 1, 2) and *Varicella zoster* virus (VZV) (Huleihel *et al.*, 2001). Another antiviral action of sulfated polysaccharides was found against the viral hemorrhagic septicemia virus (VHSV) of salmonid fish and the African swine fever virus (ASFV), which are economically significant viruses (Fabregas *et al*., 1999). Endocellular extracts from *Porphyridium cruentum*, *C. autotrophica*, *Isochrysis galbana* var. Tiso, *Ellipsoidon* sp., and *D. tertiolecta* were able to inhibit VHSV replication. The extracts from *P. cruentum*, *C. autotrophica* and *Ellipsoidon* sp. inhibited ASFV replication as well (Fabregas *et al*., 1999).

Allophycocyanin isolated from *Spirulina platensis* decreased the cytopathic effect of cells infected by enterovirus 71. Enterovirus 71 infection is a socially significant disease which causes visible morbidity and mortality among children. For this reason, the discovery of the action of allophycocyanin is important. The mechanism of its antiviral effect is a delay in the viral RNA synthesis in the infected cells and a reduction in the apoptotic process in rhabdomyosarcoma cells infected by enterovirus 71 (Shih *et al.*, 2003).

Many other polysaccharides from marine algae have important antiviral actions. Details can be found in the work of authors (Ahmadi *et al.*, 2015). A good example is the sulphated polysaccharide naviculan, isolated from the diatom *Navicula directa* (Lee *et al.*, 2006). The studies of Lee and coworkers established that naviculan has a strong antiviral activity against HSV-1 and HSV-2 (IC_{50}: 7–14 μg/mL) and the influenza virus. The activity is expressed in inhibition of the initial stages of viral replication. Remarkably, in this study naviculan demonstrated an inhibitory effect of HIV infection. The mechanism of the inhibitory action of this polysaccharide was the influence on the virus binding and penetration processes. Naviculan hinders the fusion between the cells which express CD4 receptor and the HeLa cell line, which expresses HIV gp160 glycoprotein.

The sulphated exopolysaccharide p-KG03 from *Gyrodinium impudicum* manifested impressive antiviral activity in vitro (EC_{50} = 26.9 µg/ml) against the encephalomyocarditis virus (EMCV) (Yim *et al.*, 2004). *Cochlodinium polykrikoides* produces polysaccharide A1 and A2, which inhibited the cytopathic effect of the following viruses: influenza virus types A and B in MDCK cells, respiratory syncytial virus types A and B in HEp-2 cells, and human immunodeficiency virus type 1 in MT-4 cells (Hasui *et al.*, 1995).

Calcium spirulan isolated from *Arthrospira platensis* was found to be a selective inhibitor of the viruses HSV-1 (in HeLa cells), HCMV (in HEL cells), influenza A (in MDCK cells), Coxsackie virus (in Vero cells), measles (in Vero cells), HIV-1 (in MT-4 cells), polio (in Vero cells), and mumps (in Vero cells) (Hayashi *et al.*, 1996).

Nostoc flagelliforme produces the acidic polysaccharide nostoflan. It inhibits the viruses HSV-1 and HSV-2, human cytomegalovirus and influenza A virus (Kanekiyo *et al.*, 2007). The study showed that in HSV the antiviral effect is due to preventing the virus from binding to the host cell.

Analyzing the data in this area, it can be concluded that many challenges still remain; however, the success in the current state of art emphasizes the new frontiers beyond which researchers can find the key to sustainable cure of virus diseases.

Antifungal activity

Fungal infections are known for their persistence. Pathogenic yeasts are common infectious agents among people and animals. Candidiasis is a common yeast infection in the human population. More than a half of women have experienced at least once in their life candidiasis. *Candida* spp. infections are some of the most persistent among women. If left untreated, they lead to infertility (Pellati *et al.*, 2008), arthritis (Yordanov *et al.*, 2004), and other body damages. Immunocompromised people are susceptible to fungal diseases – yeasts and mould spores.

Once again, attention is directed to the substance parsiguine isolated from *F. ambigua*, which has not only antibacterial action, as mentioned above, but is also active against the yeast *C. krusei* ATCC 44507 (Ghasemi *et al.*, 2004).

Recently, ten microalgal strains were isolated from freshwater reservoirs in Turkey. They possessed antifungal activity against the yeast species *Saccharomyces cerevisiae*, *C. albicans* and *C. tropicalis*. *Oscillatoria* sp. and *Chlorococcus* sp. performed the best results against these yeast species (Katircioglu *et al.*, 2006).

Ethanol extracts of *H. pluvialis* were tested against *C. albicans* and *Aspergillus niger* (Santoyo *et al.*, 2009). All extracts were active against *C. albicans*, but not against *A. niger.* The main compounds responsible for this antifungal activity were found to be butanoic acid and methyl lactate, both of which had previously been described to possess antimicrobial activity (Smulders *et al.*, 1986; Cherrington *et al.*, 1991).

C. reinhardtii has been showing a broad spectrum of activities. In particular, it has not only antibacterial but antifungal activities as well. Ghasemi and coworkers (Ghasemi *et al.*, 2007) found that C. *reinhardtii* inhibited the growth of *C. kefyr, A. niger* and *A. fumigatus*.

Marres and coworkers tested *Scenedesmus obliquus* extracts for antifungal activity (Marres *et al.*, 2019). The tested fungi were: *A. flavus, A. steinii, A. ochraceus, A. parasiticus, A. westerdijikia, A. carbonarius, Fusarium verticillioides, F. proliferatum* and *Penicillium verrucosum.* The diethyl ether extract of *S. obliquus* inhibited the growth of all listed fungal species. Aqueous, methanolic, ethanolic, acetone and chloroform extracts showed activity only to some of the tested fungal species. For example, the aqueous extract had activity against *A. flavus, A. steinii, A. westerdijikia* and *A. carbonarius*.

Karatungiols A and B were isolated from the marine dinoflagellate *Amphidinium* sp. (Washida *et al.*, 2006). They were identified as polyols. The investigation found that karatungiol A performed an activity against *A. niger* with a concentration of 12 µg/disc.

According to the study of Abedin and Taha, ethanol, acetone, diethyl ether and methanolic extracts of *S. quadricauda* have shown antifungal activity against *A. niger, A. flavus, P. herquei* and *F. moilifore* (Abedin and Taha, 2008).

Extracts of *C. vulgaris* and *C. minutissima* have a strong activity against *A. niger* and *F. oxysporum* when they are cultivated on Iroko tree extract water (Vehapi *et al.*, 2018). The study revealed a difference in their antifungal activity when they were grown in other media and it was lower when grown in BBM medium and Istanbul's waste water.

In the work of Ghasemi and coworkers (Ghasemi *et al*., 2007), supernatants of 15 strains of the algae *C. reinhardtii*, *C. dispersus*, *C. vulgaris*, *Chlorella* sp., *Anacystis nidulans*, *C. ellipsoidea* and *Oocystis* sp. exhibited a good and moderate antifungal activity against *C. kefyr*, *A. fumigatus* and *A. niger*. Only strain *C. dispersus* 039 had activity against *C. albicans*. The other algal extracts tested did not have any activity against *C. albicans*.

Hence, the antifungal activity of microalgal species can be optimized by using not only engineering specification and methods of cultivation, but application of modern molecular methods for redirection of algal metabolism to desired targeted intra- and extracellular metabolites.

Antialgal activity

Inhibitory phenomena among algae have been reported over the past years. Some species inhibit their own growth during a certain stage of growth by producing secondary metabolites. This phenomenon is called autoinhibition. Examples of this are *S. costatum* (Imada *et al.*, 1992) and *H. pluvialis* (Sun *et al.*, 2001). Other species can inhibit the growth and reproduction of different algal species in the surrounding environment. A third kind of microalgae at some stage of growth inhibit themselves and other algal species (Yingying *et al.*, 2008; Sun *et al.*, 2012). This interaction appears in mixed culture conditions when the product of one species is inhibitor to other ones. This phenomenon is well documented in scientific literature on bacterial mixed culture and its interactions (Botta and Cocolin, 2012; Smid and Lacroix, 2013; Zhang and Zeng, 2019). *I. galbana*, which belongs to the unranked taxon *Haptophyta* (*Prymnesiophyta*), is such an example. The growth inhibitor isolated from *I. galbana* was identified as 1-[hydroxyl-diethyl malonate]-isopropyl dodecenoic acid, $C_{22}H_{38}O_7$ (Yingying *et al.*, 2008). It inhibited the growth of *I. galbana* itself, *D. salina, P. elliptica*, *C. vugralis*, *Nitzschia closterium*, *Chaetoceros muelleri*, *C. gracilis*, *N. closterium f. minutissima* and *P. tricornutum*. The production of antialgal substances from *I. galbana* increases from the exponential to death phase of cultivation (Sun *et al.*, 2012). The ethyl acetate extract of this microalga was studied. It showed significant growth inhibition to *I. galbana* itself, to *C. muelleri, C. gracilis, P. tricornutum, N. closterium, Platymonas elliptica* and *D. salina*. Fucoxanthin is a major carotenoid in *I. galbana* (Kim *et al.*, 2012), but in the research of Sun et al. it was found that stearic acid and oleic acid are the main compounds of the studied ethyl acetate extract. Probably these substances suppress the growth of these microalgae.

The cyanobacterium *Microcystis aeruginosa* (NIES-87) produces the tetrapeptide kasumigamide, which inhibits the growth of *C. neglecta* (NIES-439) (Ishida and Murakami, 2000). A study of Proctor (Proctor, 1957) found that *C. reinhardii* and *H. pluvialis* cannot exist together in one and the same place. *C. reinhardii* liberates substances which inhibit the growth of *H. pluvialis*. It is supposed that the inhibitor is a long-chain fatty acid or mixture of such acids.

Peridinium bipes exercises an inhibitory effect over the growth of *M. aeruginosa*. The water-soluble extract from *P. bipes* caused leakage of phycobilines phycocyanin and allophycocyanin from the cells of *M. aeruginosa* (Wu *et al*., 1998).

Macroalgae can inhibit the growth of microalgae (Sun *et al.*, 2016; Sun *et al.*, 2018). The green alga *Ulva prolifera* produces substances, which inhibit the growth of red tide microalgae (Sun *et al.*, 2016). Ten substances were isolated from *U. prolifera* and they successfully inhibited the red microalgae. They are 1-O-octadecanoic acid-3-O-β-D-galactopyranosyl glycerol (2), 1-O-palmitoyl-3-O-β-D-galactopyranosyl glycerol (4), 1-O-palmitoyl-2-O-oleoyl-3-O-β-D-galactopyranosyl glycerol (5); glycerol monopalmitate (1), 9-hexadecenoic acid 2,3-dihydroxypropyl ester (3); loliolide (6), isololiolide (7); zeaxanthin (8); cholest-5-en-3-ol (9) and pyrrolopiperazine-2,5-dione (10). *U. pertusa* produces 9 antialgal compounds against red tide microalgae (Sun *et al.*, 2018).

The review of literature in this paragraph clearly shows that microalgal interactions in a mixed culture is a crucially important topic and

opens new frontiers for control and optimization of algal populations in research as well as in environmental niches.

Antiprotozoal activity

Protozoal infections affect predominantly people of the tropical regions. Very often the affected people are among the poorest in the world. According to the World Health Organization for the year 2013, one billion people suffer from protozoal diseases. Billions of animals are affected, too. Protozoa are unicellular organisms which are eukaryotic like the cells of their hosts. It means that they have similar cell structures. Hence, it is hard to invent effective antiprotozoal medicines which are not strongly toxic to the hosts. The problem with the drug resistance of protozoa has to be considered, as well. Thanks to their specific physiology, algae are an inexhaustible source of diversity of BAC. Therefore, they focus the attention of researchers around the world in the field of antiprotozoal activity. Many of the studies on antiprotozoal activity are bound with macroalgae (Torres *et al.*, 2014).

For example, the marine dinoflagellate *Amphidinium* sp. expresses antiprotozoal activity too. Karatungiol A, which was isolated from this alga, exhibited antiprotozoan activity against *Tritrichomonas foetus* at concentration 1 μg/ml (Washida *et al.*, 2006). *Calothrix* sp. produces the indole [3,2-j] phenanthridines named calothrixins A and B. They have antiplasmodial activity against *Plasmodium falciparum* FAF6 (Rickards *et al.*, 1999). Ambigol C is a natural product, isolated from *F. ambigua.* It has a moderate antiprotozoal activity against *P. falciparum* clone KI (IC_{50} = 1.5 Lg mL^{-1}) and NF54 (IC_{50} = 2.4 Lg mL^{-1}) (Perez *et al.*, 1990) and a moderate activity against *Trypanosoma rhodesiense* (Wright *et al.*, 2005). From the strain *M. aeruginosa* PCC 7806, aerucyclamides A, B (Portmann *et al.*, 2008a), C and D were isolated (Portmann *et al.*, 2008b). Submicromolar IC_{50} values were determined for aerucyclamide B against *P. falciparum.* Aerucyclamide C had low micromolar values against *T. brucei rhodesiense* (Portmann *et al.*, 2008b). Nostocarboline is a β-carboline indole alkaloid, isolated from *Nostoc* sp. 78-12A (Barbaras *et al.*, 2008). It exhibited a pronounced activity against *P. falciparum* K1. Nostocarboline inhibited *Plasmodium* sp. in nanomolar concentration.

In conclusion of this paragraph, it seems that many studies in this field give hope that algae/microalgae can be successfully used as antiprotozoal agents and their antiprotozoal activity can be monitored, controlled and optimized.

Antiparasitic activity

In addition to antiprotozoal activity, antiparasitic substances against multicellular parasitic organisms (mainly parasitic animals) can be isolated from algae and microalgae. Alkaloid and ethyl acetate extracts from *Cladophora crispata* decrease the number and the weight of the hydatid cysts of *Echinococcus granulosus* (Athbi *et al.*, 2014). The study was compared with the effect of the traditional medicine albendazole. The smallest number and size of the cysts after treatment was found after treatment with albendazole, though alkaloid and ethyl acetate extracts had similar effect on *E. granulosus* hydatid cysts.

One of the latest findings in the research of *C. vulgaris* shows that its extracts exhibit toxicity against the nematode *Steinernema feltiae* (Zielinsky *et al.*, 2020). *S. feltiae* parasitizes insects and infects them with enthomopathogenic bacteria, as well. According to the study, the hydrophilic extract of *C. vulgaris* is lethal for this nematode in concentrations of 37.5, 75 and 150 mg/mL with complete mortality.

Parasitic diseases are socially important for people and are a problem for domestic animals. More studies have been conducted on antiparasitic agents derived from macroalgae than from microalgae. Hence, many microalgae species can be researched for future antiparasitics.

Anticancer activity

The fight against cancer has been a major challenge in medicine and veterinary medicine for decades. The key problem arises from the close similarity between a normal and a cancer cell, which makes the application of effective anticancer medicines very difficult without causing side effects to normal cells. Many plants, bacteria, fungi and synthetic compounds have been studied in order to identify substances with anti-cancer activity in their metabolites. Research in this area has been of varying success. Algae, especially microalgae, appear to be one of the hopes for finding effective anticancer substances.

In this part attention will be focused on studies on anticancer activity, including those of Martinez-Andrade *et al*. (2018).

The production of BACs from algae can vary depending on the growth conditions. The changes of light, temperature and nutrients have influenced biosynthesis (Martinez-Andrade *et al.*, 2018). For example, the diatom *S. marinoi* manifested anti-cancer activity against human melanoma cells (A2058) when it was cultured in nitrogen depletion

conditions (Lauritano *et al.*, 2016).

Carotenoids are a popular group of anticancer substances isolated from microalgae. *Chlorella* spp. are a commercial source of lutein, β-carotene, zeaxanthin and astaxanthin. Carotenoids isolated from the marine *C. ellipsoidea* and freshwater *C. vulgaris* have shown antiproliferative activity (Kwang *et al.*, 2008). The main carotenoid from *C. ellipsoidea* is violaxanthin and the other two minor substances are the xanthophylls antheraxanthin and zeaxanthin, whereas the main carotenoid from *C. vulgaris* is lutein for those particular culture conditions. The extracts from both species express anticancer activity against human colon cancer cells. Violaxanthin isolated from *D. tertiolecta* showed inhibition of the growth of breast adenocarcinoma cell line (line MCF-7) (Pasquet *et al.*, 2011).

Polyunsaturated aldehydes are another important group of anticancer substances isolated from microalgae. Two decades ago, three polyunsaturated aldehydes were isolated from the marine diatoms *Talassiosira rotula, S. costatum* and *P. delicatissima* (Miralto *et al.*, 1999). The substances were 2-*trans*-4-*cis*-7-*cis*- decatrienal, 2-*trans*-4-*trans*-7-*cis*-decatrienal and 2-*trans*-4-*trans*-decadienal. Miralto and coworkers found that they had anti-proliferative activity on human colon adenocarcinoma cell line (Caco-2).

An aqueous extract from *C. sorokiniana* reduces cell viability of non-small-cell lung cancer cell line (NSCLC) (A549 and CL1-5 human lung adenocarcinoma cells) (Lin *et al.*, 2017). It is important to note that when working with extracts the mortality of cancer cells depends on the concentration of the extract, where many metabolites with different chemical structure are present. Further work is needed to identify and isolate the target chemical agent, which is area of downstream processing.

Synthetic polyunsaturated aldehydes (PUAs) (initially discovered in diatoms, including *S. marinoi*) were used in the study of Sansone and coworkers (Sansone *et al.*, 2014). *They inhibited the proliferation of* Lung adenocarcinoma (A549) and Colon adenocarcinoma (COLO 205) cell lines, but did not significantly reduce cell viability of the normal cells (BEAS-2B cells). Chrysolaminaran isolated from the diatom *Synedra acus* inhibited the growth of Colorectal adenocarcinoma (lines HT-29 and DLD-1), while being non-toxic for the normal cells (Kusaikin *et al.*, 2010).

Most probably, *Navicula* species can perform anticancer activities. Stigmasterol isolated from *N. incerta* induced apoptosis in human hepatoma HepG2 cells (Liver hepatocellular carcinoma) (Kim *et al.*, 2014).

Fucoxantine is a carotenoid found in seaweeds and diatoms (Peng *et al.*, 2011). It has a variety of bioactivities, including cancer activity. It is found, for example, in the diatom species *Chaetoceros* sp.*, Cylindrotheca closterium, P. tricornutum,* and some others. Fucoxantine reduced the viability of the following cancer cell lines: Promyelocytic leukemia (HL-60), Caco-2, colon adenocarcinoma (HT-29), DLD-1 and prostate cancer (PC-3, DU145 and LNCaP).

Eicosapentaenoic acid derived from *Cocconeis scutellum* triggers apoptotic activity in breast carcinoma cells (BT20) (Nappo *et al.*, 2012).

C. calcitrans produces substances against breast cancer, which induce apoptosis. Two studies demonstrated this phenomenon. According to Goh and coworkers, crude ethyl acetate extract of *C. calcitrans* together with *Nannochloropsis oculata* suppressed the growth of breast adenocarcinoma (MDA-MB-231) (Goh *et al.*, 2014). Nigjeh and coworkers established that the ethanol extract of *C. calcitrans* has a cytotoxic effect against the human breast cancer cell line MCF-7 (Nigjeh *et al.*, 2013).

P. tricornutum appeared to have a broad spectrum of activities. This includes anticancer activity, which is demonstrated by inducing of apoptosis. Fatty alcohol ester nonyl 8-acetoxy-6-methyloctanoate (NAMO) isolated from this diatom has anticancer activity against human promyelocytic leukemia (HL-60), human lung carcinoma (A549) and mouse melanoma (B16F10) (Samarakoon *et al.*, 2014). Galactolipids (monogalactosyl diacylglycerols) isolated from *P. tricornutum* induced apoptosis of cancer cells (Andrianasolo *et al.*, 2008). Samarakoon and coworkers studied BACs of dinoflagellate *Amphidinium carterae* (Samarakoon *et al.*, 2013). Its extracts were tested on the same cell lines of his previous study - human promyelocytic leukemia (HL-60), human lung carcinoma (A549) and mouse melanoma (B16F10). Hexane fractions and ethyl acetate fractions from *A. carterae* effectively suppressed the growth of these cell lines in vitro.

Methanolic extracts of *A. operculatum* and *Ostreopsis ovata* had cytotoxic activity against the cell line HL-60 (Shah *et al.*, 2014). Many other studies prove the cytotoxicity of microalgae extracts (Khanavi *et al.*, 2012; Ávila-Román *et al.*, 2016).

The enormous potential of microalgae and cyanobacteria to produce BAC with anticancer

activities has attracted attention in many areas of medical research (Park *et al.*, 2017; Moshfegh *et al.*, 2019; Fayyad *et al.*, 2019; James and Thomas, 2019; Abd El-Hack *et al.*, 2019; Senousy *et al.*, 2020). Therefore, future prospects and trends show bright horizons for the application of BAC from microalgae in cancer therapy as well as in all branches of medicine, especially those related to infections.

Conclusions

This review has examined the role of microalgae in the fight against infectious and parasitic diseases including cancer diseases (although not every cancer is caused by a virus all cancer cells invade the body and are therefore included in this review). The ecological diversity of algae and microalgae allows the production of a much wider diversity of substances against these diseases. Extreme environments and modern algal culturing techniques for these organisms are a premise for the biosynthesis and production of an endless variety of BACs with desired properties. There are many groups of algae which synthesize pigments. Pigments as sources of BACs can be applied in many areas of social life. Microalgae can be considered as a new, extremely useful alternative source of medicines which can improve the quality of life of humans and animals.

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