

# A Review on Potential Biotechnological applications of Microalgae

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## ARTICLE INFO

### Article history:

Received on: 17/04/2016

Revised on: 09/05/2016

Accepted on: 17/06/2016

Available online: 30/08/2016

### Key words:

Microalgae, metabolites, extraction, compound, toxins.

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## ABSTRACT

Microalgae are microscopic photosynthetic organisms that are found in both marine and freshwater environments. Microalgae belong to the fastest growing photosynthetic organisms since their cell doubling time can be as little as a few hours. They are highly efficient biological approach for converting CO<sub>2</sub> and nutrients to biomass. Eukaryotic microalgae and cyanobacteria have recently reemerged as promising organisms in the effort to develop sustainable options for production of food and fuel. Marine microalgae constitute a natural source of a variety of drugs for pharmaceutical, food and cosmetic applications—which encompass carotenoids, among others. The bioactive compounds derived from microalgae have anticancer, anti-inflammatory, antimicrobial, and antioxidant activities. The aim of this review is to discuss bioactive metabolites produced by microalgae for possible applications in the Biotechnological fields.

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## INTRODUCTION

Microalgae are marine photosynthetic microorganisms which have the ability to transform carbon dioxide into biochemicals that can be further processed into biofuels, food, feed and high value bioactive compounds (Walker *et al.*, 2005). Microalgae are present in both aquatic as well as terrestrial environment, signifying a large variety of species living in a wide range of habitats. It is predicted that more than 50,000 species of microalgae prevails, but only around 30,000, have been studied and analyzed (Richmond, 2004). The major requirement for growth of algae is sunlight, water, nutrients and arable land. Micro algae have the ability to fix CO<sub>2</sub> using solar energy with efficiency 10 times more than that of the terrestrial plants. Algae are more proficient at utilizing sunlight than terrestrial plants, and they consume harmful pollutants, resource requirements is very less and do not compete with food or agriculture for precious resources (Brennan and Owened, 2010). With regard to biofuels, the biomass obtained from algae is considered likely to be one of the most important sources of renewable energies in the

upcoming future (Demirbas, 2010). Biodiesel production from microalgae is a proven technology, it still overcomes numerous technical and economical constraints that are need to be mentioned (Pienkos and Darzins, 2009) to increase the production and thus lower the final production costs (Oltra, 2011). The extraction of secondary metabolites with potential applications in biomedicine and pharmacology is a quite new trend in microalgal biotechnology. The natural active compounds present in the microalgal biomass is responsible for distinct biological activities, such as cytotoxic, antibiotic, antioxidant, antifungal, anti-inflammatory and antihelminthic compounds (Pulz and Gross, 2004; Gouveia *et al.*, 2008; Plaza *et al.*, 2009 and Patil *et al.*, 2011). The applications of algae are very widespread, including the Biodiesel production, aquaculture feed, and the extraction of nutrients and drugs with higher value (Converti *et al.*, 2009 and Spolaore *et al.*, 2006). *Nannochloropsis oculata* is a unicellular marine algae belonging to the class Eustigmatophyceae (Durmaz, 2007). *N. oculata* contains fats, proteins, carbohydrates, chlorophylls, carotenoids, minerals and trace elements (Sukenic *et al.*, 1999). Microalgae are single celled photosynthetic organisms which have relatively simple requirements for growth, which need sunlight to convert water and carbon dioxide (CO<sub>2</sub>) into proteins, amino acids, lipids, polysaccharides, carotenoids and other bioactive compounds (Asha *et al.*, 2011; Mulbry *et al.*, 2008).

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Microalgae are a promising biomass feedstock owing to their faster growth, higher reproduction rate and reduced greenhouse gas emission. Earlier, microalgae have many broad applications in biotechnology (Walter *et al.*, 2005), including biofuels (Chisti, 2007), pharmaceuticals (Lorenz and Cysewski, 2003), aquaculture etc. (Mulbry *et al.*, 2005) Large volume of microalgal biomass cultivated using low cost resources must be carried out to realize the industrial potentials of microalgae. Currently, all methods of producing microalgal biomass for biofuels production and bioproducts are mainly based on suspension culture. Raceway ponds (Chisti, 2007) and photobioreactors (Mata *et al.*, 2010) are commonly used cultivations in large scales. However, open pond production of biomass has proved to be successful only for a limited number of cultures such as *Spirulina* sp. and *Dunaliella* sp. which can withstand extreme conditions such as very high salinity or high pH (Asha *et al.*, 2011).

### MICROALGAL METABOLITES

Microalgae are significant resource for bioactive metabolites, mainly the application as cytotoxic agents in cancer chemotherapy. From the marine microalgae *Phaeocystis* sp., plenty of antibiotic substances were listed *Phaeocystis pouchetii* is reported to produce acrylic acid, which constitutes about 7.0 % of the dry weight. The antibiotic substances produced are transferred into food chain as evidences were found in digestive tract of Antarctic penguins. Production of  $\beta$  carotene and vitamins is vast in halotolerant algae *Dunaliella* sp. These compounds have much importance for the Mariculture activities (Lipton AP, 2003). Cyanobacteria is well known for isolation of active natural

product as it is a most preferable group of organisms. Cyanobacterial strains such as *Spirulina*, *Anabaena*, *Nostoc* and *Oscillatoria* produce a large variety of secondary metabolites. Blue green algae are known to produce a wide variety of bioactive compounds, which constitutes 40% lipopeptides, 5.6% amino acids, 4.2% fatty acids, 4.2% macrolides and 9% amides. The lipopeptides obtained from cyanobacteria includes different compounds like cytotoxic, antitumor, antiviral, antibiotics and the rest activities include antimalarial, antimycotics, multi-drug resistance reversers, anti feedant, herbicides and immunosuppressive agents (Burja *et al.*, 2011); besides the immune effect, blue green algae improves metabolism.

Cyanobacteria are identified to produce antitumor, antiviral, Plant antifungal compounds and they also have cholesterol-lowering effect in animals and humans (Iwata K *et al.*, 1990). Most of the compounds in cyanobacteria are peptides, including toxins and important candidates for anti-cancer drugs which have a better application in pharmaceutical industries. Peptide synthetases are commonly found in cyanobacteria that are responsible for the production of cyanobacterial hepatotoxins and other peptides.

Among the compounds extracted from microalgae most of them have antimicrobial, antiviral, anticoagulant antienzymatic, antioxidant, antifungal, anti-inflammatory, and anticancer activity, (Priyadarshani and Rath, 2012, Blunt *et al.*, 2006, Mayer and Hamann, 2005, Plaza *et al.*, 2010, Rodríguez-Meizoso *et al.*, 2008, Carvalho *et al.*, 2013). The Microalgae such as *Arthrospira* (*Spirulina*), *Botryococcus braunii*, *Chlorella vulgaris*, *Dunaliella salina*, *Haematococcus pluvialis*, and *Nostoc* were used for extraction of bioactive compounds (Table 1), (Palavra *et al.*, 2011, Nobre *et al.*, 2006, Mendes *et al.*, 2006, Michele *et al.*, 2015).

**Table 1:** Major bioactive metabolites extracted from microalgae.

Microalgae	Bioactive compounds	Reference
<i>Spirulina</i> sp.	Polysaccharides	Amaro <i>et al.</i> , 2013
<i>Spirulina platensis</i>	Phycocyanin, C-phycocyanin, Phenolic acids, tocopherols (vitamin E), neophytadiene, phytol, PUFAs (n-3) fatty acids, oleic acid, linolenic acid, palmitoleic acid	Ibañez and Cifuentes, 2013; Markou and Nerantzis, 2013; Singh and dhar, 2011
<i>Spirulina fusiformis</i>	Diacylglycerols	Singh and dhar, 2011
<i>Haematococcus pluvialis</i>	Astaxanthin, lutein, zeaxanthin, canthaxanthin, lutein, $\beta$ -carotene, oleic acid	Markou and Nerantzis, 2013; Plaza, Herrero, 2009; Markou and Nerantzis, ]
<i>Chlorella</i> sp.	Carotenoids, sulfated polysaccharides, sterols, PUFAs (n-3) fatty acids	Markou and Nerantzis, 2013
<i>Chlorella vulgaris</i>	Canthaxanthin, astaxanthin, peptide, oleic acid	[Priyadarshani and rath 2012; plaza and Herrero, 2009 , Amaro <i>et al.</i> , 2013]
<i>Chlorella minutissima</i>	Eicosapentaenoic acid (EPA)	[Singh and dhar, 2011]
<i>Chlorella ellipsoidea</i>	Zeaxanthin, violaxanthin	Amaro <i>et al.</i> , 2013
<i>Dunaliella salina</i>	trans-Betacarotene, cis-betacarotene, $\beta$ -carotene, oleic acid, linolenic acid, palmitic acid	12, plaza and Herrero, 2009; Singh and dhar, 2011
<i>Dunaliella</i>	Diacylglycerols	Singh and dhar, 2011
<i>Botryococcus braunii</i>	Linear alkadienes (C25, C27, C29, and C31), triene (C29)	Jesus, <i>et al.</i> , 2013
<i>Chlorella zofingiensis</i>	Astaxanthin	Markou and Nerantzis, 2013
<i>Chlorella protothecoides</i>	Lutein, zeaxanthin, canthaxanthin	Markou and Nerantzis, 2013; Jesus, <i>et al.</i> , 2013
<i>Chlorella pyrenoidosa</i>	Lutein, sulfated polysaccharide	plaza and Herrero, 2009
<i>Nostoc linckia</i> and <i>Nostoc spongiaeforme</i>	Borophycin	Singh and dhar, 2011
<i>Nostoc</i> sp.	Cryptophycin	Singh and dhar, 2011

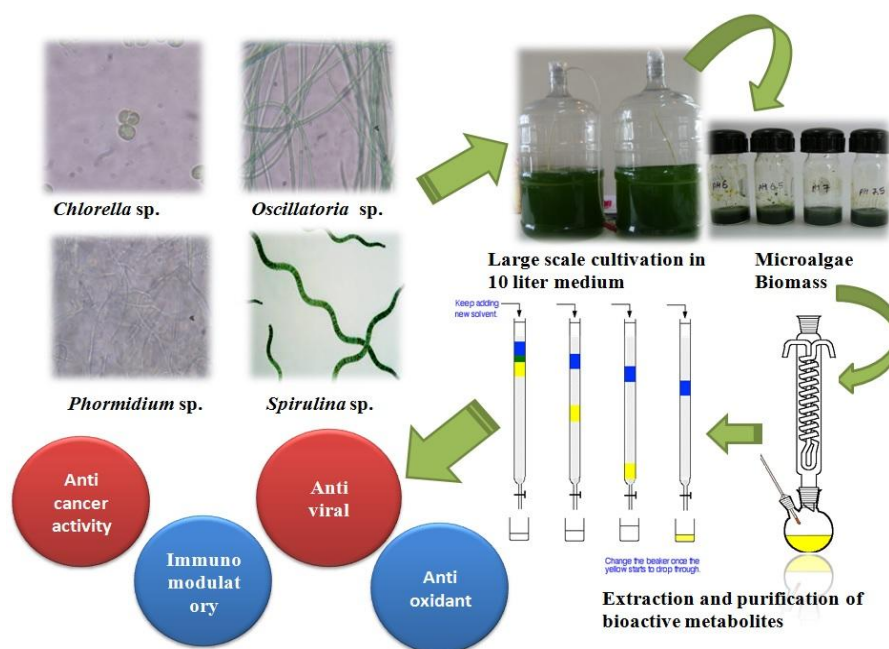


Fig. 1: Biotechnological applications of Bioactive metabolites from Microalgae.

### Microalgal metabolites effective against various Diseases

The bioactive compounds usually secondary metabolites, includes various types of substances ranging from organic acids, carbohydrates, amino acids and peptides, vitamins, growth substances, antibiotics, enzymes to toxic compounds. The metabolites show a wide range of biological activities, including anticancer, antiviral, antioxidant and immunomodulatory effects. (Figure.1) The green alga *Dunaliella salina* has been mass cultivated in open ponds for the production of  $\beta$ -carotene. The algae grows in water and is also tolerant to high saline content and is able to produce  $\beta$ -carotene up to 14% of its dry weight. (Metting, 1996) Astaxanthin a pigment obtained from microalgae is mainly used a food-colouring agent, natural feed additive for the poultry industry and for aquaculture, particularly as a feed supplement for salmon, trout and shrimp. Recently, astaxanthin has also been sold as a nutraceutical for humans in the form of encapsulated product. In addition, *Haematococcus* sp. rich in astaxanthin has been marketed as a dietary supplement for human consumption. (Lorenz RT, Cysewski, 2000) The good health benefit of this product is mainly due to its strong antioxidant activity, which is much more higher than  $\alpha$ -tocopherol (Higuera-Ciagara *et al.*, 2006). Studies have revealed that astaxanthin has protective effects against various disease such as cancers, inflammatory diseases, metabolic syndrome, diabetes, diabetic nephropathy, neurodegenerative diseases and eye diseases (Yuan *et al.*, 2011).

### Microalgae as source of Bioactive compounds

#### *Spirulina*

Some of the microalgae have been consumed as food due to their high nutritional value. For example, *Spirulina* has been harvested for food by the natives in Mexico and Chad (Africa)

since ancient times (Barsanti and Gualtieri, 2006). In Chad, *Spirulina* is regularly harvested from the alkaline lake Kossorom for dry cake known as 'dihe'. In the present day, spirulina still contributes to the economy of Chad as the local trading value of 'dihe' is worth more than US\$ 100,000 (Abdulqader *et al.*, 2000) *Spirulina* is being cultured in open ponds in countries such as Thailand, China, United States and India for the commercial production of the biomass to use them as dietary supplement in countries. The estimated amount of annual worldwide production of *Spirulina* ranges from 3000 to 4000 metric tons (Belay *et al.*, 2008). *Spirulina* is regarded as a nutritious food mainly due to high protein content. Apart from being consumed as a food product, *Spirulina* have therapeutic implications, including the health problems such as diabetes, arthritis, anaemia, cardiovascular diseases and cancer. (Mani *et al.*, 2008) *Spirulina* is also useful nutritional enhancer as it is incorporated into various food products for therapeutic administration of some diseases such as chronic disorders such as diabetes, hypertension and heart. (Iyer *et al.*, 2008) *Spirulina* is well-known for its antioxidant activity and its compounds such as phycocyanin and vitamin E. (Chu 2011: Chu *et al.*, 2010) Another cyanobacterium named nostoc has been consumed as food since 2,000 years ago. (Han *et al.*, 2004) The algae is regarded as a healthy food as it is rich in protein and pigment contents, and is also has low fat content.

#### *Chlorella*

*Chlorella* is abundantly found microalgae which has been mass cultured for production of health food in the form of pills and powder. The mass culture of *Chlorella* was first pilot tested in Boston, USA, and this was continued by other cultivation plants in Israel, Japan and Czechoslovakia. (Iwamoto, 2004) The first commercial production plant of *Chlorella* was established in Japan

in 1961 by Nihon Chlorella Inc. Following him, chlorella factories were constructed in different countries such as Taiwan, Malaysia and Indonesia. By 1980, nearly forty six large-scale plants were established in Asia which had a higher production of 1000 kg Chlorella biomass per month (Spolaore *et al.*, 2006). However, the plant in Malaysia was withdrawn in the early 70's. At present Chlorella products are marketed in Malaysia and are mainly imported from Japan and Taiwan.

#### **Cyanobacteria and dinoflagellates**

Toxic metabolites produced by microalgae (phycotoxins) are considered to be a promising group of bioactive molecules. These compounds are produced mainly by dinoflagellates and cyanobacteria, mainly those that cause harmful algal blooms in either marine or freshwater environments. Excessive growth of dinoflagellates may lead to discolouration of the sea, forming red tides whereas blooms of cyanobacteria in lakes declines the excessive nutrients. Nearly about 300 species of microalgae have been reported to form algae blooms, among them one fourth of these species are toxin producers (Hallegraeaf *et al.*, 2003). These toxins can lead to health hazard in humans, domestic animals and wildlife with toxic effects including neurotoxicity, hepatotoxicity, cytotoxicity and dermatotoxicity (Carmichael, 2001). Phycotoxins demonstrate a wide range of biological activities such as cytotoxic, antitumor, antibiotic, antifungal, immunosuppressant and neurotoxic activities, which present a great potential for biotechnological use (Garcia-Camacho *et al.*, 2007). Many patents related to toxins have been filed. As most of the algal toxins are neurotoxic compounds, they are suitable as tools used to explore brain works and for investigations on neurodegenerative diseases. For example, okadaic acid from Dinophysis used in the treatment of cognitive impairment and schizophrenia is a potent neurotoxin used in the studies on the therapeutic effects of a typical antipsychotic drugs (He *et al.*, 2005). Whereas, pectenotoxins from Dinophysis had showed cytotoxic activity against several human cancer cell lines (Jung *et al.*, 1995).

#### **Antiviral activity of Microalgal compounds**

Microalgae are a potential sources of antiviral compounds as they are yet to be fully explored. For instance, from 600 cultures of cyanobacteria, screening of extracts showed a hit rate of 10% in inhibiting cellular infection of HIV-1, HSV-2, and antirespiratory syncytia virus. (Patterson *et al.*, 1993) A novel compound named cyanovirin-N from cyanobacteria, has been proven to be a potent virucidal agent against HIV, by blocking the interaction of the viral glycoprotein gp120 with CD4 (Dey *et al.*, 2000). There is latent of developing a relevant vaginal microbicide against HIV based on this compound (Tsai *et al.*, 2004). The sulfated polysaccharide derived from *Spirulina platensis* had shown antiviral activity by hindering the entry of enveloped viruses such as Human cytomegalo viruses, Herpes simplex, and measles virus into the cell (Hayashi *et al.*, 1996; Ayehunie *et al.*, 1998). Sulfated polysaccharide extracted from the red alga

Porphyridium has also shown better antiviral activities by preventing the adsorption of the virions against HSV-1, HSV-2 and Varicella zoster virus (Huleihel *et al.*, 2001).

#### **Anticancer activity of Microalgal compounds**

Bioactive molecules showing anticancer activities are one of the targeted compounds from microalgae. On screening of about 1,000 extracts of cyanobacteria isolated from various surroundings for antineoplastic activity (Patterson *et al.*, 1991). Antineoplastic activity was totally based on the inhibitory effects on the differentiation of human leukaemic cells, and a 7% hit rate was reported. In a further screening, 501 extracts from marine microalgae were assessed using mechanism based assays, including activities against three enzymes protein kinase C, protein tyrosine kinase and inosine monophosphate dehydrogenase (Gerwick *et al.*, 1994). A novel chlorosulfolipid isolated from *Poteriochromonas malhamensis* shown inhibition of protein tyrosine kinase activity. Marine cyanobacteria that are potential producers of bioactive compounds and effective in destroying cancer cells by inducing apoptotic death, or affecting cell signaling by activation of protein kinase C family signaling enzymes (Boopathy, 2010).

A variety of mammalian cells including the epidermoid carcinoma cells have been inhibited by polyketide-derived macrolides scytophycins which was isolated from *Scytonema pseudohofmanni* (Ishibashi *et al.*, 1986). The compounds are more active against intraperitoneally implanted lymphocytic leukaemia and lung carcinoma (Furusawa, *et al.*, 1994). Another metabolite extracted from *Nostoc* ATCC 53789, cryptophycin is a effective anticancer compound (Schwartz *et al.*, 1990) whereas a protein serine inhibitor named scytonemin isolated from *Stigonema* which may provide an admirable drug with antiproliferative and antiinflammatory activities (Stevenson *et al.*, 2002).

#### **Microalgal application in Environment**

The immobilized *Chlorella vulgaris* in alginate was found to be efficient in removing colour from textile dyes (Chu *et al.*, 2009). *Chlorella vulgaris* and *Scenedesmus obliquus* were immobilized and have shown to be effective in removing phosphorus and nitrogen from urban wastewater operated on a semicontinuous mode (Ruiz-Marin *et al.*, 2010). In another research, co-immobilisation of microalgae and bacteria have proven to be more effective in removing nutrients such as nitrate, ammonium and phosphate from wastewater rather than immobilised microalgae without bacteria (De-Bashan *et al.*, 2002). While microalgae which are tolerant to toxicants are useful in bioremediation, on the other hand sensitive species are useful tools for bioassaying and biomonitoring of pollutants in the environment (Ismail, 2004). Microalgae are used in bioassay of organisms to analyze the toxicity of harmful pollutants such as heavy metals, pesticides and pharmaceuticals. Heavy metals have been detected vastly in the aquatic ecosystems and even in marine ecosystems such as fish and mussel (Irwandi and Farida, 2009).

## CONCLUSION

The aim of this paper is to review on the microalgal metabolites, the source for bioactive compounds present in different microalgae. This paper also deals with the ability of microalgae to produce bioactive compounds that makes it an important tool in various sectors of biotechnology. Microalgae have long been used as nutritional supplement or food and feed sources. Many of the pharmaceutically interesting compounds in cyanobacteria are peptides, including cyanobacterial toxins and important candidates for anti-cancer drugs. A clear picture on the ability of microalgal bioactive compounds to tackle various diseases has been put forth in this paper. The cultivation of microalgae is known to be the most profitable in the biotechnological industry.

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#### How to cite this article:

Santhosh S, Dhandapani R, Hemalatha N. A Review on Potential Biotechnological applications of Microalgae. *J App Pharm Sci*, 2016; 6 (08): 179-184.