

Bioprospecting for Algal Based Nutraceuticals and High Value Added Compounds

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Abstract

Currently there is an increased global interest on implication of nutritious diet on health sustainability. On this aspect nutraceuticals have assumed paramount importance based on their presumed safety and potential nutritional and therapeutic value. Microalgae are rich source of bioactive compounds having nutritional and therapeutic value and thus have found commercial applications as natural source of high value compounds. High value bioactive compounds from microalgae include: carotenoids, chlorophyll, polysaccharides, long chain polyunsaturated fatty acids, astaxanthin, antioxidants, micro and macronutrients, vitamins including several antimicrobial and antiviral compounds. Besides, some bioactive compounds from microalgae possess significant anti-inflammatory and antitumor activity. Potential of microalgae to produce such therapeutic compounds along with its simple growth requirement make them attractive from biotechnological perspective. Some of the biotechnologically relevant microalgal are *Chlorella*, *Spirulina*, *Dunaliella*, and *Haematococcus*. Though microalgae are known to human beings since decades, its potential biotechnological value is realized only in recent past. Microalgae still remain largely unexplored and urge for extensive investigation to explore for isolation and development of novel high value molecules. The present review highlights therapeutic and nutritional value of algal based bioactive compounds and also focuses on gaps and opportunities which should be exploited in the near future to evaluate the potential of microalgae as a novel source of health promoting compounds.

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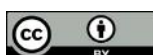
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Introduction

For millennia, diverse microorganisms have yielded important biological materials useful to humans such as antibiotics, drugs, enzymes, herbicides, growth promoters and source of energy. Moreover, microbial diversity is the key to human survival and economic well-being and provides a huge reservoir of resources which we can utilize for our benefit. Despite the acknowledged value of microorganisms, our knowledge of their diversity and many of their key roles in sustaining global life support systems is still very scarce. The biological diversity of the Indian subcontinent is one of the richest in the world owing

to its vast geographic area, varied topography and climate, and the juxtaposition of several bio geographical regions. Because of its richness in overall species diversity, India is recognized as one of the 12 mega diversity regions of the world. Chilika Lake of Orissa is one of the major mega-diversity centres of India. Lying on the eastern coast of Orissa, Chilika Lake is one of the largest lakes not only in India, but also in Asia and stretches over an area of 1,100 sq. km. In fact, Chilika is the largest brackish water lake in Asia and second largest lake in the world and inhabits a mix of estuarine, marine and fresh water ecosystem. Large diversity of algae thrives in this habitat, which enhances the possibility of isolating novel algal strains having potential



for production of nutraceuticals including high value bioactive compounds.

Recent decades have witnessed an increasing interest in nutraceuticals due to their significant therapeutic value which aid in providing human health benefits.

Nutraceuticals: Significance in human health benefit

With the emergence of industrialization, lifestyles of human beings have dramatically changed. Food habit is the first victim of this life style. Increasing work pressure, longer work schedules and various psychological pressures including increased spending capacity with rise in economy, have imposed people to develop fast eating food habits. Moreover, consumption of junk food has increased several manifolds that have led to a number of diseases related to nutritional deficiencies. These diseases include; diabetes, obesity, various cancers, vascular diseases and physiological disorder including degenerative diseases. Increasing concern for health care have dramatically raised the cost of medical care. Over the time people have realized that for maintaining normal functioning of human health, it is important to consume various foods rich in adequate nutrients. With the rise in health care cost, aging population, increasing awareness about fitness and health prompted people globally to lead healthier life by consuming functional foods rich in health enhancing compounds or 'nutraceuticals'. This development, in turn, is propelling expansion in the nutraceutical markets globally (Zhao, 2007, Pandey, 2010)^[1,2]. Apart from this, scientific studies have also extended to these areas and provided supports to nutraceuticals and therapeutic services.

The term nutraceutical was coined from 'nutrition' and 'pharmaceutical' by Dr. Stephen De Felice in 1989. 'Nutraceutical' refer to natural functional/medical foods or bioactive compounds that have health promoting, disease preventing or medicinal properties and thus provide an opportunity to improve the human health. Considering these facts, nutraceuticals have received considerable global interest. The potential of nutraceuticals to accomplish desirable therapeutic outcomes with comparatively (compared to other therapeutic agents) reduced side effects has met with great monetary success (Nelson, 1999, Whiteman, 2001)^[3,4]. Thus the preference for discovery and production of nutraceuticals is well appreciated by pharmaceutical and biotechnology industries.

Nutraceuticals help in providing protection against many diseases by acting as anti-obesity agents, cardiovascular agents, anticancer agents, anti-diabetic agent and immune boosters. Nutraceuticals include a variety of products like mineral and vitamin supplements, antioxidant supplements, probiotics, herbs, essential oils, fortified foods, health drinks and enzymes. Based on their functional properties, nutraceuticals are categorized into: functional foods, dietary supplements, medicinal food, botanicals and pharmaceuticals (Kokate, 2002, www.nutriforce.com)^[5]. Recently, nutraceuticals are receiving global recognition as being beneficial in treating coronary heart disease, obesity, diabetes, cancer, osteoporosis and other chronic and degenerative diseases like Parkinson's and Alzheimer's diseases. Mechanistic actions of nutraceuticals involve an array of biological processes that include activation of antioxidant defences, signal transduction pathways, cell survival-associated gene expression, cell proliferation, differentiation and preservation of mitochondrial integrity. These properties impart a crucial role in the protec-

tion against pathologies of various age-related chronic diseases (Mandel *et al.*, 2005)^[6].

Nutraceuticals: Global market trend

Rising global concern for health and nutrition including scientific evidence supporting health foods, are major factors that drive the worldwide nutraceuticals market. Main segments of nutraceutical market include: functional foods, dietary supplements, natural/herbal foods (Rishi, 2006)^[7]. Dietary supplements segment is fast approaching maturity levels, particularly in developed regions. As per the BCC Research the global nutraceuticals market grew to \$46.7 billion in 2002, at an AAGR (Annual Average Growth Rate) of nearly 7%. In 2007 nutraceuticals sale is projected to reach \$74.7 billion at an AAGR of 9.9% (www.bccresearch.com). The global nutraceuticals market is estimated at about \$151 billion in 2011. By 2016, it is estimated to reach nearly \$207 billion, a projected Compound Annual Growth Rate (CAGR) of 6.5% between 2011 and 2016 (www.campaniesandmarkets.com).

The present global scenario concerning the demand for nutraceuticals definitely urges for the need to focus research on exploration of robust microbial resources having potential for production of nutraceuticals and high value for the future benefit of mankind.

Microalgae: As source of 'nutraceuticals' and 'high-value compounds'

Microalgae are one of the potential organisms and useful to mankind in various ways and represent most promising resource for new products and applications (Pulz and Gross, 2004)^[8]. Owing to their diverse chemical properties, microalgae can act as a nutritional supplement as well as a source of natural food colorants (Borowitzka, 1999, Soletto *et al.*, 2005, Apt and Bahrens, 1999)^[9-11]. They are an enormous biological resource and are cultivated as a source of several bioactive high value compounds like, polyunsaturated fatty acids, carotenoids, phycobilliproteins, polyols, polysaccharides, antioxidants. These high value compounds possess antimicrobial, antiviral, antioxidant, anti-inflammatory, anti-cancer, anti-fungal activity and some act as immune modulator.

Though some microalgae like, Nostoc and Arthrospira, have been exploited for millennia, commercial potential of microalgae is recognized only in recent past. Among 30,000 species that are believed to exist (Chaumont, 1993, Radmer and Parker, 1994)^[12,13] only a few hundred are investigated for chemical content out of which very few are cultivated in industrial grade (Olaizola, 2003). Recently, microalgae biomass has been exclusively used in health food market and its commercial potential is widely recognized. The growing use of algal biomass for nutraceutical purposes is expected to provide an attractive revenue stream for algal industries.

During last decade, micro algal biotechnology has gained considerable attention owing to their substantially higher productivity compared to traditional crops including their potential to grow in areas and climate that are not suitable for agricultural crops. Further, microalgae production serves as an important natural mechanism to reduce atmospheric carbon CO₂ by bio fixation and helps in lowering the greenhouse effect. In view of this, the application of micro algal biomass and/or metabolites offers a promising and innovative approach for the development

of healthier food products.

Most biotechnologically relevant microalgae include species of green algae (Chlorophyceae): *Chlorella vulgaris*, *Haematococcus pluvialis*, *Dunaliellasalina* and species of cyanobacteria (blue green algae): *Spirulina maxima* and *Spirulina platensis* (Gouveia *et al.*, 2008, Guedes *et al.*, 2011)^[14,15].

However, microalgae especially of marine origin still remain to date largely unexplored and represent a unique opportunity to explore novel metabolites and production of cost effective known metabolites. Marine based compounds known to entail a wide diversity of molecular targets with a marked selectivity, which raises pharmaceutical interest (Guedes *et al.*, 2011)^[15].

Algal based bioactive compounds: Potential nutritional and therapeutic value

Primary and secondary metabolites that are synthesized by microalgae and are currently being commercialized or under consideration for commercial extraction include: chlorophylls, carotenoids, phycobilins, long chain polysaccharides, vitamins and minerals, tocopherols and sterols, proteins, β -carotene, astaxanthin, allophycocyanin. These bioactive compounds serve as antioxidants, anti-inflammatory agents, antimicrobial agent, antiviral agent and antitumoral agent, based on their specific activity (Borowitzka, 1999, Apt and Bahrens, 1999)^[9,11].

Chlorophylls

Chlorophyll-a present is the primary photosynthetic pigment and present in all algae. Chlorophyll-b present in species belonging to Chlorophyta and Euglenophyta group. However, several marine algae possess chlorophyll-c, -d and -e. Chlorophylls have got significant application in food and pharmaceutical colorants and in traditional medicine owing to its healing and anti-inflammatory properties. It also helps in reducing the risk of colorectal cancer (Balder *et al.*, 2006)^[16]. Oxidative stress and inflammation are implicated in several health conditions like atherosclerosis and cardiovascular diseases.

Carotenoids

Carotenoids are naturally occurring fat-soluble pigments found principally in algae and play critical role as photoprotective agent. Carotenoids are potential biological antioxidants which are able to absorb the excitation energy of Single Oxygen Radicals (SOR) into their complex ringed chain and helps in lowering tissue decay by reducing the DNA, protein and membrane lipid damage. In human beings, carotenoids can serve several important functions. Consumption of carotenoid rich diet helps in lowering the risk for several diseases including arteriosclerosis, cataracts, age-related macular degeneration, cancer, multiple sclerosis (Tapiero *et al.*, 2004)^[17]. About 50 carotenoids have provitamin-A activity which include; α -carotene, β -carotene and β -cryptoxanthin (Faure *et al.*, 1999). Among all, β -carotene and astaxanthin are attractive algal products and have high market demand. Presently, β -carotene is mainly derived from *Dunaliellasalina* and is used extensively as a yellow-orange food colouring and as anticancer agent (Plaza *et al.*, 2009)^[18].

Currently, astaxanthin is produced from *Haematococcus pluvialis* (Plaza *et al.*, 2009)^[18]. Consumption of astaxanthin helps in enhancing eye health, muscle strength, protecting skin

from premature ageing, inflammation, protects from cancer by preventing certain tumor growth. Astaxanthin also provides protection against oxidation of essential polyunsaturated fatty acids. Free radical fighting capacity of astaxanthin known to be 500 times more efficient as compared that of vitamin E (Dufoss *et al.*, 2005)^[19]. Dietary astaxanthin also helps in reducing low-density lipoprotein oxidation and is safe for human use (Iwamoto *et al.*, 2000, Spiller and Dewell, 2003)^[20,21]. Further, outstanding antitumoral activity of astaxanthin has attracted significant global interest in large scale production of this bioactive compound. Antitumoral effect of dietary astaxanthin is displayed in the post-initiation phase of carcinogen-induced colon and oral cancer models (Tanaka *et al.*, 1995)^[22]. In addition, acetylenic carotenoids like: diatoxanthin, heteroxanthin, diadinoxanthin, isolated from microalgae exhibit antitumoral properties (Dembitsky, 2006)^[23]. Significant source of acetylenic carotenoids include: *Euglenaviridis*, *Tribonemaequala*, *Gonyostomium semen*, *Vacuolariavirescens*, *Pleurochlorismeiringensis* (Oono *et al.*, 1995)^[24].

Lutein, another carotenoid pigment produced from *Chlorella pyrenoidosa* helps in preventing cancer and diseases related to retinal degeneration (Cha *et al.*, 2008)^[25].

Phycobiliproteins (phycocyanin, phycoerythrin)

Phycobiliproteins are deep coloured water soluble fluorescent pigments. Algal species belonging to Cyanobacteria, Rhodophyta and Cryptomonad group encompass these pigments. Phycobiliproteins have got significant applications and are mainly used as highly sensitive fluorescent markers in clinical diagnosis as well as in labelling antibodies. Phycocyanin and phycoerythrin are major pigments which belong to this group. Phycocyanin is blue, water soluble, light-harvesting pigment and found in cyanobacteria. Phycocyanin is strongly fluorescent and mainly used as natural colouring in chewing gums, ice creams, candies, jellies, dairy products including in cosmetics (Sekar and Chandramohan, 2007)^[26]. Apart from these, phycocyanin also serves as excellent antioxidant, anti-inflammatory agent (Eriksen, 2008, Romay *et al.*, 2003)^[27,28].

Omega-3 (n-3) and omega-6 (n-6) Poly Unsaturated Fatty acids (PUFA)

Fatty acids from microalgae are generally rich in Poly Unsaturated Fatty Acids (PUFA) and have a higher degree of unsaturation. PUFA are Essential Fatty Acids (EFA) that is required for proper functioning of cells. Human body cannot synthesize PUFA and hence requires dietary supplementation of PUFA for maintaining good health. Dietary deficiency in long chain n-3 polyunsaturated fatty acids is firmly associated with increased morbidity and mortality from coronary heart disease (Simopoulos, 2002)^[29].

Microalgae have potential to synthesize PUFAs of both omega-3 and omega-6 series. Long chain PUFAs contains straight chain carboxylic acids of 20 or more carbon atoms that contain 3 or more double bonds. Omega-3 PUFAs include: Eicopentaenoic acid (EPA) and Docosahexaenoic acid (DHA). Recently, algal based omega-3 (n-3) PUFAs got considerable attention due to their association with the prevention and treatment of several diseases like, atherosclerosis, thrombosis, arthritis and cancer, blood pressure, coronary heart disease, rheumatism. Potential sources of EPA (22:5 ω 3) and DHA (22:6 ω 3)

include: *Nannochloropsis*, *Phaedactylum*, *Nitzschia*, *Isochrysis*, *Diacronema* and *Cryptocodinium*, *Schizochytrium*, respectively (Simopoulos, 2002)^[29].

Omega-6 PUFAs include, gamma linolenic acid (GLA, 18:3w6). GLA is an 18-carbon polyunsaturated fatty acid that contains three double bonds. Sources of GLA are limited and include only few species of plant like, borage, hemp, evening primrose, black current, Echinium including fungal oil (Subudhi *et al.*, 2008). However, demand of GLA is increasing as human body cannot synthesize this PUFA and needs dietary supplement. Microalgae especially the cyanobacterium '*Spirulina*' is rich in GLA and thus serves as an attractive source of 'GLA'. Dietary GLA plays key role in prevention and treatment of several diseases like, blood pressure, atherosclerosis, cardiac arrhythmia, prostate cancer, glioma, and liver cancer, auto immune diseases like acute respiratory distress syndrome, rheumatoid arthritis, skin diseases, and diabetes including premenstrual syndrome. GLA also helps in boosting immunity and helps in proper brain functioning (Rakesh and Harikumar, 2005).

Vitamins and Minerals

Microalgae represent a significant source of essential vitamins A, B₁, B₂, B₆, B₁₂, C, E, nicotinate, biotin, folic acid and pantothenic acid and minerals, Na, K, Ca, Mg, Fe, Zn including trace minerals (Borowitzka, 1988)^[31].

Polysaccharides

Polysaccharides have got significant implications in food industry as thickening agents. Commercial polysaccharides include, agar, alginates, carrageenans from *Laminaria*, *Gracilaria*, *Macrocystis*. Sulphated polysaccharides from *Porphyridium* species contain 10 sugars in addition to glycoproteins and inorganic sulphate, which aids in inhibiting the spreading of immune cell recruitment toward inflammatory stimuli *in vivo* (Matsui *et al.*, 2003)^[32]. In addition, this polysaccharide also inhibits auto-oxidation of linoleic acid and other forms of oxidative damage in a dose dependent manner and helps in stimulating human immune system (Pulz and Gross, 2004)^[33]. Extracellular polysaccharide extracts from *Chlamydomonas mexicana* have found application as a soil conditioner (Borowitzka, 1988)^[31].

Antiviral compounds

In recent years, many infectious diseases have emerged that urge for exploration of novel antiviral compounds. In view of this, several antiviral drugs have been specifically developed. However, drug-resistance mutations take place constantly, which raises serious concern for development of novel antiviral compounds with desired properties. Microalgae represent a large reservoir for novel compounds and thus have received global attention as potential source of antiviral agents (Borowitzka, 1995)^[34]. Bioactive compound, pheophorbide-a,-b like compound extracted from *Dunaliellaprimolecta* exhibit antiviral activity and helps in acting against HSV1 virus by inhibiting cytopathic effect (Ohta *et al.*, 1998)^[35]. Allophycocyanin extracts from Cryptomonad algal group have profound antiviral activity against Enterovirus 71. Allophycocyanin acts by inhibiting cytopathic effect and delays viral RNA synthesis (Shih *et al.*, 2000)^[36]. A homopolysaccharide of galactose with uronic acid and sulphate groups from *Gyrodiniumimpudicum* strain exhibit an impressive activity *in vitro* against swine *Encephalomycardi-*

tis virus, widely found at clinical level (Yim *et al.*, 2004)^[37].

Antimicrobial compounds

Global concern for development of novel antibiotic compounds increased consequently with the emergence of multidrug resistant bacterial strains like *Staphylococcus aureus*. It is imperative to explore novel antibacterial compounds in order to overcome the multidrug resistance problem. Marine microalgae serve as unexplored reservoir for novel antimicrobial compounds.

Short chain fatty acids from *Haematococcuspluvialis* and organic extracts from *Euglena viridis*, possess significant antibacterial activity and act against *Vibrio* species and *Pseudomonas* species, respectively. Methanolic acid extracts of *Chlamydomonasreinhardtii* exhibit antifungal activity and act against *Staphylococcus aureus*.

Future Prospects

Nutraceuticals are currently receiving global recognition due to their significant nutritional and therapeutic value. Microalgae have exceptional nutraceutical and therapeutic value and thus offer as a promising biological resource to explore in future for utilization in food, feed, cosmetic and pharmaceutical industries. Considering these facts, during last decade microalgae have gained importance in industrial scale for production of nutraceuticals. In addition, other advantage of microalgae is their fast growth rate and potential to attend high cell density at optimum condition.

The acceptance of use of microalgae biomass and their bio molecules has resulted in development of many innovative food products in recent past. However, from biotechnology perspective, microalgae are far behind and needs extensive investigation for the benefit of mankind. Several secondary metabolites from microalgae have shown to possess potential therapeutic value. These results point to promising future development of microalgal biotechnology. Among 10,000 species that are identified only few are investigated to date for their potential chemical content and very few are cultivated in industrial scale. Other species need comprehensive screening for human health benefit. In the recent past, microalgae-derived product market is steadily expanding. But its substantial growth is hampered by the manufacture technology used. Major challenge is cost effective production and optimized recover operation.

The overall competitiveness of microalgae based bioprocesses entails improved performance of microalgae via genetic engineering, metabolic engineering, process engineering, strain improvement for faster growth and higher yield including comprehensive screening of existing micro algal species for novel bioactive compounds as well as isolation of novel robust micro algal species having potential for production of novel bioactive compounds. Especially marine microalgae remain largely explored and needs extensive investigation to explore for isolation of novel bioactive compounds.

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