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## Review

## Microalgae metabolites: A rich source for food and medicine

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## ABSTRACT

Microalgae are one of the important components in food chains of aquatic ecosystems and have been used for human consumption as food and as medicines. The wide diversity of compounds synthesized from different metabolic pathways of fresh and marine water algae provide promising sources of fatty acids, steroids, carotenoids, polysaccharides, lectins, mycosporine-like amino acids, halogenated compounds, polyketides, toxins, agar agar, alginic acid and carrageenan. This review discusses microalgae used to produce biological substances and its economic importance in food science, the pharmaceutical industry and public health.

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## 1. Introduction

Algae, a multicellular or unicellular form of living organisms, can be divided into either macro or micro algae based on its size. Microalgae are one of the earliest forms of life on the earth (Falkowski et al., 2004). When the earth's environment formed over 3 billion years ago, microalgae existed in Earth's oceans. The diversity of microalgae (i.e., prokaryotic cyanobacteria and eukaryotic microalgae) is vast, but this diversity has not yet been fully exposed (Massana et al., 2006; Fehling et al., 2007; Stern et al., 2010). There are more than 50,000 different types of microalgal species present in oceans and fresh water (lakes, ponds and rivers); among these species, only 30,000 have been studied (Richmond, 2004). Microalgae have been used as food by humans for thousands of years (Milledge, 2011).

Microalgae can convert solar energy to chemical energy by fixing CO<sub>2</sub>, and its efficiency is ten times greater than terrestrial plants. The commercial production of microalgae is approximately 5,000 tons/year of dry matter (Raja et al., 2008). There are approximately 110 commercial producers of microalgae present in the Asia-Pacific region, with capacities ranging from 3 to 500 tons/year. About nine-tenths of algal cultivation is located in Asia. Among these, high numbers of commercial microalgae producers are located in China, Taiwan and India. Very few species of microalgae have commercial importance, but those that do include *Spirulina*, *Chlorella*, *Haematococcus*, *Dunaliella*, *Botryococcus*, *Phaeodactylum*, *Porphyridium*, *Chaetoceros*, *Cryptocodinium*, *Isochrysis*, *Nannochloris*, *Nitzschia*, *Schizochytrium*, *Tetraselmis*, and *Skeletonema*.

Much of the microalgal biomass has been an attractive source for producing a wide range of highly valuable products, including polyunsaturated fatty acids (PUFA), carotenoids, phycobiliproteins, polysaccharides and phycotoxin. However, the products from microalgae have been widely used as a high-protein supplement in human nutrition, aquaculture and nutraceutical purposes (Del-Campo et al., 2007). The market price of algal biomass varies and has reported ranges of 100€/kg for human consumption, 5–20€/kg for animal and fish feed, 1–5€/kg for bulk chemicals and 0.40€/kg for biofuel (Wijffels, 2008). Wijffels and Barbosa, (2010) reported that microalgal products were composed of 40% lipids, 50% proteins and 10% carbohydrates; a quarter of the lipids are sold to the food and chemical industry for 2€/kg, the rest for biodiesel at 0.50€/kg, soluble proteins (20%) for food at 5€/kg, and the rest (80%) for feed at 0.75€/kg. This review focuses on the production of potentially valuable products derived from microalgae and their respective applications in the food and medical industries.

## 2. Commercial production and importance of microalgae in diet

In most developed countries, people consume high caloric food items due to the modern life style, which leads to health problems, such as obesity, heart diseases, and diabetics. A balanced nutritional diet is needed for health and should contain vitamins, minerals, PUFAs, etc. Microalgae are considered as a remarkable but poorly explored natural source for a healthy diet. Several species of microalgae are identified as rich in carbohydrates, proteins, lipids and nutritionally valuable components. Becker (2004) reported that microalgae are an abundant source of vitamins and minerals, such as vitamins A, B1, B2, C, and E; nicotinate; biotin; folic acid; pantothenic acid; niacin; iodine; potassium; iron; magnesium; and calcium (Table 1). Interestingly, the lack of polysaccharides in the cell wall of cyanobacteria makes their biomass a more easily digestible material and therefore more acceptable for human consumption (Richmond and Preiss, 1980). The Chinese

first used microalgae (*Nostoc* sp.) (over 2000 years ago) as a food and, later, the commercial forms of microalgae (*Chlorella* sp. and *Spirulina* sp.) were consumed as healthy foods in Japan, Taiwan and Mexico (Tamiya, 1957; Durand-Chastel, 1980; Soong, 1980). Currently, most of the commercialized products of microalgae are available in markets as a health food, in the forms of tablets, capsules and liquids (Pulz and Gross, 2004), and their products are mixed with pastes, snacks, candy, gums, noodles, wine, beverages, and breakfast cereals (Yamaguchi, 1997; Lee, 1997; Liang et al., 2004). *Aphanizomenon flos-aquae*, *Chlorella* sp., *Dunaliella salina* (*D. salina*), *Dunaliella tertiolecta* (*D. tertiolecta*) and *Spirulina plantensis* (*S. plantensis*) are some of the microalgae species widely used as a human food source because they are rich in protein content and have high nutritive value (Soletto et al., 2005; Rangel-Yagui et al., 2004). Among these microalgae, *Spirulina* (*Arthrospira*) and *Chlorella* are currently dominating the microalgal market.

*Spirulina* (*Arthrospira*) has a high protein content and excellent nutrient value (Spolaore et al., 2006) and has gained worldwide popularity as a food supplement (Colla et al., 2007). It has an amino acid content of 62%, and it is a rich natural source of vitamins A, B<sub>1</sub>, B<sub>2</sub>, B<sub>12</sub>, as well as phytopigments, including carotenoids and xanthophyll (Richmond, 1988). In addition, it has a considerable amount of essential fatty acids and linolenic acid, which cannot be synthesized by humans (Becker, 1994); thus, more attention has been given to the cultivation of *Spirulina*. The world production of *Spirulina* for human consumption exceeds 1000 metric tons, annually (Ciferri and Tiboni, 1985). The world's largest *Spirulina* producer is Hainan Simai Enterprising, which is located in China and has an annual algal powder production of 200 tons. There are 20 countries in the world that produce *Spirulina*-based products, such as tablets and powder. Among these countries, the USA ranks first in *Spirulina*-based products, primarily in the form of pills and spray-dried powder, followed by China, Israel, Japan, Mexico, Taiwan and Thailand (Spolaore et al., 2006). From microalgae, a wide variety of nutraceuticals are available and marketed for sale. For example, the Myanmar-*Spirulina*-factory (Yangon, Myanmar) produces tablets, chips, pasta and liquid extracts. Similarly, Cyanotech (Hawaii, USA) produces pure powder under the name "Spirulina pacifica". Phycocyanin, extracted from *Spirulina* and commercially known as 'lima blue', is used as a blue colorant for food and cosmetics. *Spirulina* also acts as a functional food, feeding beneficial intestinal flora, including *Lactobacillus* and *Bifidus* (Ciferri, 1983). In the future, these health foods are expected to be a stable market, including products such as *Spirulina* liquid CO<sub>2</sub>-extracted antioxidant capsules (Belay et al. 1993). One gram of *Spirulina* contains one-half of the adult daily requirements of Vitamin A. According to human studies, total serum cholesterol was lowered by consuming *Spirulina* (Gonzalez de Rivera et al., 1993). The purified PUFAs from *Spirulina* are added into infant milk formulas in European countries for health promoting purposes.

*Chlorella* are also known as healthy foods to humans and used for nutrient-rich feed for aquatic animals. More than 70 companies were involved in the cultivation of *Chlorella*, and the largest producer is Taiwan Chlorella Manufacturing and Co. (Taipei, Taiwan), which produces 400 tons of dried biomass/year. A significant production of *Chlorella* was achieved in a German company (Klotze, Germany) by using a tubular photobioreactor, and it produces 130–150 tons dry biomass/year. The world annual sales of *Chlorella* exceed 38 billion US\$ (Yamaguchi, 1997). Barrow and Shahidie (2008) noted that the extract of *Chlorella* sp. showed several health benefits. For instance, it can increase hemoglobin concentration, lower blood sugar levels and act as hypocholesterolemic and hepatoprotective agents during malnutrition and ethionine intoxication. The most important substance in *Chlorella* is β-1,3-glucan, which is an active immunostimulator, a free radical scavenger and a reducer of blood lipids. Plankton soup primarily consisting

**Table 1**  
Microalgae metabolites from different microalga species which are being used for commercial purpose.

| Microalgal valuable metabolites                         | Microalgal producers   | Uses   | References  |
|---|--|--|---|
| <b>1. Amino acid</b>                                    |  |  |   |
| Mycosporine-like amino acids (MAA)                      | <i>A. spiralis</i> , <i>A. flos-aquae</i> , <i>C. nivalis</i> , <i>C. luteo-viridis</i> , <i>C. minutissima</i> , <i>C. sorokiniana</i> , <i>C. sphaerica</i> , <i>Scenedesmus</i> spp., <i>Stichococcus</i> spp.,   | UV-screening agent; Sunscreen  | Xiong et al. (1999); Chu (2012); Duval et al. (2000); Karsten et al. (2007)   |
| <b>2. Antioxidant</b>                                   |  |  |   |
| Lipophilic antioxidant - Butylated hydroxytoluene (BHT) | <i>B. braunii</i>  | Food additive; Antioxidant activity; Antiviral effect  | Babu and Wu, (2008)   |
| Phenolic antioxidant                                    | <i>C. nivalis</i>  | Antimicrobial properties; Antioxidant activity   | Duval et al. 2000)  |
| <b>3. Carotenoids</b>                                   |  |  |   |
| $\alpha$ -carotene                                      | <i>C. sorokiniana</i>  | Lower risk of premature death  | Matsukawa et al. (2000)   |
| Astaxanthin   | <i>A. braunii</i> , <i>H. pluvialis</i> , <i>C. nivalis</i> , <i>Chlorococcum</i> spp., <i>Chlamydocapsa</i> spp., <i>C. nivalis</i> , <i>C. fusa</i> , <i>C. vulgaris</i> , <i>C. zofingiensis</i> , <i>Chlorococcum</i> spp., <i>C. striolata</i> , <i>Haematococcus</i> spp., <i>H. lacustris</i> , <i>H. pluvialis</i> , <i>Monoraphidium</i> sp, <i>Neosporangiococcum</i> spp., <i>S. obliquus</i> | Strong antioxidant property; Anti-inflammatory effects; Anticancer; Cardiovascular health; Pigmenter for salmon            | Chu (2012); Borowitzka (1988); Leya et al. (2009); Remias et al. (2005); Liu and Lee (2000); Yuan et al. (2002); Abe et al. (2007); Ceron et al. (2007); He et al. (2007); Jin et al. (2006); Kang et al. (2005); Lorenz and Cysewski (2000); Chattopadhyay et al. (2008); Domínguez-Bocanegra et al. (2004); Zhekisheva et al., 2005; Fujii et al., 2008; Qin et al., 2008 |
| $\beta$ -carotene                                       | <i>D. salina</i> , <i>B. braunii</i> , <i>C. nivalis</i> , <i>Chlorococcum</i> spp., <i>Chlamydocapsa</i> spp., <i>C. acidophila</i> , <i>C. sorokiniana</i> , <i>C. striolata</i> , <i>D. bardawil</i> , <i>D. salina</i> , <i>D. tertiolecta</i> , <i>P. amyliifera</i> , <i>P. obovata</i> , <i>Tetraselmis</i> spp., <i>T. wettsteinii</i>   | Food colourant; Antioxidant property; Cancer preventive properties; Prevent night blindness; Prevent liver fibrosis        | Chu (2012); Borowitzka, (1988); Garbayo et al. (2008); Matsukawa et al.,(2000); Abe et al. (2007); Rabbani et al. (1998); Coesel et al. (2008); Hejazi and Wijffels (2003); Barbosa et al. (2005); Egeland et al. (1997); Egeland et al. (1995); Sathasivam et al. (2012); Wu et al. (2016); Sathasivam et al. (2014)   |
| Cantaxanthin  | <i>C. nivalis</i> , <i>Chlorococcum</i> spp., <i>Chlamydocapsa</i> spp., <i>C. emersonii</i> , <i>C. fusa</i> , <i>C. vulgaris</i> , <i>C. zofingiensis</i> , <i>C. striolata</i> , <i>H. lacustris</i> , <i>Neosporangiococcum</i> spp.   | Creates tan color; Antioxidant property  | Leya et al. (2009); Bhosale and Bernstein (2005); Borowitzka (1988); Gouveia et al. (1996); Mendes et al. (2003); Pelah et al. (2004); Yuan et al. (2002); Abe et al. (2007); Chattopadhyay et al. (2008)   |
| Fucoxanthin   | <i>C. gracilis</i> , <i>C. calcitrans</i> , <i>O. aurita</i> , <i>C. closterium</i> , <i>Nitzschia</i> spp. <i>P. tricornutum</i> , <i>O. danica</i> , <i>Ochromonas</i> spp, <i>C. ochromonoides</i> , <i>S. marina</i> , <i>Isochrysis</i> spp., <i>I. aff. galbana</i> , <i>I. galbana</i> , <i>P. parvum</i>   | Anti-obesity; Antioxidant property   | Kim et al. (2012a, 2012b); Kim et al. (2012a); Foo et al. (2015); Xia et al. (2013); Reboloso-Fuentes et al. (2001), Eilers et al. (2016); Allen et al. (1960); Withers et al. (1981); Crupi et al. (2013)  |
| Lutein  | <i>B. braunii</i> , <i>C. nivalis</i> , <i>Chlorococcum</i> spp., <i>Chlamydocapsa</i> spp., <i>C. acidophila</i> , <i>C. fusa</i> , <i>C. protothecoides</i> , <i>C. pyrenoidosa</i> , <i>C. sorokiniana</i> ,  | Prevents cataract and age-related macular degeneration; Antioxidant property; Anticancer; Prevents cardiovascular diseases | Rao et al. (2006); Leya et al. (2009); Garbayo et al. (2008); Del Campo et al. (2000); Chen (1988); Shi et al. (2006); Wu et al. (2007); Matsukawa et al. (2000); Cha et al. (2008); Bhosale and Bernstein (2005); Del Campo et al. (2004); Barbosa et al. (2005); Blanco et al. (2007); Egeland et al. (1997); Ceron et al. (2008); Sanchez et al. (2008); Tukaj et al.    |

(continued on next page)

Table 1 (continued)

| Microalgal valuable metabolites | Microalgal producers  | Uses   | References  |
|---------------------------------|---|--|---|
|                                 | <i>C. vulgaris</i> , <i>C. zofingiensis</i> , <i>Chlorococcum</i> spp., <i>C. citrifforme</i> , <i>C. nivalis</i> , <i>C. proboscideum</i> , <i>D. tertiolecta</i> , <i>M. aurantiaca</i> , <i>Muriellopsis</i> sp., <i>N. gelatinosum</i> , <i>Pyramimonas</i> spp., <i>P. urceolata</i> , <i>S. almeriensis</i> , <i>S. armatus</i> , <i>T. intermedium</i> , <i>T. tetrasporum</i> , <i>Tetraselmis</i> spp., <i>T. wettsteinii</i>  |  | (2003); Egeland et al. (1995)   |
| Zeaxanthin                      | <i>C. ellipsidea</i> , <i>D. salina</i> , <i>C. nivalis</i> , <i>D. salina</i> ,  | Protect eye cells; Antioxidant activity; Neutralizing the free radicals  | Cha et al. (2008); Leya et al. (2009); Bhosale and Bernstein (2005)   |
| 4. Glutathione                  |   |  |   |
| Glutathione                     | <i>Dunaliella</i> spp.,   | Lowering the heart attack; Antioxidant properties; Anticancer activity; Anti-Parkinson's disease; Detoxify the metals; Lowering the blood pressure | Li et al. (2004)  |
| 5. Glycerol                     |   |  |   |
| Glycerol                        | <i>C. pulsatilla</i> , <i>Chlamydomonas</i> spp., <i>C. pulsatilla</i> , <i>C. reinhardtii</i> , <i>C. submarinum</i> , <i>Dunaliella</i> spp., <i>D. salina</i>  | Moisture to the skin and help skin smooth  | Ahmad and Hellebust (1986); Miyasaka et al. (1998); Leon and Galvan (1999); Blackwell and Gilmour (1991); Kacka and Donmez (2008); Hadi et al. (2008) |
| 6. Lipids                       |   |  |   |
| Triglycerides and hydrocarbons  | <i>B. braunii</i> , <i>C. calcitrans</i> , <i>C. muelleri</i> , <i>C. californicum</i> , <i>C. oviforme</i> , <i>C. reinhardtii</i> , <i>C. emersonii</i> , <i>C. luteo-viridis</i> , <i>C. protothecoides</i> , <i>C. sorokiniana</i> , <i>C. vulgaris</i> , <i>C. neglecta</i> , <i>C. simplex</i> , <i>C. costazyoticum</i> , <i>C. infusionum</i> , <i>C. chodati</i> , <i>C. striolata</i> , <i>C. cohnii</i> , <i>Cylinthrothea</i> spp., <i>Ellipsoidion</i> spp., <i>E. gracillis</i> , <i>H. pluvialis</i> , <i>I. galbana</i> , <i>L. culleus</i> , <i>L. segnis</i> , <i>M. salina</i> , <i>M. subterraneus</i> , <i>M. arcuatum</i> , <i>M. contortum</i> , <i>M. dybowskii</i> , <i>M. griffithii</i> , <i>M. neglectum</i> , <i>M. terrestre</i> , <i>M. tortile</i> , <i>M. aurantiaca</i> , <i>N. eucaryotum</i> , <i>Nannochloris</i> spp., <i>N. oculata</i> , <i>N. salimicola</i> , <i>N. oleoabundans</i> , <i>Nitzschia</i> spp., <i>P. kessleri</i> , <i>P. lutheri</i> , <i>P. salina</i> , <i>P. tricornutum</i> , <i>P. insigne</i> | Biofuels   | Chu (2012); Ramaraj et al. (2014); Rodolfi et al. (2009), Mata et al. (2010), Mutanda et al. (2011), and Bogen et al. (2013)                          |

**Table 1** (continued)

| Microalgal valuable metabolites              | Microalgal producers  | Uses   | References  |
|--|---|--|---|
| <b>7. Polysaccharides</b>                    |   |  |   |
| Polysaccharides                              | <i>P. cruentum</i> , <i>C. pyrenoidosa</i> ,<br><i>C. stigmatophora</i>   | Viscosifiers, lubricants and flocculants for industrial applications; Antiviral agent; Immunostim effect; Antitumor activity; Anti-inflammatory and immunosuppressive activity | Chu (2012); Sheng et al. (2007); Yang et al. (2006); Pugh et al. (2001); Guzman et al. (2003)   |
| Sulfonated polysaccharides                   | <i>C. vulgaris</i> , <i>S. quadricauda</i> ,  | Anticoagulant; Antiviral; Antioxidative; Anticancer activities   | Mohamed (2008)  |
| <b>8. Polyunsaturated fatty acids (PUFA)</b> |   |  |   |
| <b>α-linolenic acid</b>                      |   |  |   |
|  | <i>Ankistrodesmus</i> spp.,<br><i>Botryococcus</i> spp.,<br><i>Chlamydomonas</i> spp., <i>C. moewusii</i> , <i>C. vulgaris</i> , <i>D. bardawil</i> , <i>D. salina</i> , <i>D. tertiolecta</i> , <i>M. pusilla</i> ,<br><i>Muriellopsis</i> spp., <i>N. atomus</i> ,<br><i>P. subcapitata</i> , <i>S. acutus</i> , <i>S. obliquus</i> , <i>S. quadricauda</i> ,<br><i>Tetraselmis</i> spp., <i>T. suecica</i> | Preventative effect against cardiovascular diseases.   | Ben-Amotz et al. (1985); Chiang et al. (2004); Poerschmann et al. (2004); Arisz et al. (2000); Ahlgren et al. (1992); Piorreck et al. (1984); Fried et al. (1982); Martinez-Fernandez et al. (2006); Reitan et al. (1994); Patil et al. (2007); Becker (2004); D'Souza and Loneragan (1999) |
| Arachidonic acid (AA)                        | <i>Porphyridium</i> spp., <i>N. atomus</i> , <i>P. boryanum</i>   | Nutritional supplements  | Reitan et al. (1994); Zhang et al. (2002)   |
| Docosahexaenoic acid (DHA)                   | <i>Cryptocodiuimu</i> spp.,<br><i>Schizochytrium</i> spp.,<br><i>Pyramimonas</i> spp.   | Infant formula; Nutritional supplements; Aquaculture feed  | Chu (2012); Tzovenis et al. (2009)  |
| Eicosapentaenoic acid (EPA)                  | <i>Pavlova</i> spp.,<br><i>Nannochloropsis</i> spp.,<br><i>Monodus</i> spp.,<br><i>Phaeodactylum</i> spp., <i>C. minutissima</i> , <i>C. vulgaris</i> ,<br><i>Nannochloris</i> spp., <i>N. atomus</i> , <i>Tetraselmis</i> spp., <i>T. suecica</i>  | Nutritional supplements; Aquaculture feed  | Chu (2012); Seto et al. (1984); Ben-Amotz et al. (1985); Reitan et al. (1994); Patil et al. (2007); Tzovenis et al. (2009); D'Souza and Loneragan (1999)  |
| γ-linolenic acid (GLA)                       | <i>Spirulina</i> spp., <i>C. homosphaera</i> , <i>Chlorococcum</i> spp., <i>D. primolecta</i>   | Nutritional supplements  | Chu (2012); Chiang et al. (2004); Ohta et al. (1995)  |
| Hexadecatetraenoic acid                      | <i>Ankistrodesmus</i> spp.,<br><i>Chlamydomonas</i> spp., <i>C. moewusii</i> , <i>D. bardawil</i> , <i>D. tertiolecta</i> , <i>T. suecica</i> , <i>T. cylindrica</i>  | -  | Ben-Amotz et al. (1985); Arisz et al. (2000); Fried et al. (1982); D'Souza and Loneragan (1999); Gouveia and Oliveira (2009); Becker (2004)   |
| Linolenic acid                               | <i>B. braunii</i> , <i>C. moewusii</i> , <i>C. protothecoides</i> , <i>C. vulgaris</i> ,<br><i>Chlorococcum</i> spp., <i>D. bardawil</i> , <i>D. primolecta</i> , <i>D. tertiolecta</i> , <i>N. atomus</i> , <i>N. oleabundans</i> , <i>P. subcapitata</i> ,<br><i>S. obliquus</i> , <i>T. suecica</i><br><i>M. pusilla</i> , <i>T. suecica</i>   | Anti-inflammatory; Acne reductive; Moisture retentive properties   | Chiang et al. (2004); Arisz et al. (2000); Day et al. (2009); Piorreck et al. (1984); Fried et al. (1982); Gouveia and Oliveira (2009); Reitan et al. (1994); Patil et al. (2007); D'Souza and Loneragan (1999)   |
| Stearidonic acid                             |   | Increasing tissue EPA concentrations in tissues  | Fernandez et al. (2006); D'Souza and Loneragan (1999)   |
| <b>9. Proteins</b>                           |   |  |   |
| Glycoprotein                                 | <i>C. vulgaris</i> ,  | Anticancer; Anti-inflammatory activity; Anti-photoaging  | Hasegawa et al. (2002); Tanaka et al. (1998)  |

(continued on next page)

**Table 1** (continued)

| Microalgal valuable metabolites                           | Microalgal producers  | Uses   | References   |
|---|---|--|--|
| Phycocyanin   | <i>S. platensis</i>   | Natural dye for health food and cosmetics (lipsticks and eyeliners) antioxidant  | Chu (2012)   |
| Phycoerythrin   | <i>P. cruentum</i>  | Fluorescent agent; Tool for biomedical research; Diagnostic  | Chu (2012)   |
| 10. Sterols   |   |  |  |
| Sterols   | <i>P. cf. cordata</i> , <i>T. suecica</i>   | Antidiabetic; Anticancer; Anti-inflammatory; Anti-photoaging; Anti-obesity; Anti-inflammatory; Antioxidant activities                    | Ponomarenko et al. (2004); Cardozo et al. (2007)   |
| 11. Toxins  |   |  |  |
| Anatoxin  | <i>A. flos-aquae</i>  | To investigate neurodegenerative diseases  | Katircioglu et al. (2004)  |
| Microcystins  | <i>M. aeruginosa</i>  | To investigate neurodegenerative diseases  | Katircioglu et al. (2004)  |
| Okadaic acid  | <i>Dinophysis</i> spp.  | Treatment of cognitive impairment and schizophrenia  | He et al. (2005)   |
| Phycotoxins – okadaic acid, gonyautoxins, and yessotoxins | <i>Amphidinium</i> spp., <i>Prorocentrum</i> spp., <i>Dinophysis</i> spp.,  | Experimental tools for investigations on neurodegenerative diseases  | Chu (2012)   |
| Saxitoxin   | <i>A. flos-aquae</i>  | To investigate neurodegenerative diseases  | Katircioglu et al. (2004)  |
| 12. Vitamins  |   |  |  |
| Vitamin B   | <i>Chlamydomonas</i> spp., <i>C. eugametos</i> , <i>Chlorella</i> spp., <i>C. pyrenoidosa</i> , <i>S. acutus</i> , <i>S. obliquus</i> , <i>S. quadricauda</i>   | Decrease fatigue; Reducing depression; Protect against heart disease; Protect the skin; Anticancer activity                              | Vilchez et al. (1997); Uhlík and Gowans (1974); Borowitzka (1988); Becker(2004);           |
| Vitamin C   | <i>C. reinhardtii</i> , <i>Chlorella</i> spp., <i>C. protothecoides</i> , <i>C. vulgaris</i> , <i>D. tertiolecta</i> , <i>P. moriformis</i> , <i>S. acutus</i> , <i>S. obliquus</i> , <i>S. quadricauda</i> | Protect against cardiovascular disease; Prenatal health problems; Prevent from eye disease; Protect against skin wrinkling               | Borowitzka, 1988; Running et al. (2002); Becker (2004); Barbosa et al. (2005)              |
| Vitamin E   | <i>C. reinhardtii</i> , <i>C. pyrenoidosa</i> , <i>C. sorokiniana</i> , <i>C. vulgaris</i> , <i>D. tertiolecta</i> , <i>S. obliquus</i> , <i>S. acutus</i> , <i>S. quadricauda</i> , <i>T. suecica</i>      | Protect against toxic pollutants; Premenstrual syndrome, Protect against eye disorders; Anti-Alzheimer's disease; Anti-diabetic property | Borowitzka (1988); Becker (2004); Matsukawa et al. (2000); Carballo-Cardenas et al. (2003) |

**Note:** The uses for each metabolite provided in the table are general uses. Some metabolites extracted from the microalgae have not yet been clinically proved. See cited paper for more details in each case. The description of the genus was shown here as follows; *A. flos-aquae* - *Anabaena flos-aquae*; *A. braunii* - *Ankistrodesmus braunii*; *A. spiralis* - *Ankistrodesmus spiralis*; *A. flos-aquae* - *Aphanizomenon flos-aquae*; *B. braunii* - *Botryococcus braunii*; *C. calcitrans* - *Chaetoceros calcitrans*; *C. gracilis* - *Chaetoceros gracilis*; *C. muelleri* - *Chaetoceros muelleri*; *C. californicum* - *Characium californicum*; *C. oviforme* - *Characium oviforme*; *C. acidophila* - *Chlamydomonas acidophila*; *C. eugametos* - *Chlamydomonas eugametos*; *C. moewusii* - *Chlamydomonas moewusii*; *C. nivalis* - *Chlamydomonas nivalis*; *C. pulsatilla* - *Chlamydomonas pulsatilla*; *C. reinhardtii* - *Chlamydomonas reinhardtii*; *C. emersonii* - *Chlorella emersonii*; *C. fusa* - *Chlorella fusa*; *C. homosphaera* - *Chlorella homosphaera*; *C. luteo-viridis* - *Chlorella luteo-viridis*; *C. minutissima* - *Chlorella minutissima*; *C. protothecoides* - *Chlorella protothecoides*; *C. pyrenoidosa* - *Chlorella pyrenoidosa*; *C. sorokiniana* - *Chlorella sorokiniana*; *C. sphaerica* - *Chlorella sphaerica*; *C. stigmatophora* - *Chlorella stigmatophora*; *C. vulgaris* - *Chlorella vulgaris*; *C. zofingensis* - *Chlorella zofingensis*; *C. neglecta* - *Chloridella neglecta*; *C. simplex* - *Chloridella simplex*; *C. citrifforme* - *Chlorococcum citrifforme*; *C. costazygoticum* - *Chlorococcum costazygoticum*; *C. infusioformis* - *Chlorococcum infusioformis*; *C. submarinum* - *Chlorococcum submarinum*; *C. nivalis* - *Chloromonas nivalis*; *C. ochromonoides* - *Chromulina ochromonoides*; *C. chodati* - *Coccomyxa chodati*; *C. striolata* - *Coelastrum striolata*; *C. proboscideum* - *Coelastrum proboscideum*; *C. cohnii* - *Cryptocodinium cohnii*; *C. closterium* - *Cylindrotheca closterium*; *D. bardawil* - *Dunaliella bardawil*; *D. primolecta* - *Dunaliella primolecta*; *D. salina* - *Dunaliella salina*; *D. tertiolecta* - *Dunaliella tertiolecta*; *E. gracilis* - *Euglena gracilis*; *H. lacustris* - *Haematococcus lacustris*; *H. pluvalis* - *Haematococcus pluvalis*; *I. aff. galbana* - *Isochrysis aff. galbana*; *I. galbana* - *Isochrysis galbana*; *L. culleus* - *Lobochlamys culleus*; *L. segnis* - *Lobochlamys segnis*; *M. aeruginosa* - *Microcystis aeruginosa*; *M. pusilla* - *Micromonas pusilla*; *M. salina* - *Monallanthus salina*; *M. subterraneus* - *Monodus subterraneus*; *M. arcuatum* - *Monoraphidium arcuatum*; *M. contortum* - *Monoraphidium contortum*; *M. dybowskii* - *Monoraphidium dybowskii*; *M. griffithii* - *Monoraphidium griffithii*; *M. neglectum* - *Monoraphidium neglectum*; *M. terrestre* - *Monoraphidium terrestre*; *M. tortile* - *Monoraphidium tortile*; *M. aurantiaca* - *Muriella aurantiaca*; *N. atomus* - *Nannochloris atomus*; *N. eucaryotum* - *Nannochloris eucaryotum*; *N. oculata* - *Nannochloropsis oculata*; *N. salinicola* - *Navicula salinicola*; *N. oleabundans* - *Neochloris oleabundans*; *N. gelatinosum* - *Neosporococcus gelatinosum*; *O. danica* - *Ochromonas danica*; *O. aurita* - *Odontella aurita*; *P. kessleri* - *Parachlorella kessleri*; *P. lutheri* - *Pavlova lutheri*; *P. salina* - *Pavlova salina*; *P. boryanum* - *Pediastrum boryanum*; *P. tricorutum* - *Phaeodactylum tricorutum*; *P. insigne* - *Pleurastrum insigne*; *P. cruentum* - *Porphyridium cruentum*; *P. moriformis* - *Prototheca moriformis*; *P. parvum* - *Prymnesium parvum*; *P. subcapitata* - *Pseudokirchneriella subcapitata*; *P. amyliifera* - *Pyramimonas amyliifera*; *P. cf. cordata* - *Pyramimonas cf. cordata*; *P. obovata* - *Pyramimonas obovata*; *P. urceolata* - *Pyramimonas urceolata*; *S. marina* - *Sarcinochrysis marina*; *S. acutus* - *Scenedesmus acutus*; *S. almeriensis* - *Scenedesmus almeriensis*; *S. armatus* - *Scenedesmus armatus*; *S. obliquus* - *Scenedesmus obliquus*; *S. quadricauda* - *Scenedesmus quadricauda*; *S. platensis* - *Spirulina platensis*; *T. intermedium* - *Tetracystis intermedium*; *T. tetrasporum* - *Tetracystis tetrasporum*; *T. suecica* - *Tetraselmis suecica*; *T. wettsteinii* - *Tetraselmis wettsteinii*; *T. cylindrical* - *Tetraspora cylindrical*.

of *Chlorella* sp. cells was used as a dietary aid for leprosy patients, resulting in increases in their energy, weight and health. Japanese researchers have developed several trial food products (powdered green tea, soups, noodles, bread and rolls, cookies, ice cream, and soy sauce) from *Chlorella ellipsoidea*.

In addition, *Scenedesmus* sp. are also identified as a nutritional microalgal food source, but their commercial production is limited. Their extracts are incorporated into commonly used foods, such as desserts, fruit puddings, ravioli, noodles, and soups. In 1961, several studies demonstrated that the extracts of *Scenedesmus* sp. and *Chlorella* sp. can be used for human consumption (Barrow and Shahidi, 2008). Other species of microalgae, *D. tertiolecta* and *Euglena gracilis*, are being sold as health foods in Japan and are believed to be effective for health maintenance and disease prevention. Several studies are now under way to assess their use as new food materials and for other purposes.

Animal health conditions, such as survival, growth, development, productivity and fertility, depend on their feed. Microalgae play an important role in high grade animal nutrition food, from aquaculture to farm animals. Microalgae have been credited with improving the immune system, lipid metabolism, gut function, and stress resistance (Shields and Lupatsch, 2012); increasing appetite, weight, number of eggs, and reproductive performance; and reducing cholesterol levels (Svircev, 2005). Many studies have suggested algae as a potential source for feed supplement or a substitute for conventional protein sources, such as soybean meal and fish meal (Becker, 1994; Spolaore et al., 2006). Much of the current world algal production is sold for animal feed applications (Becker, 2004). More than 50% of the world's *Spirulina* production is used as feed supplement. In 1999, the production rate of microalgae for aquaculture was 1000 tons (62% for mollusks, 21% for shrimps and 16% for fish), for a global world production of  $43 \times 10^6$  tons of plants and animals.

### 3. Impact of microalgae in aquaculture

More than 40 species of microalgae are used in aquaculture. The main applications of microalgae in aquaculture are directly or indirectly associated with nutrition of various species of aquatic-farmed animals. Using some species of microalgae in the diet of fish lowers their price by 50% and increases the nutritional value in fish; it is often used in a combination of two or more species of microalgae (Svircev, 2005). Microalgae are currently used as feed for the culture of larvae and juvenile shellfish and finfish, as well as for raising the zooplankton required for feeding juvenile animals (Chen, 2003). The most frequently used genera of microalgae in aquaculture are *Spirulina*, *Chlorella*, *Tetraselmis*, *Isochrysis*, *Pavlova*, *Phaeodactylum*, *Chaetoceros*, *Nannochloropsis*, *Skeletonema* and *Thalassiosira*. Among these, the genus of *Spirulina* is widely used in feed in aquaculture, particularly in feed for tropical fish due to their rich quantities of pigments (Ciferri and Tiboni, 1985; Richmond, 1988). It improves the palatability of feed, and it has been reported that fish fed *Spirulina* have less abdominal fat and have better flavor, firmer flesh, and brighter skin (Mori, 1987). The fish fed with *Spirulina* based feed showed better growth (Palmegiano et al., 2005). The color-enhancing effects of phycocyanin-containing *Spirulina* sp. or carotenoids from *Dunaliella* sp. are exploited in ornamental fish. In addition, *Spirulina* and *Chlorella* used in common fish feed compositions appears to be a promising market. Phycocyanin from *Spirulina* stimulates hematopoiesis and emulates the effects of hormones, regulating the production of white blood cells during the damage of bone marrow stem cells (Vonshak, 1986).

The carotenoid synthesized from *Dunaliella* sp. and *Haematococcus* sp. and the lutein produced from *Muriellopsis* sp. (Del Campo

et al., 2000) play an important role in the growth of fish larvae. For example, marron fed a reference ration supplemented with the microalgae *D. salina* had greater growth and pigmentation (Sommer et al. 1991). Astaxanthin has also been shown to be essential for growth and survival during the initial feeding period of shrimp, salmon and trout (Lakeh et al., 2010; Lorenz and Cysewski, 2000; Niu et al., 2009). An astaxanthin, canthaxanthin and  $\beta$ -carotene-supplemented diet enhances the pigmentation of organisms, such as domesticated shrimp, red sea bream, salmon, trout, sea urchin, lobster and ornamental fish (Skjanes et al., 2013). In addition, *Artemia* growth rates have shown to increase when they are fed a diet with  $\beta$ -carotene. A positive correlation was observed between survival rates and pigment concentration in prawn tissue, indicating that pigment may play a vital role in improving the survival rates of prawns (Chien and Jeng 1992). Microalga *Tetraselmis* sp. increases the docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) contents of rotifers even with a short-term enrichment period in rotifer production (Reitan et al., 1997).

The marine cyanobacterium *Phormidium valderianum* is successfully used as feed in aquaculture because of its nutritional and non-toxic performance (Thajuddin and Subramanian, 2005). *Tetraselmis* sp., *Pyramimonas* sp., and *Micromonas* sp. are used for culturing bivalve mollusk larvae (Laing and Ayala, 1990). Recently, *Isochrysis galbana* and *Diacronema vlkianum* have been receiving more attention as a feed supplement because of their ability to produce long chain PUFAs, mainly EPA and DHA that accumulate as oil droplets (Gouveia et al., 2008). *Chlamydomonas reinhardtii* (*C. reinhardtii*) is known to have chloroplast features well-suited for developing a delivery system for oral vaccines (Surzycki et al., 2009), which will be helpful for developing a microalgal vaccine strategy for immunizing aquatic animals.

### 4. Beneficial effects of microalgae in poultry and pig farming

Numerous nutritional and toxicological evaluations have proved the suitability of algal biomass as a feed supplement (Becker, 2004). Due to large profiles of natural vitamins, minerals and essential fatty acids in algae, it will improve the immune response, fertility, weight control and the external appearance, such as healthy skin and a lustrous coat in animals (Certik and Shimizu, 1999). In addition, algae can directly be used to replace conventional protein sources in poultry feed, with an incorporation rate of 5–10% (Spolaore et al., 2006). The application of algae into poultry farming offers the most promising prospect for its commercial use in animal feeding (Becker, 2007). Poultry fed with *Porphyridium* sp. showed lower levels (10%) of cholesterol in egg yolks, and the color of the egg yolk was darker due to higher amounts of carotenoids (Ginzberg et al., 2000).

### 5. Carotenoids as health-beneficial microalgal metabolites

Carotenoids are lipophilic pigments with isoprenoid structures that occur in higher plants, microalgae and in non-photosynthetic organisms (Del-Campo et al., 2007; Takaichi, 2011). Most of the carotenoids have therapeutic value, including anti-inflammatory and anticancer activities, which are largely attributed to their strong antioxidant effect that is used to protect organisms against oxidative stress. The market value for carotenoids was approximately 1.2 billion US\$ in 2010, with the bulk of carotenoids production done by chemical synthesis. The synthesis of carotenoids is aided by using algae, which mainly serves as accessory pigments in photosynthesis (Cardozo et al., 2007). The compounds that consist of only hydrocarbons are carotenes, while those with oxo, hydroxyl or epoxy groups are called xanthophylls.

There are over 400 carotenoids identified in living organisms; among these,  $\beta$ -carotene and astaxanthin are widely commercialized, and lutein, zeaxanthin and lycopene are used to a lesser extent (Spolaore et al., 2006).

### 5.1. $\beta$ -carotene

$\beta$ -carotene is considered as one of the most important carotenoids because it has an active form of provitamin A, an additive to multivitamin preparations and health food products. The natural form of this pigment has a stronger effect and can be easily absorbed by the body when compared to the synthetic form (Chen et al., 1993).  $\beta$ -carotene has several applications in the food, feeds, pharmaceutical and cosmetic industries. An increasing demand for natural carotenoids has resulted in the growing interest in extracting  $\beta$ -carotene from different natural sources. *D. salina* are green, halophilic, biflagellate microalgae that produce high concentrations of  $\beta$ -carotene, up to 10–14% of algal dry weight (Sathasivam et al., 2012; Sathasivam and Juntawong, 2013). The high light intensity, high salinity, extreme temperatures, and nutrient supplements are playing a significant role in enhancing  $\beta$ -carotene production (Henley et al., 2002; Raja et al., 2004). The optimal medium and environmental conditions are useful for commercial production of  $\beta$ -carotene and, preferably, both all-*trans* and the 9-*cis* isomers (Borowitzka, 2013; Raja et al., 2008). The natural 9-*cis* isomer plays an important role in quenching free oxygen radicals, protecting the cell from oxidative damage (Borowitzka, 1992). The *trans* form of  $\beta$ -carotene is twice as active as the *cis* form in vitamin A formation, and many industries in Australia, Israel, the USA and China are producing this metabolite. Among these, a large amount is produced in Australia (García et al., 2005; Leon et al., 2003).

The algal  $\beta$ -carotene showed protective effects against atherosclerosis in both mice and humans. The administration of  $\beta$ -carotene rich *Dunaliella* inhibits low-density lipoprotein (LDL) oxidation and influences plasma triglycerides, cholesterol and high-density lipoprotein (HDL) levels (Shaish et al., 2009). Phang et al. (2007) reported that the supplementation of  $\beta$ -carotene from *Dunaliella bardawil* has been shown to inhibit oxidation of LDL in diabetic patients and may be important in delaying the development of atherosclerosis. However, many epidemiological studies suggest that humans fed a diet rich in  $\beta$ -carotene maintained their average serum levels and lowered their incidence of several types of cancer and degenerative diseases (Leon et al., 2003). In addition to  $\beta$ -carotene, other carotenoids from *Dunaliella*, such as phytoene and phytofluene, are also known to have health benefits, such as protection against UV and oxidative damage, which leads to premature aging and other disorders (Ben-Amotz, 1993). It also has a strong antioxidant to scavenge harmful oxy-radicals, which are commonly associated with the induction of certain cancers. Oral intake of  $\beta$ -carotene from *Dunaliella* sp. can prevent UV-induced erythema in humans (Heinrich et al., 2003).

### 5.2. Astaxanthin

The second important carotenoid synthesis from microalgae is astaxanthin; this pigment is a keto-carotenoid produced by the freshwater green algae *Haematococcus pluvialis* (*H. pluvialis*) (Cysewski and Lorenz, 2004). This alga is usually cultured in a two-stage process: the first step involves generating the 'green' motile algal biomass stage, followed by an astaxanthin-accumulating stage where the astaxanthin-containing aplanospores are produced. During environmentally stressful conditions, the algae changes their nature from a thin-wall, flagellated stage to a red, thick-walled resting stage due to the accumulation of astaxanthin (4–5%) in their dry weight (Boussiba et al., 1999).

There are three types of stereoisomers of astaxanthin; (3R, 3'R), (3R, 3'S) and (3S, 3'S) are reported; the synthetic astaxanthin contains an approximately 1:2:1 respective mixture of these stereoisomers. Hence, *H. pluvialis* produces only the (3S, 3'S) stereoisomer in free and esterified conditions (Grung et al. 1992). Astaxanthin is used in aquaculture as a pigmentation source, as well as in nutraceuticals, food and feed industries. The annual worldwide aquaculture market of astaxanthin is worth 200 million US\$, with an average price of 2,500 US\$/kg (Hejazi and Wijffels, 2004). On the market, astaxanthin has been sold as a nutraceutical in the form of a capsule. Astaxanthin-rich *Haematococcus* has been marketed as a dietary supplement for human consumption (Lorenz and Cysewski, 2000). This product has strong antioxidant activity, which is 100 times higher than  $\alpha$ -tocopherol (Higuera-Ciapara et al., 2006). Another microalga used for astaxanthin production is *Chlorella zofingiensis* (*C. zofingiensis*), and its production rate is less than that of *H. pluvialis*. This microalga increased astaxanthin production under nitrogen limitation and light stress (Pelah et al., 2004). During stress condition, *C. zofingiensis* generates hydroxyl radicals, which lead to an increase in the production of astaxanthin (Ip and Chen, 2005).

Astaxanthin plays a major role in protecting the alga against UV light damage and photooxidation of the poly-unsaturated astaxanthin. It shows strong free-radical scavenging activity, protects against lipid peroxidation and oxidative damage of LDL-cholesterol, cell membranes, cells and tissues. Many studies have shown that astaxanthin has protective effects against diseases, such as cancers, inflammatory diseases, metabolic syndrome, diabetes, diabetic nephropathy, neurodegenerative diseases and eye diseases (Yuan et al., 2011). Several studies have clearly shown that astaxanthin has effects on cancer cells in rats and mice. For example, the effect of astaxanthin on colon cancer in male rats has been reported. Astaxanthin enhances *in vitro* immunoglobulin antibody production by mouse spleen cells stimulated with sheep red blood cells, at least in part by exerting actions on T-cells, especially T-helper cells (Tanaka et al., 1995; Jyonouchi et al., 1993; Park et al., 2010). Studies on human blood cells *in vitro* have also demonstrated the enhancement of immunoglobulin production by astaxanthin in response to T-dependent stimuli. Tso and Lam (1996) reported that astaxanthin is effective at ameliorating retinal injury and it is also effective in protecting photoreceptors from degeneration in rats. Astaxanthin is found to easily cross the blood-brain barrier and did not form any crystals in the eye. The protective effects of astaxanthin are likely to be mediated through its prevention against oxidative damage and cellular necrosis or apoptosis induced by oxidative stress. For instance, it has been shown that administration of astaxanthin in alloxan-induced diabetic rats can partially reverse oxidative stress in neutrophils (Marin et al., 2011). The intake of astaxanthin has been shown to have a protective effect against ethanol-induced gastric ulcers caused by *Helicobacter pylori* (Kamath et al., 2008) and affects cholesterol levels in blood, which could be helpful for curing heart disease (Olaizola, 2005), preventing obesity (Ikeuchi et al., 2007) and preventing age-related cognitive function in humans (Satoh et al., 2009).

### 5.3. Canthaxanthin

Canthaxanthin is a type of carotenoid used as a food dye, giving color to egg yolks and chicken skin. When included in dietary supplements to poultry, it has been shown to be associated with increased vitamin E contents of the liver (Surai et al., 2003). This secondary level of carotenoid also has antioxidative, anti-inflammatory and neuroprotective effects (Chan et al., 2009). *Coccoloba striolata* and *C. zofingiensis* produce large amounts of canthaxanthin under salt stress and nitrogen-deprivation conditions



(Abe et al., 2007; Pelah et al., 2004). Some other microalgae, such as *Scenedesmus komareckii* (Hanagata, 1999) and aplanospores of *D. salina* (Borowitzka and Huisman, 1993) enhance the accumulation of canthaxanthin.

#### 5.4. Lutein

Lutein is one of the most important carotenoids in foods and human serum. It is an essential component of pigment present in the macula lutea (or yellow spot) in the retina and lens of eyes. Lutein is used as a colorant in cosmetics and food products (Jin et al., 2003), and it is responsible for pigmentation in fish and poultry. Thus, it is sold as a feed additive. Epidemiological studies revealed that lutein is currently considered an effective agent for preventing a wide variety of human diseases. *Muriellopsis* sp. and *Scenedesmus almeriensis* accumulate high amounts of lutein. The optimal temperature induces the higher accumulation of lutein in algal cells (Del Campo et al., 2000; 2007). However, the production rate of lutein is different in *Chlamydomonas zofingiensis*, *Auxenochlorella* (*Chlorella*) *protothecoides* and *D. salina* under low and high pH (Jin et al., 2003). The commercial production of lutein from microalgae has not yet started, although the basis for outdoor cultivation of *Muriellopsis* sp. and *Scenedesmus* for the production of lutein at a pilot scale has already been set up (Del-Campo et al., 2007). Microalgae synthesizes other carotenoids such as zeaxanthin from *D. salina* mutants (Jin et al., 2003), echinenone from *Botryococcus braunii* (*B. braunii*) (Matsuura et al., 2012), fucoxanthin from *Phaeodactylum tricorutum* (*P. tricorutum*) (Kim et al., 2012a, 2012b), and the colorless carotenoids phytoene and phytofluene from *D. salina* (von Oppen-Bezalel and Shaish, 2009). These carotenoids also have the potential to protect against oxidative stress caused by a wide spectrum of disease and aging.

### 6. Role of microalgal amino acids and fatty acids on health

A remarkable group of marine natural products are Mycosporine-like amino acids (MAAs). MAAs are a group of molecules consisting of an amino acid bound to a chromophore that absorbs low-wavelength light. MAAs have low molecular-weights (<400 kD) and are water-soluble compounds composed of either an aminocyclohexenone or an aminocyclohexenimine ring, carrying nitrogen or amino alcohol substituents (Nakamura et al., 1982). MAAs have been identified in various marine and freshwater organisms, and some have been identified in terrestrial organisms. MAAs are identified in green microalgae. These amino acids are involved in protecting the organism against UV radiation and are produced in significant amounts by *Chlamydomonas nivalis* and other green algal species. The production of MAAs is induced by exposing the culture to UV-light (Karsten et al., 2007; Xiong et al., 1999). MAAs from other algae have been shown to protect skin of higher organisms against UV damage (de la Coba et al., 2009). MAAs from algae have been explored for commercial purposes and have resulted in commercial skin-care products for UV protection (Schmid et al., 2006).

Microalgae are responsible for the production of essential fatty acids (EFAs), especially the long-chain PUFAs, such as  $\gamma$ -linolenic acid (GLA) (18:3 omega-6), arachidonic acid (AA) (20:4 omega-6), EPA (20:5 omega-3) and DHA (22:6 omega-3) (Borowitzka, 2013; Ratledge, 2010). Due to the lack of requisite enzymes to synthesize PUFAs of more than 18 carbon atoms in humans and animals, they need to obtain those fatty acids from their foods (Certik and Shimizu, 1999; Gill and Valivety, 1997). Currently, fish and fish oil are the common source to obtain PUFAs, but the application as a food additive is limited due to possible accumulation of toxins, fish odor, unpleasant taste, poor oxidative stability, and the pres-

ence of mixed fatty acids (Pulz and Gross, 2004). The higher concentration of PUFAs in fish might be caused by the consumption of microalgae, which is a reason to consider microalgae as a potential source of PUFAs (Jiang et al., 1999).

PUFAs play an important role in cellular and tissue metabolism, including the regulation of membrane fluidity, electron and oxygen transport, as well as thermal adaptation (Funk, 2001). The unsaturated fatty acids affect hyperlipidemia by lowering lipid levels, such as cholesterol and triglyceride, and thus reduce the risk of heart disease and atherosclerosis. Among all PUFAs, some of the  $\omega$ -3 EPA and DHA are of particular interest and have high nutrition. DHA is an important structural fatty acid for correct brain and eye development in infants and has been shown to support cardiovascular health in adults (Kroes et al., 2003; Ward and Singh, 2005). It is present in limited foods, such as fatty fish, organic meat and breast milk, but it is absent from cow's milk. However, gamma linolenic acid (GLA) is a  $\omega$ -6 PUFA; it is an important precursor in the synthesis of prostaglandins. Some clinical trials have shown that GLA is helpful in the treatment of diseases, such as arthritis, heart disease, obesity, alcoholism, depression, schizophrenia, Parkinson's disease, multiple sclerosis, zinc deficiency and some symptoms in elderly populations (Kerby et al., 1987). In this respect, DHA, EPA and GLA are extremely effective for human health (Richmond, 1986; Kerby et al., 1987).

Some of the microalgal species of *Cryptocodinium*, *Schizochytrium*, *Thraustochytrids* and *Ulkenia* are used to produce essential fatty acids (Ratledge, 2004; Barclay et al., 2010; Wynn et al., 2010). DHA rich in oil from *Cryptocodinium cohnii* is available on the market and contains 40–50% DHA and no EPA or other long-chain PUFAs (Jiang et al., 1999; Ward and Singh, 2005; Ratledge, 2004). *Schizochytrium* strains that produce DHA and EPA are currently used as an adult dietary supplement in food and beverages, health foods, animal feeds and maricultural products, including cheeses, yogurts, spreads and dressings, and breakfast cereals. These important essential fatty acids in this microalga are used as supplements in foods for pregnant and nursing women and cardiovascular patients (Ward and Singh, 2005). EPA is produced in high amounts in the marine green algae *Chlorella minutissima*, and the production of this fatty acid can be increased by reducing temperature and increasing salinity (Seto et al., 1984). The marine eustigmatophyte *Nannochloropsis* sp. and other forms, including *Aurora* sp. and *Nitzschia*, produce EPA-rich oil (Spolaore et al., 2006). Green algae *Parietochloris incisa* synthesizes high amounts of total lipid contents and AA (Solovchenko et al., 2008). The cyanobacterium *S. plantensis* is the best algal source of  $\gamma$ -linolenic acid (Tanticharoen et al., 1994). The fatty acid composition of several cyanobacterial strains is 16- and 18-carbon chain fatty acids, representing the most significant constituents in foods (Milovanovic et al., 2011). The highest production of relatively rare occurrences of GLA is obtained from *Spirulina* strains and *Nostoc* strains. Reports from both the WHO and FAO suggest that a balanced diet ratio of poly unsaturated fatty acids: saturated fatty acid is one above 0.4, and microalgae contain the favorable range of these ratios, from 1.65 to 3.71 (Milovanovic et al., 2012).

### 7. Microalgal antioxidants for human health

Microalgal biomass is considered a multi-component antioxidant system, which is generally more effective due to the interactions between different antioxidant components (Gouveia et al., 2008). Microalgae are rich in vitamins (Becker, 2004; Brown et al., 1999; Running et al., 2002). They have the ability to accumulate  $\alpha$ -/ $\beta$ -tocopherol/ $\alpha$ -tocotrienol (vitamin E) and fat-soluble phenols with antioxidant properties. Vitamin E has a wide range of applications. It is used to treat cancer, heart disease, eye disease,

Alzheimer's disease, Parkinson's disease and other medical conditions (Pham-Huy et al., 2008). Harvested microalgae are used in the food industry as a preservative and health-improving additive and for photoprotection in skin creams (Alberts et al., 1996). For example, microalgae, such as *D. tertiolecta* and *Tetraselmis suecica*, cultured under nitrogen-deprivation conditions increase the production of vitamin E (Carballo-Cardenas et al., 2003; Durmaz, 2007). Rodriguez-Zavala et al. (2010) identified a microalga *Euglena gracilis* for producing high concentrations of  $\alpha$ -tocopherol ( $3.7 \pm 0.2$  mg/g). Cobalamin (vitamin B<sub>12</sub>) is a water-soluble vitamin that can be produced by some microalgae. For example, *Spirulina* sp. synthesizes greater amounts of vitamin B<sub>12</sub> when compared to plant or animal foods. Some microalgae can accumulate ascorbic acid (vitamin C), which is a water-soluble vitamin with antioxidant properties. Vitamin C is essential for collagen, carnitine and neurotransmitter biosynthesis. It is used as a food additive and shows beneficial health effects, including cancer and atherosclerosis prevention, and it also acts as an immunomodulator. *Chlorella* sp. and *Dunaliella* sp. can accumulate high amounts of vitamin C (Barbosa et al., 2005; Running et al., 2002). Butylated hydroxytoluene (BHT) is a type of lipophilic antioxidant. Microalga *B. braunii* accumulates high amounts of BHT. It is used as a food additive or as an antioxidant source in other products (Capitani et al., 2009). *Dunaliella* sp. (Li et al., 2004; Sies, 1999) can produce high amounts of glutathione (GSH). GSH is a non-protein thiol compound. It has antioxidant enzymatic properties that scavenge the ROS and prevent the cellular damage due to different disease conditions. It is used in the pharmaceutical, food production and cosmetic industries.

## 8. Secondary metabolites from microalgae for health promotion

Cyanobacteria have been identified as important organisms due to their isolation of novel and biochemically active natural products. Most cyanobacteria, such as *Spirulina*, *Anabaena*, *Nostoc* and *Oscillatoria*, produce numerous varieties of secondary metabolites and bioactive compounds. Peptide synthetases are present and common in cyanobacteria and are involved in the biosynthesis of certain cyanobacterial bioactive compounds (e.g., microcystins). For example, *Chlorella* spp. and *Scenedesmus quadricauda* produce polysaccharides that function as protective agents against oxidative stress (Mohamed, 2008). *Lyngbya lagerheimii* and *Phormidium tenue* consist of active agents of sulfolipids with different fatty acid esters. Cryptophycin 1 is a natural product that was initially isolated from blue-green algae *Nostoc* sp., which has been shown to be potent in a broad spectrum of anti-tumor activity in preclinical *in vitro* and *in vivo* models. Among eukaryotic microalgae, a glycoprotein produced from a *Chlorella vulgaris* culture supernatant showed protective activity against tumor metastasis and chemotherapy-induced immunosuppression in mice (Barsanti and Gualtieri, 2006). Several cyclic or linear peptides and depsipeptides isolated from cyanobacteria are protease inhibitors, used for the treatment of diseases such as strokes, coronary artery occlusions and pulmonary emphysema (Skulberg, 2004; Singh et al., 2005). For example, aeruginosins isolated from *Microcystis aeruginosa* have been shown to have inhibitory properties against thrombin, plasmin and trypsin (Murakami et al., 1995). Other depsipeptides, such as micropeptin, microcystilide, cyanopeptolin, oscillapeptin and nostocyclin are inhibitors of enzymes such as trypsin, plasmin, thrombin and chymotrypsin (Patterson, 1996).

### 8.1. Glycerol

Glycerol is an organic osmolyte. In fact, the accumulation of glycerol in alga is regulated by external water activity, rather than

by a specific solute effect (Shariati and Lilley, 1994; Leon and Galvan, 1999). Glycerol has a wide range of applications; it is used in the cosmetic, paint, automotive, food, tobacco, pharmaceutical, pulp and paper, leather and textile industries (Wang et al., 2001). Most of the halotolerant algae accumulate large amounts of glycerol content with salt concentration. For example, *Dunaliella* species is a halotolerant microalga, and it can accumulate up to 17% w/w intracellular glycerol (Kacka and Donmez, 2008). Some of the freshwater microalgal species such as *C. reinhardtii* also produce high amounts of glycerol (Miyasaka et al., 1998).

### 8.2. Sterols

Sterols, also known as steroid alcohols, are a subgroup of the steroids and an important class of organic molecules. Microalgae produce a very wide range of phytosterols, including brassicasterol, sitosterol and stigmasterol (Patterson et al., 1994; Marshall et al., 2002; Volkman, 2003). Phytosterols have been used in pharmaceutical applications or in functional foods (Sioen et al., 2011). Francavilla et al. (2010) reported that *D. tertiolecta* and *D. salina* grown under different salt concentrations produced abundant phytosterols such as (22E, 24R)-methylcholesta-5,7,22-trien-3 $\beta$ -ol (ergosterol) and (22E, 24R)-ethylcholesta-5,7,22-trien-3 $\beta$ -ol (7-dehydroergosterol). The global market of phytosterol is growing at approximately 7–9%, annually (Borowitzka, 2013).

### 8.3. Stable isotopic compounds

Microalgae are one of the suitable sources of isotopically labeled compounds due to the ultimate choice to isolate stable isotopes from inorganic molecules, such as C-source, H-source and N-source, into high-value isotopic organic chemicals (Raja et al., 2008). To elucidate the molecular structure and for the investigations of gastrointestinal or breathing diagnostic tests (Radmer, 1996), the stable isotope-labeled biochemical can be widely used. Due to their various purposes and uses, the market value for these chemicals exceeds US\$13 million (Milledge et al., 2011). The production of <sup>13</sup>C or <sup>15</sup>N labeled biomass of microalgae on a commercial scale, combined with a process for the indoor production of <sup>13</sup>C labeled PUFAs from *P. tricornutum* Bohlin, will open a new era of easy isotope production (Acien Fernandez et al., 2005).

### 8.4. Phycotoxin

Cyanobacteria produce a highly effective bioactive phycotoxin. It has a wide range of therapeutic values, including cytotoxic, anti-tumor, antibiotic, antifungal, immunosuppressant and neurotoxic properties, which offer great potential for biotechnological exploitation (Garcia-Camacho et al., 2007). Such toxin compounds are produced mainly by dinoflagellates and cyanobacteria. Cyanobacteria, such as *Microcystis*, *Anabaena*, *Oscillatoria* and *Nostoc* species, produce the most common freshwater algal toxins, such as microcystins, homo- and anatoxin-a and saxitoxins. Common dinoflagellates include *Alexandrium*, *Dinophysis*, *Amphidinium* *Karenia* and *Gymnodinium* species, which also produce those toxins. Many algal toxins are neurotoxic compounds, and they are used for investigations on neurodegenerative diseases. For example, okadaic acid produced by *Dinophysis* sp. is a potent neurotoxin, and it is used in studies on the therapeutic effects of atypical, antipsychotic drugs in the treatment of cognitive impairment and schizophrenia (He et al., 2005).

## 9. Conclusions

Microalgae have a rich source of health-promoting and disease-suppressing metabolites. The diverse groups of carotenoids, fatty

acids, amino acids, antioxidants and other secondary metabolites in microalgae enhance the nutritional value of human and animal diets. The mass culture and commercial production of microalgae have grown in recent decades. They are useful for aquaculture, poultry and pig farming, increasing their production. The pharmacological use of microalgae has helped to cure several diseases in human and animals. Thus, this review highlights the significance of microalgal bio-active components for future developments in the food and pharmaceutical industries.

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