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Evaluation of Microalgae for use as Nutraceuticals and Nutritional Supplements

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Abstract

As proper nourishment is a growing concern with increasing world populations, sustainable sources of nutritional value are needed. Due to the diverse nutritional components algae can produce and concentrate, along with their simple and rapid growth characteristics, these autotrophic organisms are exceedingly desired for use in nutraceuticals and nutritional supplements. Many types of algae have documented health benefits from strengthening the immune system to fighting cancer and heart disease. Information presented in this article was mined from quality, peer-reviewed published literature, technical reports and books. This review evaluates the use of *Chlorella*, *Dunaliella*, *Haematococcus*, *Aphanizomenon*, and *Spirulina* as nutraceuticals and nutritional supplements, in terms of production, nutritional components, and documented health benefits.

Keywords: Algae; Nutraceuticals; Health benefits; Nutritional supplements

Introduction

Nutraceuticals are nutrients from food or food products that not only supplement the diet but also facilitate the prevention or treatment of a disease and/or disorder [1]. There are over 470 nutraceutical and functional food products commercially available with researched health benefits [2]. An increased global interest has arisen in these substances due to their documented role in health enhancement [3]. The health-seeking consumer trend has intensified the use of products aimed at promoting health as well as treating potential fatal ailments (i.e. heart disease, cancer, Parkinson's disease etc.). The current estimated global market size for nutraceutical products is 30 to 60 billion dollars, primarily in the United States, Japan, and Europe, with a potential short-term growth market demand of over 197 billion dollars [4]. With the increase in demand for nutraceuticals and food supplements, organisms that can rapidly produce nutritional compounds are desired.

Algae are a diverse group of autotrophic organisms that have the ability to grow rapidly, efficiently use light energy, fix atmospheric CO_2, and produce more biomass per acre than vascular plants [5]. Algae have been used as a food source and for treatment of various ailments for over two thousand years [6,7]. Algae can form numerous compounds that are currently present in nutraceuticals and have the potential to become more intensively exploited. Different types of algae, specifically microalgae, that could become more prevalent in food supplements and nutraceuticals are *Nostoc*, *Botryococcus*, *Anabaena*, *Chlamydomonas*, *Scenedesmus*, *Synechococcus*, *Parietochloris,* and *Porphyridium* etc. due to the capability of producing necessary vitamins including: A (Retinol), B_1 (Thiamine), B_2 (Riboflavin), B_3 (Niacin), B_6 (Pyridoxine), B_9 (Folic acid), B_{12} (Cobalamin), C (L-Ascorbic acid), D, E (Tocopherol), and H (Biotin). Also, these organisms concentrate essential elements including: Potassium, Zinc, Iodine, Selenium, Iron, Manganese, Copper, Phosphorus, Sodium, Nitrogen, Magnesium, Cobalt, Molybdenum, Sulfur and Calcium. Algae are also high producers of essential amino acids and Omega 6 (Arachidonic acid) and Omega 3 (docosahexaenoic acid, eicosapentaenoic acid) fatty acids [8]. Due to their abundant production of beneficial compounds and nutritive contents, the market for increased algae production for nutraceuticals is lucrative and imminent.

As proper nourishment is a growing concern with increasing world populations, easy to produce and cost-effective sources that can rapidly produce large amounts of nutritional value are needed. Algae can provide a significant source of a diverse number of critical nutrients to support human health. Algae are ubiquitous throughout the world and have persisted and thrived in numerous types of environments. The adaptations they have developed and propagated are accompanied by benefits to organisms up the food chain. Many of these unique characteristics (carotenoids, micronutrient accumulation, amino acids etc.) have led to an extensive base of compounds that are critical in human health. Discovering of these algae and contained compounds is in its infancy, though numerous beneficial products are currently present. The goal of this article is to review the current status of nutraceutical products and food supplements when it regards common cultured microalgae production and use as well as to outline the positive health benefits documented from these algae. The specific objectives of this research were to (1) Review common types of microalgae (i.e., *Chlorella*, *Dunaliella*, *Haematococcus*, *Aphanizomenon*, and *Spirulina*) currently used in nutraceuticals; (2) Describe their characteristics, nutritional benefits, and possible side effects; and (3) Evaluate the potential for increased nutraceutical production through currently used algae as well as up and coming sources.

Materials and Methods

The literature selected for use in this review was obtained through database and internet search engines (i.e., Web of Science, BioOne, Google Scholar). No internet citations are present; all information was mined from peer-reviewed published literature, technical reports

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and books. Sources were selected based upon their quality of research and content. Only studies with an appropriate experimental design and valid measurements of presented data were used. Due to the vast amount of published literature on this topic and the limited number of articles that can be cited, only a fraction of the available literature was selected for this article.

Results

Chlorella

Chlorella is a unicellular, green alga found in many aquatic systems and is widely sold as a health food, food supplement, and nutraceutical [9]. The United States, Japan, China, Taiwan, and Indonesia produce over 2500 tons of dried *Chlorella* each year [10]. It is considered an important functional food and source of nutrients in many areas due to its abundance and positive health effects. *Chlorella* is sold and distributed by numerous vendors such as Lucky Vitamin™, Prime Chlorella™ Distribution Inc., Sun Chlorella, HerbMark, Puritan's Pride and more. Due to its rapid growth characteristics and nourishing qualities, *Chlorella* will likely continually supplement our dietary needs, as it has for many decades.

Chlorella is composed of 55-67% protein, 1-4% chlorophyll, 9-18% dietary fiber and numerous minerals and vitamins [11]. The protein of *Chlorella* contains all essential amino acids required for the nutrition of heterotrophic organisms. Porphyrin rings in chlorophyll or glutathione induced pathway production by vitamin B_{12} in *Chlorella* [12] have been shown to detoxify problematic metals and pesticides [11,13]. *Chlorella* is a large producer of lutein, which has been shown to prevent and treat macular degeneration and contains anti-cataract properties [14]. Extracts of *Chlorella* have been documented as possessing diverse antitumor [15,16], antioxidant [17], anti-inflammatory [18], and antimicrobial activities [19]. *Chlorella* is able to decrease blood pressure, lower cholesterol levels, accelerate wound healing, and enhance the immune system [20]. It also has the potential to relieve symptoms and improve quality of life in people with fibromyalgia, hypertension, or ulcerative colitis [21,22]. The presence of aortic atheromatous lesions was significantly inhibited and low-density lipoprotein (LDL) cholesterol levels were greatly suppressed upon consumption of *Chlorella* [23].

Chlorella consumption as a nutritional product has initiated investigations to its possible side effects. Some consumers have indicated a potential correlation between some brands of *Chlorella* tablets and nausea, vomiting, and other gastrointestinal issues. Poor digestibility if not processed efficiently has been documented and may lead to certain gastrointestinal issues [24]. *Chlorella* tablets have been indicated in the causation of acute tubulointerstitial nephritis often resulting in renal failure [25]. *Chlorella* has been labeled as a weak allergen and may be of clinical significance to certain types of people [24]. Aside, from the potential for negative effects of *Chlorella* supplementation, culturing may prove challenging as well. *Chlorella* cultivation systems may be extremely costly and often become contaminated by other algae or bacteria, thereby hindering production [20].

Dunaliella

Dunaliella (*D. salina* dominant in nutraceutical production) is a unicellular, green alga that produces large amounts of beta carotene, glycerol, and protein that can easily be extracted through its thin cell wall [26,27]. Due to its unique growth environment and halo tolerance of saline conditions (up to 100 g NaCl/L) it does not utilize waters appropriate for agricultural and domestic uses. Also, few other organisms can survive in such conditions so the opportunity for contamination by other algae, fungi, animals and bacteria is minimal and open outdoor cultures can be utilized [28-30]. Global production of *Dunaliella* is estimated to be 1,200 tons dry weight per year [31]. The dominant companies that produce *Dunaliella*, mainly for beta-carotene production, are located in Israel, China, United States, and Australia and include: Betatene, Western Biotechnology, AquaCarotene LTD, Cyanotech Corp., Nature Beta Technologies and more [32].

Dunaliella produces numerous carotenoid pigments with the dominant being beta-carotene and smaller amounts of alpha-carotene, lutein, and lycopene [27]. Some strains of *Dunaliella* contain up to 14% dry weight beta-carotene [33]. The total carotenoid content of *Dunaliella* varies with growth conditions, although the ideal environment can yield around 400 mg beta-carotene/m^2 of cultivation area [34]. Carotenoids from *Dunaliella* are potent free radical scavengers that reduce levels of lipid peroxidation and enzyme inactivation, thereby restoring enzyme activity [27]. Beta-carotene is an antioxidant that can trap reactive oxygen species involved in the aging process [35,36]. Studies have shown beta-carotene to prevent cancer of various organs like lungs, stomach, cervix, pancreas, colon, rectum, breast, prostate and ovary by means of antioxidant activity [37]. It has also been shown to promote regression of certain types of cancer [38]. Beta-carotene from *Dunaliella* can positively influence intracellular communication [39], immune response [40], and protection against many types of neoplasms [41]. Supplements of *Dunaliella* have also shown excellent hepatoprotective effects and reduced the occurrence of liver lesions [42].

Despite the advancement in the production of beta-carotene from natural sources like *Dunaliella*, more than 90% of commercialized beta-carotene is produced synthetically [33]. However, natural (i.e., produced by organisms) beta-carotene has a higher bioavailability compared to synthetically manufactured beta-carotene [43]. The activity and amount of the antioxidant enzymes catalase, peroxidase, and superoxide dismutase were significantly greater in naturally produced beta-carotene from *Dunaliella* compared to synthetic [27]. The potential health benefits from *Dunaliella* are numerous and little data are present on risks associated with consumption of supplements containing this alga. Multigenerational studies with rats consuming up to 10% *Dunaliella* in their diets showed no significant negative effects and was indicative of the safety of *Dunaliella* for human consumption [44].

Haematococcus

Haematococcus (*H. pluvialis* predominantly produced) is a unicellular, green alga that is a common component of nutraceuticals, pharmaceuticals, cosmetics, aquaculture, and numerous food products [45]. Approximately 300 tons dry weight of *Haematococcus* is produced annually in the United States, India and Israel [46]. Under conditions not favorable for cell growth *Haematococcus* goes into a resting stage, indicated by the pigment astaxanthin, making the cells appear red. Astaxanthin sells for $2,500 per kilogram dry weight with an annual worldwide market estimated at $200 million; although 95% of this market consumes synthetically derived astaxanthin [45,47]. Numerous patents exist on the usages of it, primarily in the arenas of food and health. *Haematococcus* is cultivated commercially in large-scale outdoor systems and controlled photobioreactors. Companies that mass produce *Haematococcus*, predominantly for astaxanthin, include: Cynotech Corporation, Parry Nutraceuticals, BioReal, Inc., Fuji Health Science, Valensa International, Alga Technologies, and Aquasearch Inc.

Despite the other vitamins and minerals in *Haematococcus*,

the primary nutraceutical market is incorporated in astaxanthin. *Haematococcus* is the largest natural source of astanxanthin, which comprises 1.5-3% of its dry weight [47]. Astaxanthin is a carotenoid pigment with antioxidant activity at least 10 times stronger than beta-carotene and 1000 times more effective than vitamin E [48,49]. It is effective at decreasing arterial blood pressure, plasma levels of triglycerides and non-esterified fatty acids [50]. Astaxanthin has important metabolic functions in humans like protection against oxidation of essential polyunsaturated fatty acids, protection against UV radiation effects, enhanced vision, immune response, pigmentation and reproductive behavior [51]. This pigment possesses anti-oxidative [52], anti-cancer [53], anti-inflammatory, and anti-bacterial activities [54]. Astaxanthin is also useful for prevention and treatment of neural damage associated with age-related macular degeneration and effective at treating Alzheimer's disease, Parkinson's disease, spinal cord damage, and other central nervous system injuries [55,56].

Haematococcus has not been reported in any discovered peer reviewed literature to possess negative consequences upon ingestion. Animal studies with rats revealed no adverse effects of consuming 5 to 18 g/kg/day [57]. *Haematococcus* algal extract containing astaxanthin was tested on humans for eight weeks and no significant differences were measured for adverse clinical parameters [58]. Further human studies at exposures of 20 mg/day for four weeks revealed no negative effects on blood chemistry, hematology, or other adverse experiences during treatment [59]. Also, no negative effects were measured on human health following exposures to pharmaceuticals containing dietary astaxanthin [60]. *Haematococcus pluvialis* was approved for marketing as a new dietary ingredient in the United States by the Food and Drug Administration (FDA) in August 1999. No confirmed reports or documentation could be found regarding non-compliance with safety trial parameters in astaxanthin exposures [61].

Aphanizomenon

Aphanizomenon is a prokaryotic cyanobacterium (blue-green alga) commonly found in freshwater systems throughout the world. Approximately 500 tons of dried *Aphanizomenon* is produced annually for use in food and pharmaceutical products [31]. This alga has been cultivated for consumption for many years and is currently being produced in many countries. The dominant production source of *Aphanizomenon* in North America is Upper Klamath Lake, Klamath Falls, Oregon and currently constitutes a significant part of the health food supplement industry throughout North America [62]. The primary companies responsible for the harvesting and distribution of supplements containing *Aphanizomenon* are Cell Tech International Inc., Life Enthusiast Co-op, AquaSource and Klamath Valley Botanicals, Inc.

Aphanizomenon contains a significant amount of chlorophyll (1-2% dry weight) which is shown to stimulate liver function and increase bile secretion [63]. C-Phycocyanin, another light-harvesting pigment it contains, has antioxidant and anti-inflammatory properties [64]. *Aphanizomenon* also has high hypo cholesterolemic activity, significantly greater than soybean oil, which causes a decrease in blood cholesterol and triglyceride levels [65,66]. *Aphanizomenon* is a large producer of polyunsaturated fatty acids (i.e., omega 3 and omega 6), a deficiency of which has been linked to immunosuppression [67], arthritis [68], cardiovascular diseases [69,70], mental health issues [70,71], and dermatological problems [72]. Additionally, components of this alga have been shown to decrease certain cancer risks [73], inflammation [68], and prevent platelet accumulation [74]. Manoukian et al. [75] found *Aphanizomenon* to increase natural killer cells that induce programmed cell death in virus-infected and cancerous cells and Ostensvik et al. [76] identified antibacterial properties. There are also reports of improved behavior and attention span in humans that consume *Aphanizomenon* [62,77].

There has been some interest in the possible negative health effects of consuming *Aphanizomenon*. The primary concerns address toxin production and exposure upon consumption. *Aphanizomenon flos-aquae*, the dominant species used in production has not been shown to produce hepatotoxins (microcystins), although can produce neurotoxins (anatoxin and saxitoxin; [78,79]). *Aphanizomenon* often grows amongst other toxin producing cyanobacteria including *Anabaena* and *Microcystis* that could be harvested unknowingly and contribute to toxin loads including microcystins and nuerotoxins [79]. However, with extensive studies on the possible exposures and responses little risk has been observed in current nutritional supplements. Schaeffer et al. [62] found no growth depression, organ malfunction or other deleterious effects on adult mice and no effects on fetus or neonate development with exposures of ≤ 333 µg microcystin-LR/kg body weight/day. Concentrations of constituents that may pose risks upon exposure should be evaluated prior to using any product.

Spirulina

Spirulina is a prokaryotic cyanobacterium that has been commercially produced for over thirty years for uses including: fish food, vitamin supplements, food dyes, aquaculture, pharmaceuticals and nutraceuticals [80,81]. Approximately 3,000 tons dry weight is currently produced annually in the United States, Thailand, India, Taiwan, China, Pakistan, and Burma [31,82,83]. *Spirulina* is manufactured by a variety of companies some of which include: Puritan's Pride, Springtime Inc., Valley Naturals, Bio-Alternatives, and Watershed Wellness Center. This alga is thought of as a super food and is widely cultured, primarily in specifically designed raceway ponds and photobioreactors, to meet the current demand.

Spirulina is a rich source of nutrients such as B vitamins, phycocyanin, chlorophyll, vitamin E, omega 6 fatty acids and numerous minerals [84]. *Spirulina* is 60-70% protein by weight (including many amino acids) and contains up to 10 times more beta-carotene than carrots per unit mass [85]. *Spirulina* has assisted in health areas like weight loss [86], diabetes [87], high blood pressure and hypertension [88]. It has well documented antiviral [69,70,89], and anticancer properties [90-92]. *Spirulina* can also enhance the phagocytic activity in macrophages and produce antigen-specific antibody production to help treat depression and attention-deficit hyperactivity disorder [71,93,94]. *Spirulina* positively affects cholesterol metabolism by increasing HDL levels, which can lead to healthy cardiovascular functions [95]. Romay et al. [64] described the antioxidant and anti-inflammatory properties of C-phycocyanin, which is a prevalent pigment in *Spirulina*. Tsuchihashi et al. [96] showed a significant increase in the bacteria *Lactobacillus* in rats following *Spirulina* amendments in their diet; which if occurred in humans would improve digestion, food absorption, and stimulate the immune system to help fight infections [97].

Some question has been raised on the digestion capacity and bioavailability of nutrients like vitamin B_{12} from *Spirulina* [98]. However, efficient processing claims to release nutrients into a digestible form for humans. Some *Spirulina* supplements have been shown to contain traces of the toxin microcystin due to invasion of other algae (like *Microcystis* spp.) in culturing areas, which acts primarily on decreasing liver function and could cause liver cancer and other diseases [99]. Also, since *Spirulina* can concentrate elemental constituents it may

Component	*Spirulina*	*Dunaliella*	*Haematococcus*	*Chlorella*	*Aphanizomenon*
Protein	63	7.4	23.6	64.5	1.0
Fat	4.3	7.0	13.8	10.0	3.0
Carbohydrates	17.8	29.7	38.0	15.0	23.0
Chlorophyll	1.15	2.2	0.4 (red), 1.1 (green)	5.0	1.8
Magnesium	0.319	4.59	1.14	0.264	0.2
Beta-Carotene	0.12	1.6	0.054	0.086	0.42
Vitamin B_1 (Thiamin)	0.001	0.0009	0.00047	0.0023	0.004
Vitamin B_2 (Riboflavin)	0.0045	0.0009	0.0017	0.005	0.0006
Vitamin B_3 (Niacin)	0.0149	0.001	0.0066	0.025	0.013
Vitamin B_5 (Pantothenic acid)	0.0013	0.0005	0.0014	0.0019	0.0008
Vitamin B_6 (Pyridoxine)	0.00096	0.0004	0.00036	0.0025	0.0013
Vitamin B_9 (Folic Acid)	0.000027	0.00004	0.00029	0.0006	0.0001
Vitamin B_{12} (Cobalamine)	0.00016	0.000004	0.00012	0.000008	0.0006

Table 1: Summary of referenced average nutritional compositions of the described microalgae expressed as g per 100 g dry weight.

contain elevated amounts of unnecessary elements like mercury and create potential risks, depending on the growth environment. Some of the potential side effects of *Spirulina* products are diarrhea, nausea, and vomiting. Also, allergic reactions, though rare, may result it insomnia and anxiety [100,101].

Conclusion

As the human population continues to increase, demand for nutritive food and health products increases concomitantly. Sources of nutritive biomass that can meet this demand are pursued rampantly. Algae have shown viability in meeting nutritive demands due to their rapid growth, health benefits, and enriched compounds they produce. Algae have been used for centuries to nourish humans but are now being much more intensely cultured and harvested [102]. The role of algae in human health and nutrition will continually increase with additional research in the areas of health benefits and culturing.

Usage of currently produced algae primarily includes: food, food additives, aquaculture, colorants, cosmetics, pharmaceuticals, and nutraceuticals [103]. Only a small fraction of the total number of algal species is being cultivated for human use. There are likely more species of algae that have not been identified than ones that have and those still numbers in the thousands. Therefore, the potential for algal use in the realms of food consumption, health supplements, energy production, and many more is likely to intensify in the years to come. Geographic uses of algae for human nutrition will parallel distribution and specific growth habitat characteristics and capacity.

Nutraceuticals harness and concentrate the nutritive algal components to increase positive health effects. Some types of algae that are currently mass produced for nutritive and other uses have been discussed and there compositions outlined (Table 1). These algae have been integrated into many nutritional programs throughout the world and likely to increase in human consumption. Increased research and development is constantly being funneled to greater production and use of these algae to meet the ever-growing demand and identify benefits of additional types of algae. The ability of algae to treat and prevent numerous types of serious diseases (especially viral infections, heart disease, and cancer) will undoubtedly continually surge interest and investigation into their value for human health and nutrition.

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