Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 14, Issue 2, 2024, 32
https://doi.org/10.33263/BRIAC142.032

Some Applications of *Arthrospira platensis* and Algae in Pharmaceutical and Food Technologies

Ivaylo Pehlivanov [1], Galia Gentscheva [2,3], Krastena Nikolova [4,*], Velichka Andonova [1]

[1] Medical University of Varna, Department of Pharmaceutical Technologies, 55 Marin Drinov Str., 9000 Varna, Bulgaria; Ivaylo.Pehlivanov@mu-varna.bg (I.P); Velika.Andonova@mu-varna.bg (V.A);
[2] Medical University–Pleven, Department of Chemistry and Biochemistry, 1, Saint Kliment Ohridski Str., 5800 Pleven, Bulgaria; e-mail: Galia.Gentscheva@mu-pleven.bg (G.G.);
[3] Institute of General and Inorganic Chemistry, Bulgarian Academy of Sciences, Akad. G. Bonchev Str, Bl. 11, 1113 Sofia, Bulgaria
[4] Medical University of Varna, Department of Physics and Biophysics, 55 Marin Drinov Str., 9000 Varna, Bulgaria; Krastena.Nikolova@mu-varna.bg (K.N.);
* Correspondence: Krastena.Nikolova@mu-varna.bg;

Scopus Author ID 14631065000
Received: 4.02.2023; Accepted: 19.03.2023; Published: 3.02.2024

Abstract: Algae, as well as *Arthrospira platensis*, have a wide range of biologically active constituents that determine different pharmacological properties. They are also the basis for developing various new nutritional compositions and supplements. This review summarizes the application of algae and *Arthrospira platensis* in pharmaceutical technology and food over the last 20 years with an emphasis on the beneficial effects of spirulina on human health, considering its nutritional value and therapeutic properties. A detailed literature review was conducted in scientific databases for over 20 years, such as PubMed, ScienceDirect, ResearchGate, and Google Scholar. Relevant information is summarized and interpreted. The permanent research process leads to the development of new preparations to inhibit the growth of cancer cells, reduce the aging of cells, increase the immune system's efficiency, protect against infectious diseases, etc. *In vivo* studies show specific mechanisms of neuroprotection, appetite regulation, and prevention of neurodegenerative and psycho-cognitive pathologies. Algae and *Arthrospira platensis*, with their biologically active metabolites, are essential raw materials for producing various pharmaceutical products and functional foods with high nutrient content. Their use depends on the preservation of their biodiversity. In connection with their biosafety and the understanding of the biological effects on the human organism, it is necessary to continue their study.

Keywords: *Arthrospira platensis*, algae, food applications, pharmaceutical, and medical applications.

1. Introduction

Algae are classified according to their size as microalgae and macroalgae and according to their pigment content in red (Rhodophyta), brown (Phaeophyta), and green (Chlorophyta). Some species are an essential source of oils and various other compounds and can also be used as a source of renewable energy [1]. Algae are interesting natural sources of new biologically active substances, with variable composition depending on geographical region, season, environment, ecological conditions of their habitat, and others [2-4]. Some microalgae species produce a protein with high nutritional value and, hence, are used as an abnormal protein [5]; others can accumulate significant quantities of polysaccharides [6-7] with different properties. Species such as *Dunaliella salina*, *Haematococcus lacustris*, *H. pluvialis*, and *Porphyridium*

cruentum are rich in pigments such as beta-carotene and astaxanthin that are of interest for the pharmaceutical, cosmetic, and food industries [8-10].

The European Union adopted a strategy aimed at the innovative development of the biotechnology sector, named the “Blue bioeconomy,” One of the strategy’s main directions is microalgae production as a source of precious compounds for human beings [11]. According to Regulation (EC), №258/97 of the European Parliament, “food and food ingredients consisting of or isolated from algae which have not been used to a significant extent” can be employed as new products.

Interesting is the inclusion of algae in various "functional" foods for the absorption of fatty acids and improving digestion. Furthermore, due to their diverse and rich chemical composition, algae present many pharmacological properties such as antioxidant, anti-diabetic, antimicrobial [12], anti-tumor, anti-inflammatory [13], photoprotective, and antiviral that increase their potential value for the pharmaceutical industry [14].

According to Sprygin *et al*., [15] brown algae contain large amounts of polyphenols. Up to 50% of the dry residue of the *S. pallidum* extract is presented by polyphenols [16]. According to the authors, the species *S. pallidum* can be considered a promising raw material for developing highly effective anti-stress products with pronounced antioxidant properties. The conclusion is based on a study on the influence of biotic and abiotic stress factors, creating many superoxide and hydroxyl radicals and the subsequent peroxidation of lipids in cell membranes. The protective effect on the gastric mucosa of mice of an aqueous extract of *S. pallidum* has been proven [17]. Mhadhebi *et al*. and Fuente *et al.* [18-19] studied the anti-inflammatory activity of brown algae of *Cystoseira crinita*, *Cystoseira sedoides*, and *Cystoseira compressa*.

Recently, the relationship between nutrition and disease prevention has been increasingly sought [20]. There is a growing interest in developing nutritional supplements and functional foods [21-22], with many authors reporting the production of new soft drinks from rice bran, papaya, and algae or those obtained after algal fermentation [23-25]. Others observe an increase in polyphenolic levels of rye bread during the fermentation phase in the presence of algae [26]. Adding algae to pâtés leads to lower oxidation of the fats contained in them and lower content of microorganisms [27]. Such pâtés show lower cooking losses and have a 50% softer texture than algae-free pâtés. Algae present antioxidant properties since they are rich in polyphenols. Selected seaweed species from the Danish coast have been studied in detail [28], and Polysiphonia fucoids species and all Fucus class species have been shown to have high free radical scavenging activity, high reducing power, can inhibit oxidation in a liposome model system, and can be used as natural antioxidants for food preservation. Algae contain substances that prevent the adverse effects of free radicals. These compounds, called antioxidants, and their impact on human health are summarized in Table 1.

Table 1. Antioxidant components of algae and their effect on human health.

Antioxidant	**Algae content**	**Source**	**Effect on health**	**Literature**
β-carotene lutein	*Chondrus crispus* Red algae	[29] [30]	Antiproliferative	[37]
Fucoidan	*Laminaria japonica, Turbinaria conoides*	[31] [32]	Inhibition of α-glucosidase Anti-tumor effect Anti-HIV effect Neurodegenerative disorders protection	[38] [39] [40] [41] [32]
Fucoxanthin	Brown algae	[33]	Protective effect against retinol deficiency	[42] [43]

Antioxidant	Algae content	Source	Effect on health	Literature
Phlorotanins	*Sargassum pallidum* *Fucus vesiculos*	[34] [35]	Anti-inflammatory and bactericidal effects Photochemoprotective effect	[44] [45]
Phycoerythrin	*Sargassum pallidum* *Fucus vesiculos*	[34] [35]	Improving diabetic complications	[46]
Polyphenols	*Halimeda* sp.	[36]	Vascular chemoprotection Antimicrobial effects Inhibition of α-glucosidase	[47]

Ganesan [14] has studied the antioxidant activity of three edible species of green algae of the genus Enteromorpha (*E. compressa*, *E. linza,* and *E. tubulosa*) from the northwest coast of India [14]. The authors note that extracts of these algae can be used as natural antioxidants or as ingredients in pharmaceuticals or food supplements. Some types of green algae contain cellulose with high surface area and inertness, and these properties make them a suitable alternative carrier for drug delivery. Strømme found that the cellulose obtained from Cladophora, after its purification and hydrolysis, forms agglomerates that are stronger than the commercially available analogs, and it is a suitable carrier for liquid pharmaceuticals such as nicotine [48]. Algae species such as *C. fulvescens* contain biologically active substances that are inhibitors of different enzymes: aldose reductase, choline esterase, and end products of glycation. The red alga (Rhodophyta) is rich in vanillic acid, gallic acid, and syringic acid [49], while brown seaweeds produce phlorotannins [50].

The organic substances have immunomodulating and hepatoprotective effects and can induce cancer cell apoptosis [51-53]. According to Wu, green algae have higher antioxidant activity than many terrestrial plants due to the higher content of non-enzymatic antioxidant complexes such as ascorbic acid, reduced glutathione, phenols, and flavonoids [54]. Some species, such as Halophila spp., are effective against malaria, several skin diseases, and the early stages of leprosy. Cymodocea spp. is used for cough and malaria [54]. Furthermore, some algae are consumed in salads, puddings, jellies, and soups by the population of Myanmar [55].

Scientists rank cyanobacteria (blue-green algae) as one of the oldest and most primitive life forms of nearly 4 billion years. The primary pigments in them are chlorophyll and phycobiliproteins, such as allophycocyanin (blue), C-phycocyanin (blue), and phycoerythrin (red). These pigments are responsible for photosynthesis and capture the light in the spectrum's green, yellow, and orange parts.

In recent years, the interest in cyanobacteria is because they exist in any environment, such as hot springs, salt marshes, and moist soils, do not require fertile soils or clean water, have rigid cell walls that protect them from the outside world, and maintain homeostasis [56]. These species are susceptible to accumulation in photoreactors, where it is possible to maintain continuous optimal conditions. They are characterized by high productivity per unit area compared to other photosynthetic organisms or higher plants. Due to the same habitat conditions in the bioreactor, a relatively constant mineral, fatty acid, sterol-, and polyphenolic composition is achieved.

Spirulina has recently gained popularity and is a nutritional supplement for astronauts in NASA space missions. One kg of spirulina has the nutritional value of 1000 kg of fruits and vegetables [57].

This review summarizes the applications of algae and spirulina in pharmaceutical technology, cosmetics, and food over the last 20 years with an emphasis on human health.

2. Phytochemical composition and beneficial effects of algae

The main phytochemicals in algae are fatty acids, phospholipids, phytosterols, and proteins. The fatty acid composition of algae is important in the development of dietary supplements, as some polyunsaturated fatty acids have an inflammatory effect, while others have an anti-inflammatory effect. The percentage of saturated and unsaturated fatty acids depends not only on the type of algae but also on several factors such as temperature, salinity, presence or absence of pollution, sunshine, harvesting season, etc. [58]. According to most authors, palmitic acid (C16:0) is predominant in the phytochemical composition of algae [59]. Studies of five types of algae from the Bulgarian Black Sea and it is shown that palmitic acid C16:0 dominates the group of saturated fatty acids (UNFA), and among the monounsaturated fatty acids (MMA) with the highest values are oleic C18:1 and palmitoleic C16:1 n-7. Within the group of polyunsaturated fatty acids (PUFA), there are differences in the fatty acid profile: linoleic acid (C 18:2 n-6) predominates in the green algae *Ulva rigida* and *Chaetomorpha linum*, arachidonic acid (C 20:4 n-6) – in the red algae *Gelidium crinale*, and eicosapentaenoic (C20:5 n-3) – in the brown algae *Cystoseira barbata* and *Cystoseira crinite* [60]. The significant amount of fatty acids in some algae makes it possible to use them as food additives [61-62].

Polyunsaturated fatty acids play a significant role in the growth of organisms, have a beneficial effect on coronary heart disease, and are therefore recommended for cardiovascular disease, high blood pressure, and diabetes. In addition, the fatty acids in algae help maintain the integrity of the skin and preserve its hydration [63]. When the polysaccharides in some microalgae are broken down, a wax ester is obtained that can be applied in cosmetics [64].

In addition to fatty acids, algae are rich in phospholipids and phytosterols. There is evidence that phytosterols reduce serum glucose levels in rats with proven diabetes and may reduce the level of bad cholesterol in the blood [65].

About 65-70% of the dry mass of algae are proteins. In comparison, wheat germ, peanuts, chicken, fish, and beef contain 27%, 26%, 24%, 22%, and 22% crude protein, respectively [66-68].

3. Phytochemical composition of *Spirulina*

In addition to significant protein content, it contains essential fatty acids, vitamins, polysaccharides, minerals, and vitamins [69]. The World Health Organization named it one of the most suitable superfoods on Earth. According to Wu *et al*. (2016), spirulina contains more calcium than milk, iron than spinach, and beta carotene than carrots [70]. It has a high amount of B vitamins and is the only plant source with about 2.5 times higher B12 content than in the liver. It also contains high amounts of zinc, magnesium, manganese, and potassium [71-72]. Therefore, spirulina could provide most of the body's essential and replaceable amino acids. It contains a large amount of beta-carotene, a precursor of vitamin A [73-74]. Its high protein content is similar to meat, eggs, and legumes [68]. Values of these substances have been cited by various authors who have studied spirulina in different regions of the world [56-60]. Tables 2, and 3, present the essential fatty acids [75] and pigments [76] with their structural formulas and content according to literature data.

Thanks to its well-balanced, rich chemical composition, spirulina has found its application as a component in various foods and pasta products. It is often included as a component in various diets.

Table 2. Main fatty acids in *spirulina.*

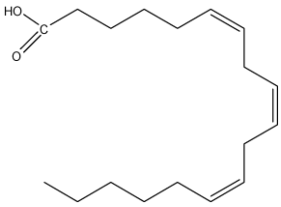
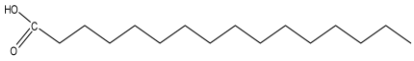
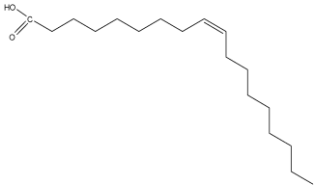
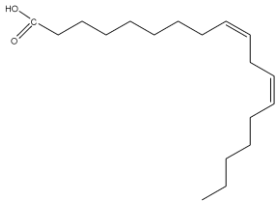
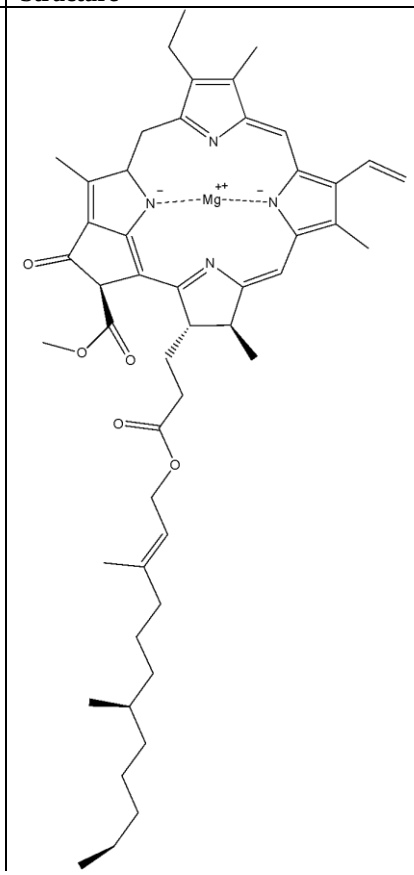
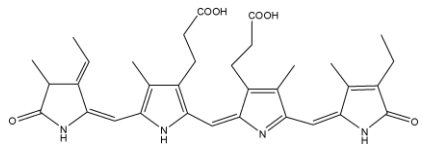
Fatty acid	Structure	Content, %
γ-Linolenic Acid C18:3		8.87
Palmitic acid C16:0		46.07
Oleic acid C18:1		5.2
Linoleic acid C18:2		17.43

Table 3. Main pigments in spirulina.

Pigment	Structure	Content, %
Chlorophyll a		1000 mg/100g

C-Phycocyanin		8000 mg/100g

4. Application of *Spirulina* in food technology

The complex chemical composition of algae improves the quality of fermented dairy products. The addition of spirulina has a stimulating effect during the fermentation process and during the storage of beneficial bacteria such as *Lactobacillus acidophilus* [77-78] and *Lactobacillus bulgaricus* [79]. Biomass from spirulina is an additive for innovative and healthy products [80]. Furthermore, the cyanobacteria improved some physicochemical and sensory characteristics in pasta [81].

Donato *et al*. have developed cookies mixed with 0, 5, 10, and 15% spirulina powder [82]. They found that as the concentration of spirulina increased, the percentage of protein also increased, with the highest content of minerals and proteins being the biscuits with the highest content of spirulina – 15%. Winarni *et al*. prove that concentrations from 1% to 2% of spirulina in the total mass of ice cream and melted cheese significantly affect water, fat, and protein and significantly affect their texture and point of melting [83]. Setyaningsih *et al*. found that at room temperature, biscuits with coconut cream and spirulina retain their sensory and textual properties for up to 2.5 months and have higher protein and lower lipid content [84].

Spirulina powder is considered beneficial for athletes to increase their endurance under load, and in older people, it improves metabolism and increases the percentage of nutrients absorbed. It can be taken as a powder of algae added to sports drinks, green fruit, vegetable juice, or tablets before, after, or during a meal [85].

5. Spirulina application in pharmaceutical practice

5.1. Antioxidant properties.

Some foods, such as blueberries, spinach, and especially spirulina, have a high oxygen scavenging capacity (oxygen radical absorbance capacity, ORAC). According to ORAC, the antioxidant activity of blueberry samples is 320 μmol, and of *spirulina* – 13,000 μmol [86]. *Spirulina* possesses these high antioxidant properties due to its rich chemical composition. Antioxidants are compounds that neutralize free radicals generated due to oxidative stress. Free radicals can damage a healthy cell and can even lead to its death. Oxidative stress is the cause of several diseases, such as diabetes, atherosclerosis, rheumatoid arthritis, and several cancers [86]. However, *spirulina* also has a neuroprotective effect, and these properties continue to be actively studied. Some diseases are associated with undefined oxidative stress. Activation of enzymes under oxidative stress is associated with damage to cellular systems [87]. Antioxidants contained in cyanobacteria can protect the body from free radicals. Rabbits treated with 0.5 g of *spirulina* have been shown to reduce total cholesterol and triglycerides and increase high-density lipoproteins [88]. The high antioxidant activity of spirulina is due to the individual or synergistic effect of tocopherol, β-carotene, and phenolic compounds [89]. *Spirulina* inhibits up to 65% of lipid peroxidation, compared with α-tocopherol and β-carotene, which inhibit it by 35% and 48%, respectively [90]. There is evidence that *spirulina* extracts in hot water have an antioxidant effect of up to 76%. In contrast, chlorogenic and gallic acid affect only 56% and 54%, respectively [91]. *Spirulina* extracts have high antioxidant activity

due to the high content of carotenoids and tocopherols [92]. In addition, its extracts are rich in two main phycobiliproteins – C-phycocyanin and phycocyanin, acting on superoxide radicals [93-94]. Experimental studies were performed in C-phycocyanin-treated rats from *spirulina* after CCl_4 intoxication. As a result, decreased lipid peroxidation in rat liver has been demonstrated [94]. Furthermore, several studies described that after consuming this alga, it relieved the symptoms of liver cirrhosis [95-96] and reduced the oxidative stress of alpha-toxin-fed pets [97-98].

5.2. Antimicrobial activity.

Spirulina is increasingly used as a natural antimicrobial agent [99]. Kokou *et al.* confirmed its antibacterial activity against six strains of Vibrio: *V. anguillarum*, *V. splendidus*, *V. parahaemolyticus*, *V. scophthalmir*, *V. lentus*, and *V. alginolyticus* [98]. Algae methanol extract has been shown to have high antimicrobial activity against gram-positive *Streptococcus faecalis*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*; gram-negative bacterium *Escherichia coli*, and antifungal activity against *Candida albicans* [100, 101]. However, such extracts do not affect the bacteria *Pseudomonas aeruginosa*, *Salmonella typhirium*, and *Klebsiella pneumonia* [101]. The addition of spirulina extract in synthesizing biofunctionalized gold nanoparticles enhances the antibacterial activity against gram-positive organisms.

Santoyo *et al*. applied a pressure liquid extraction varying temperature, solvent, and extraction time to obtain *Arthrospira platensis* extracts in antioxidant and antimicrobial compounds. The authors confirmed that extracts obtained with ethanol, hexane, and petroleum ether possess antimicrobial activity against S. aureus ATCC 25923, E. coli ATCC 11775, C. albicans ATCC 60193, and Aspergillus niger ATCC 16404 as C. albicans has been the most sensitive microorganism to all spirulina extracts [102]. In another study, it was found that purified C-phycocyanin, obtained from spirulina, inhibits the growth of drug-resistant bacteria such as *E. coli*, *K. pneumoniae*, *Ps. aeruginosa*, and *S. aureus*. However, no activity of C-phycocyanin has been reported in Acinetobacter baumannii and *Enterococcus durans* [103]. Arun *et al*. also confirmed that a methanol Spirulina extract has antifungal activity against *C. albicans* and antimicrobial activity against gram-positive S. aureus [104].

5.3. Antiviral activity.

Consumption of a supplement containing Spirulina extract leads to an increase in T-helper lymphocytes in HIV-infected patients, and a reduction in viral load has also been found [105-108]. There have been other reports of the antiviral activity of spirulina against viruses such as cytomegalovirus, human immunodeficiency virus-1 (HIV-1), influenza A virus, Herpes simplex mumps virus, and measles [109-110]. Water-based spirulina extract inhibits the penetration and replication of herpes simplex virus-1 (HSV-1) cells [111]. Spirulina methanol extracts are significantly effective against adenovirus type 40 and reduce infection if non-toxic concentrations of 2 mg/ml sections are used [112]. Purified phycocyanin extracted from spirulina has antiviral activity against enterovirus. The pigment thus extracted slows down the synthesis of viral RNA and activates apoptosis in both human and renal cells from the green monkey Afrin [113]. In addition, spirulina has been shown to activate macrophages, T and B cells and increase infection resistance in humans, chickens, and fish [114].

5.4. Other health effects.

In people with cardiovascular disease, consuming a dietary supplement of this seaweed leads to lowering LDL cholesterol in the blood. In diabetics, it reduces the ratio of LDL/HDL cholesterol [115]. The decrease in lipid content is associated with C-phycocyanin extracted from spirulina [116].

Spirulina improves red blood cell production [117]. Older women recover faster from anemia when taking a spirulina supplement [118]. In addition, hemoglobin levels in malnourished children increase with the inclusion of spirulina in the diet [119].

Decreased secretion has also been found in cyanobacteria supplements in patients with allergic rhinitis [120]. Inflammation in patients with arthritis is reduced due to the stimulation of secretions that reduce the body's inflammatory response [120].

Spirulina is used in Saudi Arabia to fight obesity [121], and its extracts inhibit α - glucosidase and amylase [122-123]. In addition, the administration of 6.5 g of spirulina per day for six weeks decreased systolic and diastolic blood pressure [116].

5.5. Application in cosmetics.

Spirulina accumulates specific secondary metabolites that can enhance the activity of various organic and inorganic commercial compounds used in cosmetics.

Moreover, those compounds act as sun protection factors against free radicals and against the effects of UV radiation [124, 125]. *Arthrospira platensis* extracts are utilized in India as a moisturizer and skin-softener agent in body serums (Iraya Algae Serum Body Lotion). Cyanobacterial protein extracts are used in the USA to produce hair conditioning masks (Blue Green Algae Hair Rescue Conditioning Mask) that help strengthen hair and prevent breakage and split ends. Protein-rich extracts of *Arthrospira platensis* are used as skin astringents, protecting agents against signs of premature skin aging and preventing stretch marks [126,127]. Rich in blue-green pigments, cyanobacteria are used as natural colorants in eyeliners, eye shadows, and lipsticks [128, 129].

Based on antimicrobial activity data, some researchers have investigated the effectiveness of topical Spirulina creams applied *in vivo* in treating impetigo [130]. The authors noted good efficacy during the follow-up period. According to them, this is due to the synergism of some fatty acids and the relatively high content of linoleic and palmitic acids.

The high beta carotene and superoxide dismutase content in spirulina allows its inclusion in creams to maintain skin resilience and remove blemishes from the skin to relieve dermatitis symptoms. Extracts of tropical microalgae are added to famous French cosmetics as they have several regenerating effects on the skin and improve protein synthesis in keratinocytes and collagen synthesis in fibroblasts. In addition, calcium extracted from spirulina prevents the attachment of herpes simplex virus type-1 (HSV-1) to human keratinocytes [131].

The blue-green pigments in spirulina are used as natural dyes in makeup and eyeliner products and as an antioxidant, protecting against harmful UV rays in lipsticks and sunscreens [126-127]. In addition, Spirulina supplementation can reduce or prevent skin erythema because of excessive exposure to sunlight [132].

Nihal *et al*. developed a topical anti-acne formulation of a cosmetic product using spirulina extract rich in phycocyanin protein [133]. Many cosmetic companies around the world have developed products using spirulina. Piruline AP® is a water-soluble extract of blue

algae supplied by SEPPIC (head office in France) with anti-radical action [134]. Eau de toilette with *Arthrospira platensis* extract stabilized by citric acid, sodium benzoate, and potassium sorbate is supplied by Phenbiox [135].

6. Between toxicity and benefits

Arthospira platensis contains many functional groups /carboxyl, hydroxyl, sulfate, and others/ that provide the possibility of binding with a large number of elements [136]. Some reports in the literature state its ability to sorb Zn^{2+}, Pb^{2+}, Cr^{3+}, Ni^{2+}, etc. [136, 137, 138, 139]. That makes spirulina a good biosorbent of toxic elements and provides opportunities for new applications; however, because of that, their use in the food and pharmaceutical industry requires permanent control of the content of those elements. Industrial cultivation of spirulina is a good option as it is done in controlled conditions.

7. Recent perspectives on the use of *spirulina*

The possibility of effectively combining spirulina with probiotics to improve the microflora in the stomach and intestines after inflammatory processes have been investigated [140]. To reduce the risk of vision loss due to oxidative damage to the retina and eliminate the effect of dry eye and others, a combined nutritional supplement containing spirulina and lutein has been developed and studied [141, 142, 143]. Treatment with Spirulina extract leads to a large reduction in macrophage and monocyte-induced TNF-α secretion levels. This is a prerequisite for developing preparations against macrophage activation syndrome and, subsequently, hypercytokinemia, commonly referred to as a cytokine storm [144]. Spirulina is increasingly used as an additive in new food products: biscuits [145], crackers, etc. [146]. Pasta, macaroni, and sushi are combined with spirulina in order to increase the protein content and therapeutic benefits without significantly changing the caloric value [147, 148].

7. Conclusion

Algae and spirulina, with their biologically active metabolites, are essential raw materials for producing various pharmaceutical products and functional foods with high nutrient content. In connection with their biosafety and the understanding of the biological effects on the human organism, it is necessary to continue their study.

Funding

This study is financed by the European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project № BG-RRP-2.004-0009-C02.

References

1. Moreno-Garciaa, K.; Adjalléb, S.; Barnabéb, G.S.V.; Raghavana. Microalgae biomass production for a biorefinery system: Recent advances and the way towards sustainability. *Renewable and Sustainable Energy Reviews* **2017**, 76, 493-506. https://doi.org/10.1016/j.rser.2017.03.024
2. Malibari, R.; Fotoon, S.; Ahmed, M.; Elazzazyac, M.; Baeshend, N.; Douroue, M.; Aggelisae, G. Reuse of shrimp farm wastewater as growth medium for marine microalgae isolated from Red Sea – Jeddah. *Journal of Cleaner Production* **2018**, 198, 160-169. https://doi.org/10.1016/J.JCLEPRO.2018.07.037.

3. Dourou, M.; Olga, N.; Tsolcha, AG.; Tekerlekopoulou, D. B.; Aggelis, G. Fish farm effluents are suitable growth mediafor Nannochloropsis gaditana, a polyunsatu-rated fatty acid producing microalga. *Eng. Life Sci.* **2018**, 18, 851–860. https://doi.org/10.1002/elsc.201800064.
4. Dourou, M.; Dritsas, P.; Baeshen, M.N.; Elazzazy, A.; Al-Farga, A.; Aggelis, G. High-added value products from microalgae and prospects of aquaculture wastewaters as microalgae growth media. *FEMS Microbiol. Lett.* **2020**, *367*, https://doi.org/10.1093/femsle/fnaa081.
5. Stiefvatter, L.; Neumann, U.; Rings, A.; Frick, K.; Schmid-Staiger, U.; Bischoff, S.C. The microalgae Phaeodactylum tricornutum Is well suited as a food with positive effects on the intestinal microbiota and the generation of SCFA: Results from a preclinical Study. *Nutrients*, **2022**, *14*, 2504. https://doi.org/10.3390/nu14122504.
6. Bellou, S.; Aggelis G. Biochemical activities in Chlorella sp. and Nannochloropsis salina during lipid and sugar synthesis ina lab-scale open pond simulating reactor. *J. Biotechnol.* **2012**, *164*, 318–329. https://doi.org/10.1016/j.jbiotec.2013.01.010.
7. Moreira, J.B.; Vaz, B.d.S.; Cardias, B.B.; Cruz, C.G.; Almeida, A.C.A.d.; Costa, J.A.V.; Morais M.G. Microalgae Polysaccharides: An Alternative Source for Food Production and Sustainable Agriculture. *Polysaccharides* **2022**, *3*, 441-457. https://doi.org/10.3390/polysaccharides3020027.
8. Wu, J.; Gu, X.; Yang, D.; Xu, S.; Wang, S.; Chen, X.; & Wang, Z.. Bioactive substances and potentiality of marine microalgae. *Food Science & Nutrition* **2021,** *9*, 5279–5292. https://doi.org/10.1002/fsn3.2471
9. Bellou, S.; Baeshe, M.N.; Elazzazy, A.M.; Aggeli D; *et al*. Mi-croalgal lipids biochemistry and biotechnological perspectives. *Biotechnol. Adv*. **2014,** *32*, 1476–1493. https://doi.org/10.1016/j.biotechadv.2014.10.003.
10. Lu, Z.h.; Deng, D.F.; Dominy, W. A defatted microalgae (Haematococcus pluvialis) meal as a protein ingredient to partially replace fish meal in diets of Pacific white shrimp (Litope-naeus vannamei, Boone, 1931). *Aquacultures.* **2012**, *354*, 50–55. https://doi.org/10.1016/j.aquaculture.2012.04.028.
11. European Commission, Directorate-General for Research and Innovation, *Bioeconomy: the European way to use our natural resources: action plan 2018*. Publications Office; 2019. https://doi.org/10.2777/79401.
12. Stirk, W. A.; Reinecke, D.L; Van Staden, J. Seasonal variation in antifungal, antibacterial and acetylcholineesterase activity in seven South African seaweeds. *J Appl Phycol.* **2007**; *19*, 271–276. https://doi.org/10.1016/j.copbio.2012.09.012
13. Souza, B. W. S.; Cerqueira, M. A.; Bourbon, A.I.; Pinheiro, A.C.; Martins, J.T.; Teixeira, J.A.; Coimbra, M.A.; Vicente, A. A. Chemical characterization and antioxidant activity of sulfated polysaccharide from the red seaweed Gracilaria birdiae. *Food Hydrocoll.* **2012,** *27*, 287–292. https://doi.org/10.1016/j.copbio.2012.09.012
14. Ganesan, K.; Suresh, K.; Subba, P.V. Comparative assessment of antioxidant activity in three edible species of green seaweed, Enteromorpha from Okha, Northwest coast of India. *Innov Food Sci Emerg Technol.* **2011**, *12*, 73–78. https://doi.org/10.1016/j.ifset.2010.11.005
15. Fernando, I.P.; Kim, M.; Son, K.T.; Jeong, Y.; Jeon, Y. J. Antioxidant Activity of Marine Algal Polyphenolic Compounds: A Mechanistic Approach. *J Med Food*. **2016**, *19*, 615-28. https://doi.org/10.1089/jmf.2016.3706.
16. Fomenko, S.E.; Kushnerova, N.F.; Sprygin, V.G. Antioxidant Properties of the Extract From the Brown Seaweed Sargassum pallidum at Stress Impact. *Journal of Stress Physiology & Biochemistry.* **2016**, *12*, 15-22. ISSN 1997-0838, https://agris.fao.org/agris-search/search.do?recordID=RU2018100010.
17. Zhang, C.Y.; Wu, W.H.; Wang, J.; Lan, M.B.; Antioxidant properties of polysaccharide from the oxalate crystallization. *Mar. Drugs.* **2012**, 10, 119–130. https://doi.org/10.3390/md10010119.
18. De La Fuente, G.; Fontana, M.; Asnaghi, V.; Chiantore, M.; Mirata,S.; Salis, A.; Damonte, G.; Scarfì, S. The Remarkable Antioxidant and Anti-Inflammatory Potential of the Extracts of the Brown Alga Cystoseira amentacea var. stricta. *Mar. Drugs* **2021**, *19*, 2. https://dx.doi.org/10.3390/md19010002
19. Mhadhebi, L.; Dellai, A.; Laroche, A.; Robert, J. and Bouraoui, A. Anti-inflammatory and antiproliferative activities of organic fractions from the Mediterranean brown seaweed Cystoseira compressa. *Drug Develop. Res.* **2011**, *10*, 16682-16690. https://doi.org/10.1002/ddr.20491.
20. Charoensiddhi, S.; Franco, Ch.; Su, P.; Zhang, W. Improved antioxidant activities of brown seaweed Ecklonia radiata extracts prepared by microwave-assisted enzymatic extraction. *J Appl Phycol.* **2015**, *27*, 2049–2058. https://doi.org/10.1007/s10811-014-0476-2

21. Bernal, J.; Mendiola, J.A.; Ibáñez, E.; Cifuentes, A. Advanced analysisof nutraceuticals. *J Pharm Biomed.* **2011**, 55, 758–774. https://doi.org/10.1016/j.jpba.2010.11.033
22. Freitas, A.C.; Rodrigues. D.; Rocha-Santos. T.A.P.; Gomes, A., Duarte, A.C. Marine biotechnology advances towards applications in new functional foods. *Biotechnol Adv.* **2012**, *30*, 1506–1515. https://doi.org/10.1016/j.biotechadv.2012.03.006.
23. Prachyakij, P.; Charernjiratrakul, W.; Kantachote, D. Improvement in the quality of a fermented seaweed beverage using an antiyeast starter of Lactobacillus plantarum DW3 and partial sterilization. *World J. Microbiol. Biotechnol.* **2008**, *24*, 1713–1720. https://doi.org/10.1007/s11274-008-9662-1.
24. Ke, B.; Xu, Z.; Ling, Y.; Qiu, W.; Xu, Y.; Higa, T.; Aruoma, O. I. Modulation of experimental osteoporosis in rats by the antioxidant beverage effective microorganism-X (EM-X). *Biomed. Pharmacother.* **2009,** *63*, 114 – 119. https://doi.org/10.1016/j.biopha.2008.03.008
25. Gupta, S.; Abu-Ghannam, N.; Scannell, A.G.M. Growth and kinetics of Lactobacillus plantarum in the fermentation of edible Irish brown seaweeds. *Food Bioprod. Processing.* **2011**, *89*, 346 – 355. https://doi.org/10.1016/j.fbp.2010.10.001;
26. Kariluoto, S.; Vahteristo, L.; Salovaara, H.; Katina, K.; Liukkonen, K.; Piironen, V. Effect of baking method and fermentation on folate content of rye and wheat breads. *Cereal Chem.* **2004**, *81*, 134–139. https://doi.org/10.1007/s11130-005-5097-0
27. Sabrina, C.; Nissreen, A.G. Enhancement of the phytochemical and fibre content of beef patties with Himanthalia elongata seaweed. *International Journal of Food Science and Technology.* **2013**, *48*, 2239–2249. https://doi.org/10.1111/ijfs.12210
28. Sabeena, Farvin KN.; Jacobsen, Ch. Phenolic compounds and antioxidant activities of selected species of seaweeds from Danish coast. *Food Chemistry.* **2013,** *138*: 1670-1681. https://doi.org/10.1016/j.foodchem.2012.10.078.
29. Lermontovap, I.; Schubert, V.; Fuchs, J.; Klatte, S.; Macas, J.; Schubert, I. Loading of Arabidopsis Centromeric Histone CENH3 Occurs Mainly during G2 and Requires the Presence of the Histone Fold Domain. *The Plant Cell* **2006**, *18*, 2443–245, https://doi.org/10.1105/tpc.106.043174
30. Lohrmann, N. L.; Logan, B. A.; Johnson, A.S. Seasonal acclimatization of antioxidants and photosynthesis in Chondrus crispus and Mastocarpus stellatus, two co-occurring red algae with differing stress tolerances. *Biol. Bull.* **2004**, *207*, 225-232. https://doi.org/10.2307/1543211
31. Chattopadhyay, N.; Ghosh, T.; Sinha, S.; Chattopadhyay, K.; Karmakar, P.; Ray, B. Polysaccharides from Turbinaria conoides: structural features and antioxidant capacity. *Food Chem.* **2010**, *118*, 823-829. https://doi.org/10.1016/j.foodchem.2009.05.069
32. Luo, D.; Zhang, Q.; Wang, H.; Cui, Y.; Sun, Z.; Yang, J.; Zheng, Y.; Jia, J.; Yu, F.; Wang, X.; Wang, X. Fucoidan pro-tects against dopaminergic neuron death *in vivo* and in vitro. *Eur. J. Pharmacol.* **2009**, 617, 33-40. https://doi.org/10.1016/j.ejphar.2009.06.015
33. Sachindra, N. M.; Sato, E.; Maeda, H.; Hosokawa, M.; Niwano, Y.; Kohno, M.; Miyashita, K. Radical scavenging and singlet oxygen quenching activity of marine carotenoid fucoxanthin and its metabolites. *J. Agric. Food Chem.* **2007**, *55*, 8516-8522. https://doi.org/10.1021/jf071848a
34. Ye, H.; Wang, K.; Zhou, C.; Liu, J.; Zeng, X. Purification, antitumor and antioxidant activities in vitro of polysaccharides from the brown seaweed Sargassum pallidum. *Food Chem.* **2008**, *111*, 428-432. https://doi.org/10.1016/j.foodchem.2008.04.012
35. Díaz-Rubio, M.E.; Pérez-Jiménez, J.; Saura-Calixto, F. Dietary fiber and antioxidant capacity in Fucus vesiculosus products. *Int. J. Food Sci. Nutr.* **2009,** 60, 23-34. https://doi.org/10.1080/09637480802189643
36. Devi, K.P.; Suganth, N.; Kesika, P.; Pandian, S.K. Bioprotective properties of seaweeds: in vitro evaluation of antioxidant activity and antimicrobial activity against food borne bacteria in relation to polyphenolic content. *BMC Complement. Altern. Med.* **2008**; *8*, 38-40. https://doi.org/10.1186/1472-6882-8-38. https://doi.org/10.1186/1472-6882-8-38.
37. Lourenço-Lopes, C.; Fraga-Corral, M.; Jimenez-Lopez, C.; Carpena, M.; Pereira, A.G.; Garcia-Oliveira, P.; Prieto, M.A.; Simal-Gandara, J. Biological action mechanisms of fucoxanthin extracted from algae for application in food and cosmetic industries. *Trends Food Sci. Technol.* **2021**, *117*, 163–181. https://doi.org/10.1016/j.tifs.2021.03.012.
38. Kim, E.Y.; Kim, D.G.; Kim, Y.R.; Hwang, H. J.; Nam, T.J.; Kong, I.S. An improved method of protein isolation and proteome analysis with Saccharina japonica (Laminariales) incubated under different pH

conditions. *Journal of Applied Phycology*. **2011,** *23*, 123–130. https://doi.org/10.1007/s10126-013-9498-z

39. Haijin, M.; Xiaolu, J.; Huashi, G. A k-carrageenan derived oligosaccharide prepared by enzymatic degradation containing anti-tumor activity. *J. Appl. Phycol.* **2003**, *15*, 297-303. https://doi.org/10.1023/A:1025103530534
40. Moo-Puc, R.; Robledo, D.; Freile-Pelegrin, Y. Enhanced Antitumoral Activity of Extracts Derived from Cultured Udotea flabellum (*Chlorophyta*). *Evid. Based. Complement. Alternat. Med.* **2011**, *969275*, 21-25. https://doi.org/10.1155/2011/969275
41. Veena, C.K.; Josephine, A.; Preetha, S.P.; Varalakshmi, P. Benefcial role of sulfated polysaccharides from edible seaweed Fucus vesicuolosus in experimental hyperoxaluria. *Food. Chem.* **2007,** *100*, 1552-1559. https://doi.org/10.1016/j.foodchem.2005.12.040
42. Sugawara, T.; Matsubara, K.; Akagi, R.; Mori, M. Hirata T. Antiangiogenic activity of brown algae fucoxan thin and its deacetylated product, fucoxanthinol. *J. Agri. Food. Chem.* **2006**, *54*, 9805-9810. 06 https://doi.org/10.1021/jf062204q
43. Sangeetha, R.K.; Bhaskar, N.; Baskaran, V. Comparative effects of β-carotene and fucoxanthin on retinol defciency induced oxidative stress in rats. *Mol .Cell. Biochem.* **2009**, *331*, 59-67. https://doi.org/10.1007/s11010-009-0145-y
44. Shin, H.C.; Hwang, H.J.; Kang, K.J.; Lee, B.H. An antioxidative and anti-infammatory agent for potential treatment of osteoarthritis from Ecklonia cava. *Arch. Pharm. Res.* **2006**, *29*, 165-171. https://doi.org/10.1007/BF02974279
45. Meng, W.; Mu, T.; Sun, H.; & Garcia-Vaquero, M((2021). Phlorotannins: A review of extraction methods, structural characteristics, bioactivities, bioavailability, and future trends. *Algal Research* **2021**, *60*, 102484. https://doi.org/10.1016/j.algal.2021.102484
46. Yabuta, Y.; Fujimura, H.; Kwak, C.S.; Enomoto, T.; Watanabe, F. Antioxidant activity of the phycoerythrobilin compound formed from a dried Korean purple laver (*Porphyra sp.*) during in vitro digestion. *Food Sci. Technol. Res.* **2010**, 16347-351. https://doi.org/10.3136/FSTR.16.347
47. Jimenez-Colmenero, F.; Sanchez-Muniz, J.; Olmedilla-Alonso, B. Design and development of meat-based functional foods with walnut: technological, nutritional and health impact. *Food Chemistry*. **2010**, *123*, 959–967. https://doi.org/10.1007/s11010-009-0145-y
48. Strømme, M.; Mihranyan, A.; Ek, R. Influence of cellulose powder structure on moisture-induced degradation of acetylsalicylic acid. *Eur. J. Pharm. Sci.* **2006**, *27*, 220–225. https://doi.org/10.1016/j.ejps.2005.10.002
49. Kalasariya, H.S.; Pereira, L.; Patel, N.B. Pioneering role of marine macroalgae in cosmeceuticals. *Phycology* **2022**, *2*, 172–203; https://doi.org/10.3390/phycology2010010.
50. Lomartire, S.; Cotas, J.; Pacheco, D.; Marques, J.C.; Pereira, L.; Gonçalves, A.M.M. Environmental impact on seaweed phenolic production and activity: An important step for compound exploitation. *Mar. Drugs* **2021**, *19*, 245. https://doi.org/10.3390/md19050245.
51. Fang, Z.; Yang, Jeong S.; Ah, Jung H.; Sue, Choi J; Sun, Min B.; Hee, Woo. M. Capsofulvesins A-C, cholinesterase inhibitors from Capsosiphon fulvescens. *Chem Pharm Bull.* **2012**, *60*, 1351–1358. https://doi.org/10.1248/cpb.c12-00268.
52. Islam, M.N.; Choi, S.H.; Moon, H.E; Park, J.J.; Jung, H. A.; Woo, M.H.; Woo, H.C.; Choi, J.S. The inhibitory activities of the edible green alga Capsosiphon fulvescens on rat lens aldose reductase and advanced glycation end products formation. *Eur J Nutr.* **2014**, *53*, 233–242. https://doi.org/10.1007/s00394-013-0521-y
53. de Arruda, M. C. S.; da Silva, M. R. O. B.; Cavalcanti, V. L. R.; Brandao, R. M. P. C.; Viana Marques; D. D. A., de Lima; L. R. A.; Porto A. L. F.; Bezerra, R. P.. Antitumor lectins from algae: A systematic review. *Algal Research* **2023,** *70*, 102962. https://doi.org/10.1016/j.algal.2022.102962
54. Wu, S.C.; Wang, F. J.; Pan, C.L. The comparison ofanti-oxidative properties of seaweed oligosaccharides fermented by two lactic acid bacteria. *J. Mar. Sci.Technol.* **2010**, *18*, 537-545. https://doi.org/10.51400/2709-6998.1908
55. Sreenath, K. C.; Dronamayu, V.; Sarada, L.; Gideen, T.P and Rengasamy R. Antibacterial activity of three south Indian seagrasses Cymodocea serrulata, Halophila ovalis and Zostera capensis. *World J. Microbiol. Biotech.* **2008**, *24*, 1989–1992. https://doi.org/10.1007/s11274-008-9695-5

56. Olguín, E.J. Dual purpose microalgae-bacteria-based systems that treat wastewater and produce biodiesel and chemical products within a biorefinery. *Biotechnol. Adv.* **2012**, *30*, 1031-1046. https://doi.org/10.1016/j.biotechadv.2012.05.001
57. Ravi, M.; De, S.L.; Azharuddin, S.; Paul, S.F.D. The beneficial effects of *spirulina* focusing on its immunomodulatory and antioxidant properties. *Nutrition and Dietary Supplements* **2002**, *2*, 73- 83. https://doi.org/10.2147/NDS.S9838
58. Pattama, Ratana-arporn; Anong, Chirapart. Nutritional Evaluation of Tropical Green Seaweeds Caulerpa lentillifera and Ulva reticulate. *Kasetsart Journal - Natural Science* **2006**, *40*, 73-85. https://li01.tci-thaijo.org/index.php/anres/article/view/244017.
59. Gressler, V; Yokoya, N.S.; Fujii, M.T.; Clepicolo, P.; Filho, J.M.; Torres, R.P.; Pinto, E. Lipid, fatty acid, protein, amino acid and ash contents in four Brazilian red algae species. *Food Chemistry* **2010**, *120*, 585–599. https://doi.org/10.1016/j.foodchem.2009.10.028
60. Ramadan, K.M.A.; El-Beltagi, H.S.; Shanab, S.M.M.; El-fayoumy, E.A.; Shalaby, E.A.; Bendary, E.S.A. Potential Antioxidant and Anticancer Activities of Secondary Metabolites of Nostoc linckia Cultivated under Zn and Cu Stress Conditions. *Processes* **2021**, *9*, 1972. https://doi.org/10.3390/pr9111972.
61. Menaa, F.; Wijesinghe, U.; Thiripuranathar, G.; Althobaiti, N.A.; Albalawi, A.E.; Khan, B.A.; Menaa, B. Marine Algae-Derived Bioactive Compounds: A New Wave of Nanodrugs? *Mar. Drugs* **2021**, *19*, 484. https://doi.org/10.3390/md19090484.
62. Ivanova, V.; Stancheva, M.; Merdzhanova, A. Fatty acids composition of macroalgae from Bulgarian Black Sea coast. *Annals of Chemistry*. **2012,** *23*, 35-40. https://doi.org/10.2478/v10310-012-0005-6
63. Aslam A.; Bahadar A.; Liaquat R.; Saleem M.; Waqas A.; Zwawi M. Algae as an attractive source for cosmetics to counter environmental stress. *Sci Total Environ.* **2021**, *772*, 144905. https://doi.org/10.1016/j.scitotenv.2020.144905.
64. De Luca, M.; Pappalardo, I.; Limongi, A.R.; Viviano, E.; Radice, R.P.; Todisco, S.; Martelli, G.; Infantino, V.; Vassallo, A. Lipids from Microalgae for Cosmetic Applications. *Cosmetics* **2021**, *8*, 52. https://doi.org/10.3390/cosmetics8020052.
65. Namvar, F.; Mohamed, S.; Fard, S. G. *et al*. Polyphenol-rich seaweed (Eucheuma cottonii) extract suppresses breast tumour via hormone modulation and apoptosis induction. *Food Chem.* **2012**, *130*, 376–382. https://doi.org/10.1016/j.foodchem.2011.07.054
66. Ramos-Romero, S.; Torrella, J.R.; Pagès, T.; Viscor, G.; Torres, J.L. Edible microalgae and their bioactive compounds in the prevention and treatment of metabolic alterations. *Nutrients* **2021**, *13*, 563. https://doi.org/10.3390/nu13020563.
67. Benelhadj, S.; Gharsallaoui, A.; Degraeve, P.; Attia, H; Ghorbel, D.; Effect of pH on the functional properties of *Arthrospira (Spirulina*) platensis protein isolate. *Food Chem.* **2016**, *194*, 1056-1063. https://doi.org/10.1016/j.foodchem.2015.08.133
68. Notowidjojo, L. Seaweed as novel food for prevention and therapy for life style related disease. *World Nutr J.* **2021**, 5, 1–5. https://doi.org/10.25220/WNJ.V05.i1.0001.
69. Liestianty, D.; Rodianawati, I.; Arfah, R.A.; Assa, A. Nutritional analysis of spirulina sp to promote as superfood candidate.*IOP Conf. Ser. Mater. Sci. Eng.* **2019**; *509*, 012031. https://doi.org/10.1088/1757-899X/509/1/012031
70. Wu, H. L.; Wang, G.H.; Xiang, W.Z.; Li, T.; He, H. Stability and Antioxidant Activity of Food-Grade Phycocyanin Isolated from *Spirulina* platensis. *International Journal of Food Properties***. 2016**, *19*, 2349–2362. https://doi.org/10.1080/10942912.2015.1038564
71. Kennedy, D.O. B vitamins and the brain: Mechanisms, dose and efficacy—A review. *Nutrients* **2016**, *8*, 68-78. https://doi.org/10.3390/nu8020068
72. Belay, A. *Spirulina* in Human Nutrition and Health, 1st edition, Gershwin, M. E.; Belay, A. Eds., CRC Press, Taylor and Francis Group: Boca Raton: London, UK, **2008**; pp. 1-33, https://doi.org/10.1201/9781420052572
73. Khan, Z.; Bhadouria, P.; Bisen, P. S. Nutritional and therapeutic potential of *spirulina*. *Curr Pharm Biotechnol.* **2005**, *6*, 373-379. https://doi.org/10.2174/138920105774370607
74. Azabji-Kenfack, M.; Edie Dikosso, S.; Loni, E. G.; Onana, E. A.; Sobngwi, E.; Gbaguidi, E. Potential of *Spirulina platensis* as a nutritional supplement in malnourished hiv-infected adults in sub-Saharan Africa: A randomised, single-blind study. *Nutr Metab Insights.* **2011**, *4*, 29–37. https://doi.org/10.4137/NMI.S5862.

75. Saleh, T.H.; Hashim, S.T.; Obaidi, R.A.; AL-Rubaii, B.A.A. A biological study of chitinase produced by clinical isolates of Pseudomonas aeruginosa and detection of ChiA responsible gene. *Int. J. Res. Pharm. Sci.* **2012**, *11*, 1-13. https://doi.org/10.26452/ijrps.v11i2.1989
76. Capelli, B.; Cysewski, G. Potential health benefits of spirulina microalgae. *Nutrafoods* **2010**, *9*, 19-26. https://doi.org/10.1007/BF03223332
77. Mocanu, G.; Botez, E.; Nistor, O.V.; Andronoiu, D.G.; Vlasceanu, G. Influence of *Spirulina platensis biomass* over some starter culture of lactic bacteria. *Journal of Agroalimentary Processes and Technologies* **2013**, *19*, 474–479, https://journal-of-agroalimentary.ro/admin/articole/14215L75_Vol_19(4)_2013_474-479.pdf.
78. Bhowmik, D.; Dubey, J.; Mehra, S. Probiotic efficiency of *Spirulina platensis*—stimulating growth of lactic acid bacteria. *World Journal of Dairy and Food Sciences* **2009,** *4*, 160–163, https://www.researchgate.net/publication/239585056_Probiotic_Efficiency_of_Spirulina_platensis_-_Stimulating_Growth_of_Lactic_Acid_Bacteria.
79. Shazly, A.B.; Khattab, M.S.A.; Fouad, M.T.*et al.* Probiotic Yoghurt made from milk of ewes fed a diet supplemented with *Spirulina platensis* or fish oil. *Ann Microbiol* **2022**, *72*, 29. https://doi.org/10.1186/s13213-022-01686-4
80. Hussein, A.; Ibrahim, G.; Kamil, M.; El-Shamarka, M.; Mostafa, S.; Mohamed, D. Spirulina-Enriched Pasta as Functional Food Rich in Protein and Antioxidant. *Biointerface Res. Appl. Chem.* **2021**, *11*, 14736–14750. https://doi.org/10.33263/BRIAC116.1473614750.
81. Martelli, F.; Cirlini, M.; Lazzi, C.; Neviani, E.; Bernini, V. Solid-State Fermentation of *Arthrospira platensis* to Implement New Food Products: Evaluation of Stabilization Treatments and *Bacterial Growth on the Volatile Fraction. Foods* **2021**, *10*, 67. https://doi.org/10.3390/foods10010067.
82. Donato, N.R.; Queiroz, A. J. D; Feitosa de Figueirêdo, R. M.; Feitosa, R. M.; Moreira, I.D.S.; Lima, J. Production of cookies enriched with Spirulina platensis biomass. *Journal of Agricultural Studies.* **2019**, *7*, 323-326. https://doi.org/10.5296/jas.v7i4.15483.
83. Winarni Agustini, T.; Farid Ma'ruf, W.; Widayat, W.; Suzery, M.; Hadiyanto, H.; Benjakul, S. Application of *Spirulina platensis* on Ice Cream and Soft Cheese with Respect to Their Nutritional and Sensory Perspectives. *Jurnal Teknologi.* **2016**, *78*, 4–2. https://doi.org/10.11113/jt.v78.8216
84. Setyaningsih, I.; Mahmudah, P.; Trilaksani, W.; Tarman, K.; Santoso, J. *Spirulina* biscuit formulation with coconut cream substitution and its shelf life estimation. *IOP Conference Series: Earth and Environmental Science* **2020**, *414*, 012022 012027. https://doi.org/10.1088/1755-1315/414/1/012022
85. Boukid, F.; Castellari, M. Food and Beverages Containing Algae and Derived Ingredients Launched in the Market from 2015 to 2019: A Front-of-Pack Labeling Perspective with a Special Focus on Spain. *Foods* **2021**, *10*, 173. https://doi.org/10.3390/foods10010173
86. Desai, K.; Sivakami, S. *Spirulina* the wonder food of the 21st century. *Asia Pacific Biotech News* **2004**, *8*, 1298-1302. https://doi.org/10.1142/S021903030400223X
87. Romeilah, R.M.; El-Beltagi, H.S.; Shalaby, E.A.; Younes, K.M.; El Moll, H.; Rajendrasozhan, S.; Mohamed, H.I. Antioxidant and cytotoxic activities of Artemisia monosperma L. and Tamarix aphylla essential oils. *Not. Bot. Horti Agrobot. Cluj-Napoca* **2021**, *9*, 12233. https://doi.org/10.15835/nbha49112233.
88. Colla, L. M.; Muccillo-Baisch, A. L.; Costa, J. Al. *Spirulina platensis* effects on the levels of total cholesterol, HDL and triacylglycerols in rabbits fed with a hypercholesterolemic diet. *Braz. arch. biol. technol.* **2008**, *51*, 405-411. https://doi.org/10.1590/S1516-89132008000200022
89. Baicus, C.; Baicus, A. *Spirulina* did not ameliorate idiopathic chronic fatigue in four N-of-1 randomized controlled trials. *Phytother. Res.* **2007**, *21*, 570–573. https://doi.org/10.1002/ptr.2114.
90. Shao, W.; Ebaid, R.; El-Sheekh, M.; Abomohra, A.; Eladel, H. Pharmaceutical applications and consequent environmental impacts of *Spirulina (Arthrospira*). *Grasas Aceites.* **2019**, 70, e292-e297. https://doi.org/10.3989/gya.0690181.
91. Baky, Ab. El. Over production of phycocyanin pigment in blue green alga Spirulina sp. and It's inhibitory effect on growth of ehrlich ascites carcinoma cells. *J. Med. Sci.* **2003**, *3*, 314-324. https://doi.org/10.3923/jms.2003.314.324
92. Estrada, J. E. P.; Bescos, P. B.; del Fresno, A.M.V. Antioxidant activity of different fractions of spirulina platensis protean extract. *Il Farmaco*. **2001**, *56*, 497-500. https://doi.org/10.1016/s0014-827x(01)01084-9

93. Chaiklahan, R.; Chirasuwan, N.; Siangdung, W.; Paithoonrangsarid, K.; Bunnag, B. Cultivation of *Spirulina platensis* using pig wastewater in a semi-continuous process. *J. Microbiol. Biotechnol.* **2010**, *20*, 609-614. https://doi.org/10.4014/jmb.0907.07026
94. Bhat, V.B.; Madyastha, K.M. C-phycocyanin: A potent peroxyl radical scavenger *in vivo* and in vitro. *Biochem. Biophys. Res. Commun.* **2000**, *275*, 20-25. https://doi.org/10.1006/bbrc.2000.3270
95. El-Boghdady, N. A.; Kamel, M. A.; El-Shamy, R. M. Omeprazole and *Spirulina Platensis* Ameliorate Steatohepatitis in Experimental Nonalcoholic Fatty Liver Disease. *Metabolic Syndrome and Related Disorders* **2020,** *18*, https://doi.org/10.1089/met.2019.0129.
96. Khan, M.; Shobha, J.C.; Mohan, I.K.; Naidu, M.U.R.; Sundaram, C. Protective effect of *spirulina* against doxorubicin-induced cardiotoxicity. *Phytother. Res.*, **2005**, *19*, 1030-1037. https://doi.org/10.1002/ptr.1783
97. Hassan, F.M., Hadi, R. A.; Kassim, T. I.; Al-Hassany, J.S. Systematic study of epiphytic algal after restoration of Al-Hawizah marshes, southern of Iraq. *International journal of aquatic science* **2012**, *3*, 37-57. http://www.journal-aquaticscience.com/article_93750.html
98. Kokou, F.; Makridis, P.; Kentouri, M.; Divanach, P. Antibacterial activity in microalgae cultures. *Aquacult. Res.* **2012**, *43*, 1520–1527. https://doi.org/10.1111/j.1365-2109.2011.02955.x
99. Ozdemir, G.; Karabay, N.U.; Dalay, M.C.; Pazarbasi, B. Antibacterial activity of volatile component and various extracts of *Spirulina platensis*. *Phytotherapy Research* **2004**, *18*, 754–757. https://doi.org/10.1002/ptr.1541
100. Kaushik, P.; Chauhan, A. In vitro antibacterial activity of laboratory grown culture of *Spirulina platensis*. *Indian Journal of Microbiology* **2008**, *48*, 348–352. https://doi.org/10.1007/s12088-008-0043-0
101. Uma Suganya, K.S.; Govindaraju, K.; Ganesh Kumar, V. Blue green alga mediated synthesis of gold nanoparticles and its antibacterial efficacy against Gram positive organisms. *Materials Science and Engineering* **2015**, *47*, 351–356. https://doi.org/10.1016/j.msec.2014.11.043
102. Santoyo, S.; Herrero, S.; Señorans, M.; Cifuentes, F.; Ibáñez, A. Functional characterization of pressurized liquid extracts of *Spirulina platensis*. *Eur. Food Res. Technol.* **2006**, *224*, 75–81. https://doi.org/10.1007/s00217-006-0291-3
103. Sarada, D.L.; Kumar, C.S.; Rengasamy, R. Purified C-phycocyanin from *Spirulina platensis* (Nordstedt) Geitler: A novel and potent agent against drug resistant bacteria. *World J. Microb. Biot.* **2011**, *27*, 779–783. https://doi.org/10.1007/s11274-010-0516-2
104. Arun, N.; Gupta, S.; Singh, D.P. Antimicrobial and antioxidant property of commonly found microalgae Spirulina platensis, Nostoc muscorum and Chlorella pyrenoidosa against some pathogenic bacteria and fungi. *Int. J. Pharm. Sci. Res*. **2012**, *3*, 4866–4875, https://ijpsr.com/bft-article/antimicrobial-and-antioxidant-property-of-commonly-found-microalgae-spirulina-platensis-nostoc-muscorum-and-chlorella-pyrenoidosa-against-some-pathogenic-bacteria-and-fungi/.
105. Teas, J.; Irhimeh, M. R. Dietary algae and HIV/AIDS:proof of concept clinical data. *Journal of Applied Phycology*. **2012**; *24*, 575–582. https://doi.org/10.1007/s10811-011-9766-0
106. Ngo-Matip, M. E.; Pieme, C.A.; Azabji-Kenfack, M. Impact of daily supplementation of Spirulina platensis on the immune system of na¨ıve HIV-1 patients in Cameroon: a 12- months single blind, randomized, multicenter trial. *Nutrition Journal* **2015**, *14*, 70-75. https://doi.org/10.1186/s12937-015-0058-4
107. Azabji-Kenfack, M.; Dikosso, S.E.; Loni, E. G. Potential of Spirulina platensis as a nutritional supplement in malnourished HIV-infected adults in Sub-Saharan Africa: a randomised, single-blind study. *Nutrition and Metabolic Insights* **2011**, *4*, 29–37. https://doi.org/10.4137/NMI.S5862
108. Simpore, J.; Zongo, F.; Kabore, F.; Dansou, D.; Bere, A.; Nikiema, J.B.; Pignatelli, S; Biondi, D. M.; Ruberto, G.; Musumeci, S. Nutrition rehabilitation of HIV-infected and HIV-negative undernourished children utilizing *spirulina*. *Ann Nutr Metab.* **2005**, *49*, 373-380. https://doi.org/10.1159/000088889
109. Singh, R.K.; Tiwari, S.P.; Rai, A. K.; Mohapatra, T. M. Cyanobacteria: an emerging source for drug discovery. *The Journal of Antibiotics* **2011**, *64*, 401–412. https://doi.org/10.1038/ja.2011.21
110. Hernández-Corona, A.; Nieves, I.; Meckes, M.; Chamorro, G.; Barron, B. L.; Antiviral activity of *Spirulina maxima* against herpes simplex virus type 2. *Antiviral Res.* **2002**, *56*, 279-85. https://doi.org/10.1016/s0166-3542(02)00132-8
111. Mader, J.; Gallo, A.; Schommartz, T.; Handke, W; Nagel, C.H..; Günther, P.; Brune, W.; Reich, Kr. Calcium spirulan derived from *Spirulina platensis* inhibits herpes simplex virus 1 attachment to human

keratinocytes and protects against herpes labialis. *Journal of Allergy and Clinical Immunology* **2016**, *137*, 197-203, https://doi.org/10.1016/j.jaci.2015.07.027

112. Shih, S.R.; Tsai, K. N.; Li, Y.S.; Chueh, C. C.; Chan, E. C. Inhibition of enterovirus 71 – induced apoptosis by allophycocyanin isolated from a blue – green alga *Spirulina platensis*. *J.Med. Virol.* **2003**, *70*, 119 – 25. https://doi.org/10.1002/jmv.10363
113. Li B.; Gao M.H.; Zhang X.C.; Chu X. M. Molecular immune mechanism of C-phycocyanin from *Spirulina platensis* induces apoptosis in HeLa cells in vitro. *Biotechnol Appl Biochem*. **2006** , *43*, 155-64. https://doi.org/10.1042/BA20050142. PMID: 16316316.
114. Mani, U.V.; Desai, S.; Iyer, U. Studies on the long-term effect of *Spirulina* supplementation on serum lipid profile and glycated proteins in NIDDM patients. *J. Nutraceuticals Funct. Med. Foods.* **2000**, *2*, 25-32. https://doi.org/10.1300/J133v02n03_03
115. Nagaoka, S.; Shimizu, K.; Kaneko, H.; Shibayama, F.; Morikawa, K.; Kanamaru, Y. A novel protein C-phycocyanin plays a crucial role in the hypocholesterolemic action of *Spirulina platensis* concentrate in rats. *J Nutr.* **2005**, *135*, 2425- 2430. https://doi.org/10.1093/jn/135.10.2425
116. Carmel, R. Nutritional anemias and the elderly. *Semin Hematol.* **2008**, *45*, 225–234. https://doi.org/10.1053/j.seminhematol.2008.07.009
117. Selmi, C.; Leung, P.S.; Fischer, L.; German, B.; Yang, C. Y.; Kenny, T. P. The effects of *spirulina* on anemia and immune function in senior citizens. *Cellular and Molecular Immunology* **2011**, *8*, 248–254. https://doi.org/10.1053/j.seminhematol.2008.07.009
118. AlFadhly, N.K.Z.; Alhelfi, N.; Altemimi, A.B.; Verma, D.K.; Cacciola, F.; Narayanankutty, A. Trends and Technological Advancements in the Possible Food Applications of *Spirulina* and Their Health Benefits: A Review. *Molecules* **2022**, *27*, 5584. https://doi.org/10.3390/molecules27175584
119. Abed E.; Ihab A.N.; Suliman E.; Mahmoud A.; Impact of *Spirulina* on nutritional status, haematological profile and anaemia status in malnourished children in the Gaza Strip: randomized clinical trial. *Matern Pediatr Nutr* **2016,** *2*, 110, https://www.longdom.org/open-access/impact-of-spirulina-on-nutritional-status-haematological-profile-and-anaemia-status-in-malnourished-children-in-the-gaza-14251.html.
120. Elrggal, M. E.; Alamer, S. I.; Alkahtani, S. A.; Alshrahili, M. A.; Alharbi, A.; Alghamdi, B.A.; Zaitoun, M.F. Dispensing Practicesfor Weight Management Products in Eastern Saudi Arabia: A Survey of Community Pharmacists. *Int. J. Environ. Res. Public Health*, **2021**, *18*, 13146. https://doi.org/10.3390/ijerph182413146.
121. Naveen, J.; Baskaran, R.; Baskaran, V. Profiling of bioactives and in vitro evaluation of antioxidant and anti-diabetic property of polyphenols of marine algae Padina tetrastromatica. *Algal Res.* **2021**, *55*, 102250. https://doi.org/10.1016/j.algal.2021.102250.
122. Abdel-Karim, O.H.; Abo-Shady, A.M.; Ismail, G.A.; Gheda, S.F. Potential effect of Turbinaria decurrens acetone extract on the biochemical and histological parameters of alloxan-induced diabetic rats. *Int. J. Environ. Health Res.* **2021**, *202*, 1–22. https://doi.org/10.1080/09603123.2021.1888895.
123. Gheda, S.F.; Khalil, M.A.; Gheida, Sh. F. In vitro and *in vivo* preliminary results on *Spirulina platensis* for treatment of impetigo: Topical cream application. *African Journal of Biotechnology* **2013,** *12*, 2498-2509, https://www.ajol.info/index.php/ajb/article/view/129721.
124. Mourelle, M.L.; Gómez, C. P.; Legido, J. L. The Potential Use of Marine Microalgae and Cyanobacteria in Cosmetics and Thalassotherapy. *Cosmetics* **2017**, *4*, 46-49. ; https://doi.org/10.3390/cosmetics4040046.
125. Delsin, S.; Mercurio, D.; Fossa, M.; Campos, P.; Clinical efficacy of dermocosmetic formulations containing Spirulina extract on young and mature skin: effects on the skin hydrolipidic barrier and structural properties. *Clin. Pharmacol. Biopharm.* **2015**, *4*, 1000144–1000149. https://doi.org/10.4172/2167-065X.1000144
126. Li, H.; Xu, J.; Liu, Y.; Ai, S.; Qin, F.; Li, Z.; Zhang, H.; Huang, Z. Antioxidant and moisture-retention activities of the polysacchari de from Nostoc commune. *Carbohydrate Polymers* **2011**, *83*, 1821-1827. https://doi.org/10.1016/J.CARBPOL.2010.10.046
127. Chakdar, H.; Jadvar, S.D.; Dhar, D.W.; Pabbi, S. Potential applications of blue green algae. *Journal of Scientific & Industrial Research* **2012**, *71*, 13-20.
128. Vigliante, I.; Mannino, G.; Maffei, M.E. OxiCyan®, a phytocomplex of Bilberry (*Vaccinium myrtillus*) and *Spirulina (Spirulina platensis*), exerts both direct antioxidant activity and modulation of ARE/Nrf2 pathway in HepG2 cells. *J. Funct. Foods* **2019**, *61*, 103508–103516. https://doi.org/10.1016/J.JFF.2019.103508

129.. Hamed, I. The Evolution and Versatility of Microalgal Biotechnology: A Review. Compr. Rev. Food Sci. Food Saf. **2016**, *15*, 1104-1123. https://doi.org/10.1111/1541-4337.12227

130. Ong, P.Y.; Leung, D.Y. Bacterial and viral infections in atopic dermatitis: a Comprehensive Review. *Clin Rev Allergy Immunol.* **2016**, *51*, 329-337. https://doi.org/10.1007/s12016-016-8548-5

131. Hamed I. The evolution and versatility of microalgal biotechnology: A Review. *Compr. Rev. Food Sci. Food Saf.* 2**016**, *15*, 1104–1123. https://doi.org/10.1111/1541-4337.12227

132. Souza, C., Campos, P. M. Development and photoprotective effect of a sunscreen containing the antioxidants spirulina and dimethylmethoxy chromanol on sun-induced skin damage. *Eur. J. Pharm. Sci.* **2017**, *104*, 52-64. https://doi.org/10.1016/j.ejps.2017.0v3.026

133. Nihal, B.; Gupta, N. V.; Gowda, D. V.; Manohar, M. Formulation and development of topical anti acne formulation of Spirulina Extract. *Int. J. Appl. Pharm.* **2018**, *10*, 229–233. https://doi.org/10.22159/ijap.2018v10i6.26334

134. Beauty Care-Ingredient Book. https://www.seppic.com/sites/seppic/files/2020/03/17/2020-seppic_indexbeauty-care.pdf.pdf/.

135. Phenbiox.: https://www.phenbiox.it/en/s/index.jsp.

136. Li, Z.Y.; Guo, S. Y.; Li, L. Study on the process, thermodynamical isotherm and mechanism of Cr (III) uptake by *Spirulina platensis*. *J Food Eng.* **2006**, *75*, 129-36. https://doi.org/10.1016/j.jfoodeng.2005.04.003

137. Palaniswamy, R.; Veluchamy, C. Biosorption of Heavy Metals by *Spirulina platensis* from Electroplating Industrial Effluent. *Environ Sci Ind J.* **2017**, *13*, 139, https://www.tsijournals.com/articles/biosorption-of-heavy-metals-by-spirulina-platensis-from-electroplating-industrial-effluent-13335.html.

138. Malakootian, M.; Khodashenas Limoni, Z.; Malakootian, M. The Efficiency of Lead Biosorption from Industrial Wastewater by Micro-alga *Spirulina platensis*. *Int. J. Environ. Res*. **2016**, *10*, 357-366. https://doi.org/10.22059/IJER.2016.58755.

139. Ferreiraa, l. S.; Rodrigues, M. S.; Monteiro de Carvalho, J.C.; Lodi,Al.; Finocchio, El.; Perego, P.; Converti, At. Adsorption of Ni $^{2+}$, Zn $^{2+}$ and Pb $^{2+}$ onto dry biomass of *Arthrospira (Spirulina*) platensis and *Chlorella vulgaris*. I. Single metal systems. *Chemical Engineering Journal* **2011**, *173*, 326–333. https://doi.org/10.1016/j.cej.2011.07.039

140. Schroeder Bjoern, O.; Bäckhed, F. Signals from the gut microbiota to distant organs in physiology and disease. *Nat. Med.* **2016,** *22*, 1079–1089. https://doi.org/10.1038/nm.4185

141. Okamoto, T.; Kawashima, H.; Osada, H.; Toda, E.; Homma, K.; Nagai, N.; Imai, Y.; Tsubota, K.; Ozawa, Y. Dietary spirulina supplementation protects visual function from photostress by suppressing retinal neurodegeneration in mice. *Transl. Vis. Sci. Technol*. **2019**, *8*, 20. https://doi.org/10.1167/tvst.8.6.20.

142. Amato, R.; Canovai, A.; Melecchi, A.; Pezzino, S.; Corsaro, R.; Dal Monte, M.; Rusciano, D.; Bagnoli, P.; Cammalleri, M. Dietary Supplementation of Antioxidant Compounds Prevents Light-Induced Retinal Damage in a Rat Model. *Biomedicines* **2021**, *9*, 1177. https://doi.org/10.3390/biomedicines9091177.

143. Cho, H.M.; Jo, Y.D.; Choung, S.Y. Protective Effects of *Spirulina maxima* against Blue Light-Induced Retinal Damages in A2E-Laden ARPE-19 Cells and Balb/c Mice. *Nutrients* **2022,** *14*, 401. https://doi.org/10.3390/nu14030401

144. Tzachor, A.; Rozen, O.; Khatib, S.; Jensen, S.; Avni, D. Photosynthetically Controlled *Spirulina*, but Not Solar *Spirulina*, Inhibits TNF-α Secretion: Potential Implications for COVID-19-Related Cytokine Storm Therapy. Mar. *Biotechnol.* **2021**, *23*, 149–155. https://doi.org/10.1007/s10126-021-10020-z.

145. Sonam, K.; Neetu, S. A comparative study on nutritional profile of *spirulina* cookies. *Int. J. Food Sci. Nutr*. **2017**, 2, 100–102, https://www.researchgate.net/publication/330848407_A_comparative_study_on_nutritional_profile_of_spirulina_cookies.

146. Batista, A.P.; Niccolai, A.; Bursic, I.; Sousa, I.; Raymundo, A.; Rodolfi, L.; Biondi, N.; Tredici, M.R. Microalgae as Functional Ingredients in Savory Food Products: Application to Wheat Crackers. *Foods* **2019**, *8*, 611. https://doi.org/10.3390/foods8120611.

147. Grahl, S.; Strack, M.; Weinrich, R.; Mörlein, D. Consumer-Oriented Product Development: The Conceptualization of Novel Food Products Based on Spirulina (*Arthrospira platensis*) and Resulting Consumer Expectations. *J. Food Qual.* **2018**, 1919482, https://doi.org/10.1155/2018/1919482.

148. Mostolizadeh, S.; Moradi, Y.; Mortazavi, M.S.; Motallebi, A.A.; Ghaeni, M. Effects of incorporation Spirulina platensis (Gomont, 1892) powder in wheat flour on chemical, microbial and sensory properties of pasta. *Iran. J. Fish. Sci*. **2020**, *19*, 410–420, http://jifro.ir/article-1-2692-en.html.