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ALGAE AS SUPPLEMENTS: REVIEW

BIRIȘ-DORHOI Elena-Suzana*, Ioana TALOȘ, Maria TOFANĂ
University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca,
Faculty of Food Science and Technology
*Corresponding author: elena.biris@usamvcluj.ro

Abstract: *Ulva lactuca*, *Undaria pinnatifida* and *Porphyra yezoensis* are the main cultivated and consumed algae. The interest in algae and their beneficial properties has seen an increase in recent years (both micro-and macroalgae). Edible algae are low- calorie and low-fat. One of the most studied group of bioactive components of microalgae are pigments due to their anticarcinogenic, antioxidative and antihypertensive properties. Algae present many biological activities including anti-inflammatory, anti-cancer (*Undaria pinnatifida*), antiviral, and anti-obesity effect. The bioactive compounds found in algae include amino acids, carotenoids, sulphated polysaccharides, essential fatty acids, polypeptides, lectins, terpenes, phytohormones, betaines, polyamines, and sterols, vitamins and minerals whose content and biological activity vary significantly within and between taxonomic groups. These characteristics coupled with many other make them a valuable supplement.

Keywords**:** algae, functional, supplement.

Introduction

Edible algae can be directly consumed or used as a material for preparing food or supplements. Regarding the species, there are many cultivated large-scale including *Porphyra yezoensis*, *Ulva lactuca*, *Undaria pinnatifida, Chlorella vulgaris* or *Spirulina platensis* (Vigani *et al*., 2015). Algae contain a large amount of bioactive components such as proteins, dietary fibre, vitamins, minerals, polyphenols, polysaccharides, sterols, flavonoids, alkaloids, fatty acids, and many other (Teng *et al*., 2013; Buono *et al*., 2014; Jmel *et al*., 2019).

Microalgae is administered as a nutritional supplement (*Chlorella*, *Spirulina*) because of its wide range of nutrients such as minerals, proteins, vitamins, dietary fibre, fatty acids, chlorophyll, and carotenoids. Therapeutic effects of *Chlorella* ingestion were investigated in experimental studies on animals. Administration of *Chlorella* had antioxidative, anticataract, antihyperglycemic activities in diabetic rats and anti-inflammatory, immunomodulatory, antihypertensive, neuroprotective, antimicrobial, and detoxifying effects. In studies performed on rabbits and obese mice, *Chlorella* integrated in food and feed showed lipid-reduction and anti-atherosclerotic actions (Shibata *et al*., 2003; Bedirli *et al*., 2009; Chen *et al*., 2014; Fallah *et al*., 2018).

The regular consumption of algae presents many benefits (Figure 1). Clinical trials were performed using many algae. One showed that regular consumption of *Undaria* seaweed can minimize with efficiency the risk of breast cancer in women. Other studies showed that oral administration of macroalgae extracts (*Fucus vesiculosus, Macrocystis pyrifera* and *Laminaria japonica*) with their high content of zinc, manganese and vitamin B6, decreased osteoarthritis symptoms (Ganesan *et al*., 2019). New studies suggest that macroalgae extracts can be used in the treatment of Alzheimer's Disease (Choi *et al*., 2018; Olasehinde *et al*., 2019).

Nostoc species was often consumed by the Chinese population as food and later *Chlorella* and *Spirulina* species were added in the diet as functional healthy foods and supplements in Taiwan, Japan and Mexico (Sathasivam *et al*., 2017).

Figure 1. Important benefits of algae

Algae species

From the many species of algae used in the food industry we chose to focus on the most common. From microalgae family, the most common used in food industry as food or supplement are *Chlorella vulgaris* and *Spirulina platensis*, and from macroalgae, *Undaria pinnatifida*, *Ulva lactuca* and *Porphyra yezoensis*.

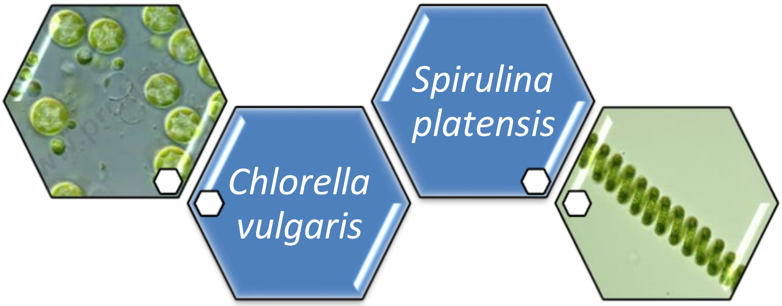

Figure 2. *Spirulina platensis* (Borowitzka, 2018)
and *Chlorella vulgaris* (https://eol.org)

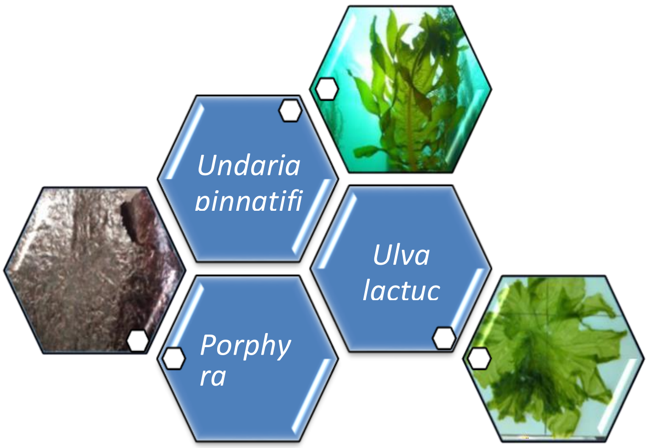

Figure 3. *Undaria pinnatifida* (https://www.waikaitu.com),
Ulva lactuca and *Porphyra yezoensis* (original)

Chlorella vulgaris

Chlorella vulgaris is a unicellular green alga, widely dispersed in freshwater, marine water, soil, or are even symbiotic with lichens and protozoa and is able to reproduce within several hours, requiring only sunlight, carbon dioxide, water, and a small amount of nutrients (Liu and Chen, 2016).

Chlorella vulgaris cells are spherical or ellipsoidal and the cell size may range from 2 to 15 μm in diameter (Figure 2). *Chlorella* species are known to contain high level of protein, lipid, vitamins, antioxidants such as lutein, alpha and beta-carotene, ascorbic acid, tocopherol and minerals (Guzman *et al*., 2001; Yamagishi *et al*., 2005; Jeong *et al*., 2009; Gallo, 2018). *Chlorella* species are also known for containing a high amount of carbohydrates (40-50%), which are a group of reducing sugars and polysaccharides (Safi *et al*., 2014; Cheng *et al*., 2017; Yuan *et al*., 2020).

The species has the ability to remove free radicals and has positive effects on regulating and maintaining physiological function of body in stress-induced diseases (Yun *et al*., 2011). *Chlorella* can improve lipid profile and decrease lipid peroxidation (Shibata *et al*., 2007; Haidari *et al*., 2018).

Chlorella species are marketed as 'healthy foods', 'super foods' and 'green healthy food' by Food and Agriculture Organization of the United Nations (FAO) (Nicoletti, 2016). The species was integrated in many studies and is able to prevent, cure or help manage diseases such as Alzheimer's disease, cancer and many others (Caporgno *et al*., 2018; Koyande, 2019). Therapeutic effects of *Chlorella* ingestion were investigated in experimental studies on animals.

Lutein, which is the most abundant carotenoid in *Chlorella*, coupled with zeaxanthin has been shown to have positive effects on eye health and function. Regarding cardiovascular diseases beta- carotene is known to be inversely related to the risk (Johnson, 2002). Alpha and β-carotene have the added advantage of being able to convert to vitamin A, which is involved in developing and preventing chronic diseases (Rao and Rao, 2007; Ryu, 2014). Lycopene from *Chlorella marina* showed anti-inflammatory activity against arthritis in rat model studies (Mishra *et al*., 2015).

Chlorella vulgaris increased the survival rates of *Lactobacillus brevis* strains (Scieszka and Klewicka, 2020).

Spirulina platensis

Spirulina is the common name of filamentous and multicellular microalgae belonging to two genera *Spirulina* and *Arthrospira* (Figure 2).

Spirulina platensis consists of 55-70% protein (which exceeds the content of eggs, meat grains or even soybeans) and 5-6% lipid (w/w dried cell), separated into a saponifiable fraction (83%) and a non-saponifiable fraction (17%), and also contains essential pigments (chlorophyll a, xanthophyll, betacarotene, myxoxanthophyll, zeaxanthin, canthaxanthin, beta-cryptoxanthin, oscillaxanthin, phycobiliproteins, and allophycocyanin), paraffin, sterols and terpene alcohol (Matos, 2017). Polyunsaturated fatty acids (PUFAs) constitute 1.5-2% of the total lipid content of these algae, ɣ-linolenic acid being 36% of the total PUFAs. *Spirulina* spp. is also a great spurse of vitamins (B1, B2, B3, B6, B9, B12, C, D and E), minerals (K, Ca, Cr, Cu, Fe, Mg, Mn, P, Se, Na and Zn), and enzymes (e.g. lipase) (Hosseini, 2013).

Spirulina is presented to be the richest whole-food source of vitamin B12 and provitamin A (about 20g of this microalgae fulfils body requirements of vitamins B1, B2 and B3). *Spirulina platensis* contains notable levels of many micronutrients including iron 0.58-1.8, calcium 1.3-14, phosphorus 6.7-9.0 and potassium 6.4-15.4 g/kg) (Hosseini, 2013).

Therefore, the rich biomass as well as its primary or secondary metabolites produced by it can be used as feed and food additives. This species was used in many industries, as supplements, in science, and in/as medicine as fertilizer, colouring agent, feed, supplements, pollution control and cosmetics (Chen *et al*., 2009; Prasanna *et al*., 2010). *Spirulina platensis* is the most used and studied microalgae from the genera.

This species of microalgae presents many biological activities. It was found to have anticancer, antiviral and antibacterial effect and it is found in the market as food supplement (Hosseini, 2013). The sulfated polysaccharide isolated from the microalgae Spirulina *platensis* (calcium Spirulan) exhibits antiviral activity because it inhibits in vitro replication of various viruses (Raposo *et al*., 2013; Vaz *et al*., 2016).

Spirulina contains natural mixed carotene, xanthophyll phytopigments and phycocyanin that seem to be related to its antioxidant activity as indicated by the *in vitro* and *in vivo* studies (Ravi *et al*., 2010). *Spirulina* is often used for human consumption in form of powder, tablets, capsules and extracts, but the functional features of *S. platensis* led to be used in processing usual foods (Rahman *et al*., 2006; Scotter, 2011).

When in the food *Spirulina* has been incorporated, antioxidant effects, better food stability, modified rheological and anti-stalling properties were observed (Hosseini, 2013).

Spirulina based nutraceuticals can be integrated into the current research and clinical trials for immunity stimulation, disease prevention and treatment of disorders related to severe coronavirus infections such as tissue repair in ACE2 dominated organs and anti-inflammatory treatment (Ratha *et al.*, 2020).

Undaria pinnatifida

Undaria pinnatifida (Figure 3) is a macroalage commonly consumed. The species contains a percentage of 9.14% of carbohydrates including monosaccharides, polysaccharides (sacran, mannan and xylan), dietary fiber, lipid (a percentage of 0.64%) and fatty acids (unsaturated fatty acid and saturated fatty acid). The macroalgae is also rich in protein (3.03%), vitamins, amino acids and its derivatives (methacrylic acid) and tauric acid, minerals, polyphenols, flavonoids, alkaloids and sterols (Chiu *et al*., 2012; Gurpilhares *et al*., 2019; Jun *et al*., 2019).

In recent years, the research has been focused on searching antioxidant agents for development of a therapeutic agent or functional food. It is known that oxidative stress promotes inflammation, tumour, obesity, diabetes, cardiovascular diseases and other chronic diseases. Different studies on rats regarding the lipid peroxidation of the liver were performed and it was proven to be decreased when polysaccharides were added in their feed compared with the ones with high- fat diet only.

U. pinnatifida was linked to anti-inflammatory effect (Wang *et al.*, 2019). *U. pinnatifida* has a proven antioxidant activity linked to the phenolic compound rich extract (30.85 mg of gallic acid equivalents/g of extract). The extract is also rich in protocatechuic acid and syringic acid. In their research Kang *et al.* (2008) noted that fucoidan isolated from *U. pinnatifida* has strong protective effects against carbon tetrachloride (CCl4)-induced oxidative stress in an in vivo rat model (Hata *et al*., 2001). Fucoidan from brown seaweed species, *Undaria pinnatifida*, has numerous bioactive properties such as antioxidant and anticancer activities (Koh *et al.*, 2019)

In their study Yang *et al*. (2008) presented that fucoidan isolated from *U. pinnatifida* presents anti-cancer activity in human lung cancer cell line (A549) by reducing cell growth by 37.6% and their results indicated that 40% of cell proliferation, 40% of cell migration, and 61% of tube formation were inhibited when cells were treated with a concentration of 400 μg/mL fucoidan (Boo *et al*., 2011; Billakanti *et al*., 2013; Boo *et al*., 2013).

Algae can also have effects against obesity. Obesity is a medical condition in which a human’s body weight is above their normal body mass index as a result of accumulation of excess fat. This condition is related to many negative effects on health such as liver steatosis, cardiovascular disease, osteoarthritis, diabetes, and even some types of cancer, that has become a vast health issue in the recent years (Chandrasekaran *et al*., 2012; Djalalinia *et al*., 2015). Many reports support the theory that *U. pinnatifida* also possesses anti-obesity activity. It was proven that fucoxanthin and fucoxanthinol from *U. pinnatifida* are able to suppress adipocyte differentiation and intercellular lipid accumulation through down-regulation of proliferator-activated receptor gamma with fucoxanthinol having stronger effects than fucoxanthin (Jeon *et al*., 2010).

Cardiovascular diseases cause many deaths each day. Species like *U. pinnatifida* have a good potential to fight them through the reduction of hypertension and prevention of blood-clotting (Cai and Harrison, 2000; Shannon and Abu-Ghannam, 2019). In many studies the potential of reducing the blood pressure of *U. pinnatifida* was proved. It was stated that a daily dose of 5 g dried *U. pinnatifida* powder lowered the blood pressure and hypercholesterolemia levels of hypertensive patients in rat models (Hata *et al*., 2001; Taboada *et al*., 2013; Song *et al*., 2019; Hui *et al*., 2019).

Ulva lactuca

Ulva lactuca, commonly known as sea lettuce, is a marine green macroalgae (Figure 3). The colour of the species has variations from green to dark green (Pereira *et al*., 2012; Tang *et al*., 2016). The most important components with biological activity of *U. lactuca* include dietary fibre (16.5% of water-soluble and 13.3% insoluble dietary fibres), amino acid, and tocopherol compounds. In their study El Sayed *et al*. (2011) studied the heteropolysaccharides isolated from *U. lactuca* and it was found that they can stimulate macrophage - and T-cells in mice.

Oligosaccharides from green algae *Ulva lactuca* were used for investigation of anti-ageing effects mechanism in mice and they were found to enhance the glutathione, superoxide dismutase, catalase, and telomerase levels and total antioxidant capacity. Takin that into account it can be stated that oligosaccharides from *U. lactuca* reduce oxidative damage, protect brain neurons and reduce inflammatory factor levels. Further studies show that *U. lactuca* oligosaccharides are highly efficient at preventing apoptosis (Xiao-Yan *et al*., 2019).

Significant anti-inflammatory activity of methanolic extract of *U. lactuca* (Figure 1) (500 mg/kg b.wt) can be linked to inhibition of the mediators of inflammation (histamine, serotonin and prostaglandin) (Athukorala *et al*., 2007). *U. lactuca* extract treatment significantly decreased the elevated serum pro-inflammatory cytokines. It was proved that high lipid peroxidation was an indicator of increased oxidative stress and reduced antioxidant capacity. Superoxide radicals are the first product of molecular oxygen reduction (Osama *et al.*, 2017; Sanna *et al.*, 2019).

Regarding antioxidant activity *Ulva lactuca* was proves to have beneficial effects, including on liver and kidney after they were subjected to toxicity from an insecticide (Kammoun *et al.*, 2019). The ulvan extracts displayed excellent scavenging activity towards DPPH radical (Hela *et al.*, 2017).

The species can be used as homeopathic medicine (Renoux, 2020).

Porphyra yezoensis

Porphyra yezoensis is a species of macroalgae often used as medicine (Zhao *et al.*, 2011). The species was found to present anticancer activity, but more research is needed (Zhang *et al.*, 2011; Cao *et al.*, 2016).

The *in vitro* antioxidant activities were proved by different studies. Nori, a dried sheet product of *Porphyra yezoensis* (Figure 3), is known to contain an exceptionally high (12.5-51.5% w/w) protein content among macroalgae. From that result the species can be expected to produce a high quantity of free amino acids after degradation (Uchida *et al*., 2017). The species also shows antihypertensive activity (Qu *et al*., 2010).

Bioactive components and bioactivities of algae

One of the most studied components from the algae with therapeutic benefits is sulfated polysaccharides. They have also been tested in engineering of blood vessels, heart valves, cartilage and intervertebral disks, bones, skeletal muscle, skin, liver, and nervous tissue (Korzeniowska, 2018).

Chlorophyll pigments are one group of bioactive compounds present in edible algae and have been linked to important biological properties, such as antioxidant, antimutagenic and anti-inflammatory effects. The pigments are bioavailable and distributed in the serum.

Aldehydes from the species *Ulva pertusa* were 54% of the total volatiles belonging to similar aliphatic compounds (Madhusudan *et al*., 2011).

Alkaloids are also quite common and important compounds found in algae. They have rarely been isolated from macroalgae; they are commonly extracted from plants. The main difference between the alkaloids present in plants and algae is that indoles and halogenated alkaloids are found specifically in algae. Marine algae many (44 alkaloids), consisting of 1 phenylethylamine, 41 indoles, and 1 naphthyridine derivates. In red algae alkaloids are more abundant whereas in brown algae are rarely. There is a case where alkaloids are produced by host organisms on algae (communesin which was isolated from the mycelium of a strain of *Penicillium* sp. on the *Enteromorpha intestinalis* and citrinadin A was isolated from *Penicillium citrinum* separated from a marine red algae (Guven *et al*., 2013).

Gracilaria canaliculata has a protein content of 8.51% on an average and hence it is found to be the most suitable as an alternative additive for diet containing high protein content and is consumed in the form of powder added to food items and ready to use (Madhu *et al*., 2011).

The cosmetics industry most often uses *Ulva lactuca* and *Spirulina platensi*s which contains vitamins A, B, C, and E, magnesium, iron, and aosaine, a protein containing the same amino acids as the human elastin (glycine, proline, lysine) (Łęska, 2018).

Polyunsaturated fatty acids (PUFA) are vital components in human nutrition and are known to have several beneficial effects for human health. Both *n*-3 and *n*-6 fatty acids included in a diet are known to help modulate inflammatory processes and other cell functions. Some Phaeophyta and Rhodophyta species exhibit higher concentrations of PUFA whereas phylum Chlorophyta presents the lowest PUFA/SFA ratios (0.27–0.68), being considered that it has a lower potential compared to the other two phyla (Pereira *et al*., 2012; Vinayak *et al*., 2019). Several studies suggest that *n*-3 fatty acids, mainly EPA and DHA, may have a significant potential in the treatment of autoimmune and inflammatory diseases. Red macroalgae present the highest percentage of *n*-3 fatty acids (16%–27% of total FAME), followed by brown macroalgae (0%–15%). From Chlorophyta, *Ulva* sp. that has 18% of *n*-3 FAME, all other species present lower values of *n*-3 fatty acids (1%–9%) (Pereira *et al*., 2012). Macroalgae can also be used for pharmaceutical purposes. Many of the PUFA detected in macroalgae are considered powerful molecules against several diseases.

Some marine algae are also known for their anti-cancer activity. Tumour is an abnormal tissue mass existing as fluid-filled or solid form and are classified into three types (benign, pre-malignant and malignant- known as cancer, which grows rapidly and metastasizes) based on their characteristics. In recent years, cancer has been the leading cause for death around the world (Samarakoon *et al*., 2014) with the World Health Organization reports that state that 9.6 million people died of cancer in 2018 (https://www.who.int/news-room/fact-sheets/detail/cancer; Adrien *et al*., 2019). The molecular mechanisms of algal anticancer activity include dysregulation of the mitochondrial dynamics, caspases activation, amplification of death signals through death receptors and others (Ruchita *et al*., 2020). From the bioactive compounds of algae that have anti-cancer effect laminaran and fucoidana are the most known (Sanjeewa *et al*., 2017).

Marine algae also possess antimicrobial activity (Sung *et al*., 2012). *Ulva lactuca* L., in a concentration of 1%, extract in methanol 70%, presented a good antimicrobial activity against *Enterococcus faecalis*, *Staphylococcus aureus* and *Escherichia coli* with the best activity against the *Enterococcus faecalis*. In lower concentrations the effect was diminished or non-existent (Biriș-Dorhoi, 2018). There are reports that state that *U. lactuca* methanolic extracts inhibit a range of Staphylococci. The same report state that lunar phase of macrolagae harvest significantly impacts antimicrobial activity, therefore, suggesting that antimicrobial properties can be maximized by manipulating time of algal harvest (Deveau *et al*., 2016).

Regarding antiviral effect *Spirulina platensis* and *Chlorella vulgaris* were both tested. *Spirulina platensis* was found to have antiviral effect on herpes viruses and it was linked to the content of polysaccharides (Rechter *et al*., 2006). Other microalgae such as *Dunaliella salina* and *Haematococcus pluvialis* were also found to present antiviral activity (Santoyo *et al*., 2012). The results show potential for antiviral effect, but more research is needed (Basheer *et al*., 2020).

Conclusions

Algae are a powerful source of mineral elements that can account up to 36% for its dry mass (sodium, calcium, magnesium, potassium and chloride as macronutrients and for micronutrients iodine, iron, zinc, selenium). Seaweed is alkaline and has digestible sugars. Chlorophyll content is only slightly reduced by the cooking methods (exception green macroalgae). Microalgae as *Chlorella* have been known for years for their benefits for human health. *Chlorella* and *Spirulina* can be found as supplements that were proven to have positive effects on human health, including boosting the immune system.

Algae bioactivities include antioxidant, anti-obesity, antiviral, anticancer and anti-inflammatory potential which make them suitable their use in or as supplement.

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