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Microalgae of the Chlorophyceae Class: Potential Nutraceuticals Reducing Oxidative Stress Intensity and Cellular Damage

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1. Introduction

Nutraceutical is a term combining the words nutrition and pharmaceutical. It is a food or food product that provides health and medical benefits, including the prevention and treatment of disease. A nutraceutical has beneficial effects because it possesses many compounds with antioxidant and intracellular signalling-pathway modulator effects. In recent years, it has been demonstrated that microalgae of the Chlorophyceae class could be excellent nutraceuticals because they contain polyphenols, chlorophyll, β-carotene, ascorbic acid, lycopene, α-tocopherol, xanthophylls, and PUFAs. For this reason, some research groups, including ours, have studied the nutraceutical properties of the genera *Dunalliela*, *Haematococcus*, and *Chlorella*. However, our research group has put special emphasis on the genera *Chlorella* and *Chlamydomonas*. For these genera, we present new results that reveal antioxidant effects in different models of oxidative stress and cell damage

2. Nutraceuticals

For a long time, natural products obtained from plants have been used as prominent sources of prophylactic agents for the prevention and treatment of disease in humans, animals, and in plants. Hippocrates (460-370 BC) started “let food be your medicine and medicine be your food”. Now, the relationship between food and drugs is getting closer.

As we enter the third millennium, with increased life expectancy and greater media coverage of the health care issue, consumers are understandably more interested in the potential benefits of nutritional support for disease control or prevention. A recent survey in Europe concluded that diet is rated more highly by consumers than exercise or the hereditary factor for achieving good health (Hardy, 2000). For that reason, many entrepreneurs seek to introduce different products into the health and nutritional market. Marketing strategies have exploited the words "functional food" and "nutraceuticals" in their advertisements. Nutraceuticals and functional foods are the fastest growing segment of today´s food industry, although nutraceuticals should be treated as pharmaceutical

products as we will detail. Nutraceuticals and functional foods are a market estimated at between $6 billion US and $60 billion US and it is growing at 5% per annum. Unfortunately, entrepreneurs in an effort to make money attract, as irresponsible market entrants, products that do not comply with biosafety tests. This is because there are few laws that regulate the production and sale of such products. Because the products are not submitted for standardized toxicology testing, sometimes they may be toxic for human consumption. There are no specific regulation in any country to control nutraceuticals, and they need to be established and should be considered under the same laws that regulate pharmaceuticals and food (Bernal et al., 2011). For our purposes, we will first define "nutraceuticals" and "functional foods" and how the microalgae could be excellent nutraceuticals.

The term nutraceutical was first mentioned in 1989 to describe the union between nutrition and pharmaceuticals, both key contributors to human wellness. Stephen DeFelice MD is the founder and chairman of the Foundation for Innovation in Medicine (FIM) and he defined a nutraceutical as a food (or part of the food) that provides medicinal health benefits, including the prevention or treatment of a disease. It was proposed that a nutraceutical is not a drug, which is a pharmacologically active substance that potentiates, antagonizes, or otherwise modifies any physiological function. A nutraceutical may be a single natural nutrient in powder, tablet, capsule, or liquid form. It is not necessarily a complete food but equally not a drug (Hardy, 2000). Also, it was proposed that a nutraceutical is a product that delivers a concentrated form of a presumed bioactive agent from a food, presented in a nonfood matrix, and it is used with the purpose of enhancing health in a dosage that exceeds those that could be obtained from normal food (Zeisel, 1999).

Functional food and nutraceutical are terms used incorrectly and indiscriminately for nutrients or nutrient-enriched food that can prevent or treat disease. Functional food is a product that resembles traditional food but it possesses demonstrated physiological benefits (Shahidi, 2009). For example a functional food could be a lutein-rich food as chicken, spinach, tomatoes, or oranges, or the omega-3 fatty acids found in fish oil. All functional foods are processed and consumed as food. A nutraceutical is not a nutritional supplement because the latter are nutrients that are added to the diet to correct or prevent deficiencies of vitamins, minerals, and proteins, and often used in the recovery of a patient suffering an illness or has undergone surgery, and also taken to improve overall health (Mandel et al., 2005). The beneficial effects of nutraceuticals and functional foods have been attributed to their components, such as polyphenols, polyunsatured fatty acids (PUFAs), terpenes, chlorophyll, and accessory pigments of the photosynthetic apparatus in cyanobacteria such as *Spirullina*. In general these compounds are antioxidants that reduce intensity of oxidative stress or modulate intracellular communication

3. Nutraceutical effects of polyphenols, particularly flavonoids

The polyphenols are compounds characterized by a benzene ring bearing one or more hydroxyl groups attached to the ring. They are ubiquitous in the plants, vegetables, fruit, vines, tea, coffee and microalgae. The polyphenols in food originate from one of the main classes of secondary metabolites in plants. They are involved in the growth and reproduction and are produced as a response to defend injured plants against pathogens, and to participate in the defense mechanism against ultraviolet radiation (Biesalski, 2007). Polyphenols have different nutraceutical properties, such as an antioxidant, antiinflammatory (Biesalski, 2007), anticancer (Oz & Ebersole, 2010), antibacterial (Du et al.,

2011), antiatherogenic, and antiangiogenic (Rimbach et al., 2009). There are now polyphenols with therapeutic properties for which the mechanism of action at the molecular level has been discovered and they are used in clinical trials, e.g. flavonoids.

Flavonoids comprise the most common group of polyphenols and provide much of the flavor and color to fruit and vegetables. More than 6000 different flavonoids have been described and it is estimated that humans consume about 1 g/day.

The structure of flavonoids is C6-C3-C6 and they consist of two aromatic rings linked through three carbons usually forming an oxygenated heterocycle nucleus, named the flavan nucleus, and shown in figure 1. In general, the flavonoids are classified into six groups (Grassi et al., 2009).

1. **Flavones**: These kinds of flavonoids are used by angiosperms to color their flowers. Natural flavones include apigenin (4',5,7-trihydroxyflavone), (3',4',5,7-tetrahydroxyflavone), (4',5,6,7,8-pentamethoxyflavone), chrysin (5,7-dihydroxyflavone), baicalein (5,6,7-trihydroxyflavone), scutellarein (5,6,7,4'-tetrahydroxyflavone), wogonin (5,7-Dihydroxy-8-methoxyflavone). There are synthetic flavones such as diosmin and flavoxate.
2. **Flavonols**: These compounds are used by organisms to protect them from UV radiation. Their diversity stems from the different positions of the hydroxyl groups on the benzene rings (show figure 1). There are flavonols as kaempferol (3,4',5,7-tetrahydroxy-2-phenylchromen-4-one), quercetin (3,3',4',5,7-pentahydroxy-2-phenylchromen-4-one), myricetin (3,3',4',5',5,7-hexahydroxy-2-phenylchromen-4-one), galangin (3,5,7-trihydroxy-2-phenylchromen-4-one), and morin (2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one). **Flavanones**: These flavonoids are the direct precursors of the vast majority of flavonoids. Some examples of flavanones are: naringenin (4',5,7-trihydroxyflavanone) and butin (7,3',4'-trihydroxyflavanone).
3. **Catechin or flavanols**: These flavonoids have two chiral centers on the molecule on carbons 2 and 3, yielding four diastereoisomers. Two of the isomers are in the *trans* configuration and are called catechins and the other two are in the *cis* configuration and are called epicatechins. These flavonoids are present in food as a complexs or oligomerics and polymerics as procyanidins or proantocyanidins. The catechins are found in different fruits, i.e. apples, apricots, blackberries, and grapes. Catechins are also in red wine, but black tea and cocoa are the richest sources. The flavanols in finished food products depend on the cultivar type, geographical origin, agriculture practice, postharvesting handling, and food processing (Scalbert et al., 2005).
4. **Antocyanidins**: Antocyanidins are a large group of natural colorants. The color of most fruits, flowers, and berries are made from a combination of anthocyanins and anthocyanidins. Anthocyanins always contain a carbohydrate molecule, whereas anthocyanidins do not. Examples of antocyanidins are cyanidin (3,3',4',5,7-pentahydroxyflavylium chloride), pelargonidin (3,5,7-trihydroxy-2-(4-hydroxyphenyl) benzopyrylium chloride), and malvidin (3,5,7,4'-tetrahydroxy-3',5'-dimethoxyflavylium)
5. **Isoflavones**: This group is a class of organic compounds that sometimes act as phytoestrogens in mammals and are called antioxidants because of their ability to trap a singlet oxygen. Genistein (4',5,7-trihydroxyisoflavone) and daidzein (4',7-dihydroxyisoflavone) are two examples of isoflavones.

Some authors have proposed that aurones are another flavonoid group, however we consider that aurones are derived from chalcones (Fowler & Koffas, 2009).

The flavonoid synthesis is shown in figure 1. It begins when a cell transforms phenylananine or tyrosine into phenylpropanoic acid or cinnamic acid by phenylalanine-tyrosine ammonia lyase (PAL; EC 4.3.1.25/TAL; EC 4.3.1.25). Then cytochrome-P450 cinnamate 4-hydroxylase (C4H; EC 1.14.13.11) adds a 4´-hydroxyl group to form p-coumaric acid. The CoA esters are subsequently synthetized from cinnamic acid, caffeic acid, or *p*-coumaric acid by 4-coumaryl:CoA ligase (4CL; EC 6.2.1.12). The type III polyketide chalcone synthase (CHS; EC 2.3.1.74) catalyzes the sequential condensation of three malonyl-CoA moieties with one CoA-ester molecule to form chalcones. The flavanones are formed when chalcones are isomerized into (2S)-flavanones by chalcone isomerase (CHI; EC 5.5.1.6). Many enzymes can modify the flavanones. For example the flavanones could be reduced to form isoflavones by isoflavone synthase (IFS; EC 1.14.13.86). After that, isoflavones are modified by different enzymatic systems to produce hydroxylation, reduction, alkylation, oxidation, and glucosylation alone or in combination in the three-ring phenylpropanoid core. Enzymes such as O-methyltransferse (IOMT, EC 2.1.1.150), isoflavone 2´-reductase (I2´R; EC 1.3.1.45), andisoflavone reductase (IFR; EC 1.3.1.45) can yield over 8000 different chemical structures from isoflavone (Winkel-Shirley, 2001; Fowler & Koffas, 2009). Another branch of the biosynthetic pathway of flavonoids is the flavones that are synthesized from flavanones through the action of the flavone synthase type I and II (FSI; EC 1.14.11.22). Flavonones are hydroxylated and then with flavonol synthase (FLS; EC 1.14.11.23) form flavonols. These compounds are the precursors of anthocyanins.

The beneficial effects can be divided into

1. **Antioxidants**: Flavonoids suppress the formation of reactive oxygen species (ROS) either by inhibiting enzymes or chelating trace elements involved in free radical production. Thus flavonoids help maintain an ROS steady state in the case of physical and chemical injury of the cell (Corradini et al., 2011). Not all flavonoids are ROS scavengers because some flavonoids, as nucleophiles, trap electrons from the ROS and become a free radical themselves, which then propagate a chain reaction causing a deleterious effect in the cell (Grassi et al., 2009).
2. **Modulators of intracellular communication**: The flavonoids and their metabolites act in the phosphoinositide 3-kinase (PI3K), Akt-protein kinase B (Akt-PKB), tyrosine kinase, and protein kinase C (PKC) signalling cascade. The inhibition or activation of these cascades modifies cellular function by altering the phosphorylation state of target molecules that modulate the expression of genes. This can explain the anticancer and neuroprotector flavonoid activities (Williams et al., 2004).
3. **Enzyme activity modulator**: Flavonoids offer cardiovascular protection because of their indirect inhibition of the angiotensin-converting enzyme (ACE; EC 3.4.15.1) (Actis-Goretta et al., 2006). Other enzymes inhibited by flavonoids are aromatase (EC 1.14.14.1) and α–amylase (EC 3.2.2.1) (Hargrove et al., 2011). The inhibition of enzymes that have a Fe-S cluster has been demonstrated (Mena et al., 2011).

In general, flavonoids are molecules responsible of some of the beneficial effect of nutraceuticals and functional foods. The different effects of flavonoids are described in table 1.

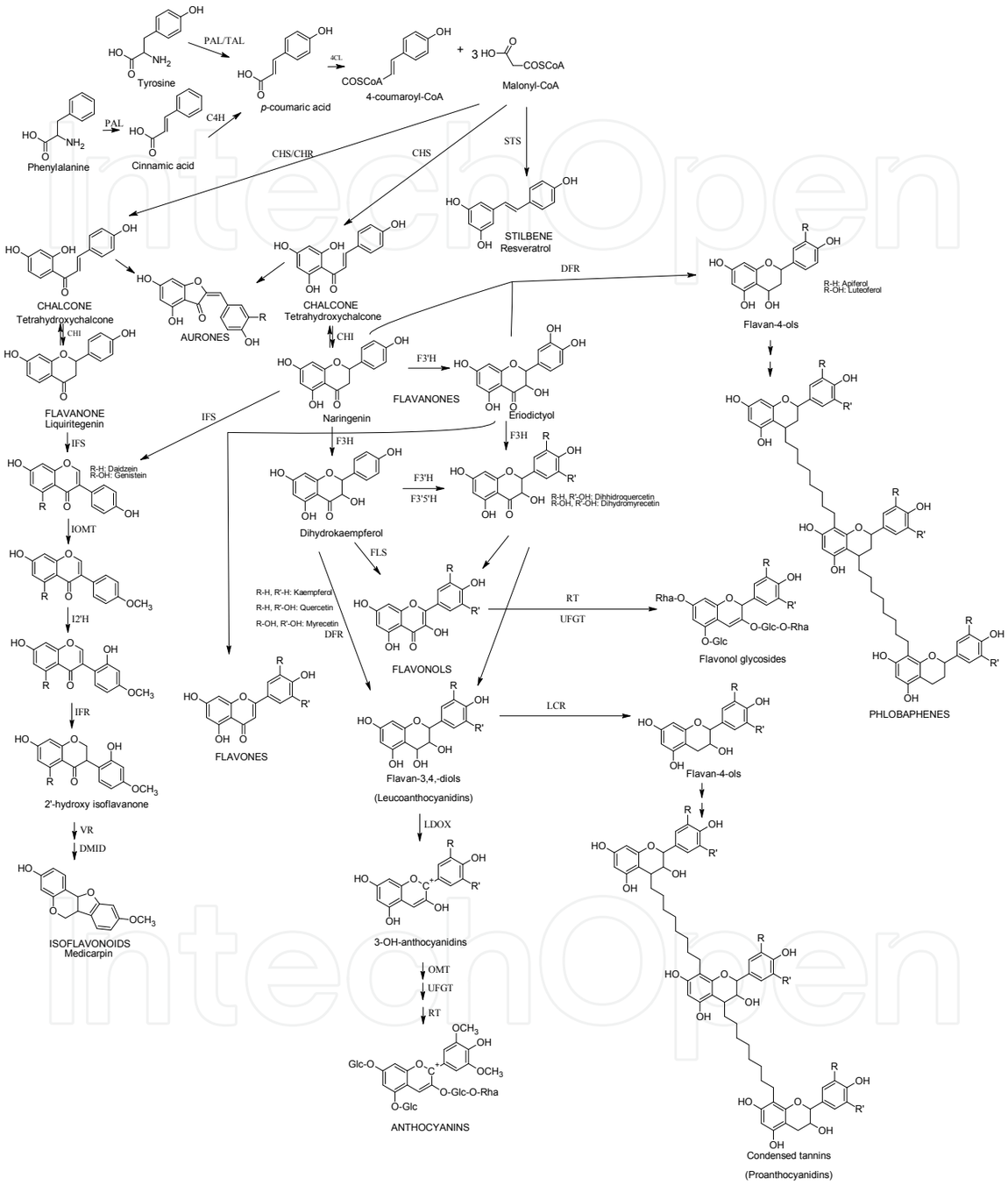

Fig. 1. Scheme of the major branch pathways of flavonoid biosynthesis, starting with general phenylpropanoid metabolism and leading to the nine major subgroups; chalcones, aurones, isoflavonoids, flavones, flavonols, flavandiols, anthocyanins, condensed tannins, and phlobaphene pigments

Flavonoid	Nutraceutic application	Reference
Flavanones	LDL oxidation (atherosclerosis) Cyclooxygenase inhibitory ability (cancer) Malaria chemotherapy (malaria) Inflammation response trigger (reduce inflammation) Antiangiogenic effect Reduce lung metastases Hepatoprotective action Antibacterial action Genoprotective action Inhibitors of NOS and COX in microglia Promote apoptosis in C6 glioma cells	(Miranda et al., 2000) (Kinghorn et al., 2004) (Kumar et al., 2003) (Kontogiorgis et al., 2008) (Mojzis et al., 2008) (Qin et al., 2011) (Prabu et al., 2011) (Celiz et al., 2011) (Orsolic et al., 2011) (Chao et al., 2010) (Sabarinathan et al., 2010)
Flavones	GLUT inhibitors (diabetes) Cyclooxygenase inhibitory ability (cancer) Antitumoral activity Pancreatic cholesterol esterase inhibitor Reduce neurodegeneration Produce apoptosis in melanoma cells Colitis treatment Antiinflammatory effect	(Kwon et al., 2007) (Kinghorn et al., 2004) (Balk, 2011; Polier et al., 2011) (Peng et al., 2011) (Gasiorowski et al., 2011) (Mohan et al., 2011) (Ganjare et al., 2011) (Funakoshi-Tago et al., 2011)
Flavonols	GLUT inhibitors (diabetes) Pancreatic lipase inhibitors (diabetes) Inhibitors of cell cycle control kinases (cancer) Regulate lipid profile in diabetic rats Regulate serum glucose Reduce apoptosis in cell culture Hepatoprotective action Promote new bone formation Anti-inflammatory effect Reduce neuronal damage	(Kwon et al., 2007; Park & Levine, 2000) (Nakai et al., 2005) (Hsu & Yen, 2006) (Liu et al., 2012) (Fontana Pereira et al., 2011) (Jang et al., 2011) (Singab et al., 2010) (Yang et al., 2010) (Mahat et al., 2010) (Lagoa et al., 2009) (Hirose et al., 2009)
Isoflavonoids	Alpha-glucosidase inhibitor (diabetes) GLUT inhibitor (diabetes) Improves cholesterol regulation (diabetes) Inhibitor of tyrosine kinase and antiinflammatory effect in kidney Induce apoptosis in leukemia Neuroprotective action Antiinflammatory action	(Kim et al., 2000) (Kwon et al., 2007; Song et al., 2002) (Lee, 2006) (Elmarakby et al., 2011) (Li et al., 2011a) (Xi et al., 2011) (Neelakandan et al., 2011)
Anthocyanins	Pancreatic lipase and glucosidase	(Kim et al., 2000)

Flavonoid	Nutraceutic application	Reference
	inhibitor (diabetes) Regulate adipocyte function (Obesity) Improves glucose and lipid metabolism (diabetes) Modulate blood hormone levels (multiple sclerosis) Suppress body fat accumulation(obesity) Reduce neuropathic hyperalgesia in diabetic rats Antioxidant effect Neuroprotective action produce cytotoxicity in colon cancer cells	(Tsuda, 2008) (Wolfram et al., 2006) (Sternberg et al., 2008) (Tokimitsu, 2004) (Mirshekar et al., 2010) (Wang et al., 2010) (Roghani et al., 2010) (Cvorovic et al., 2010)

Table 1. Nutraceutical applications of flavonoids.

The mechanism of bioavailability and metabolism of particular flavonoids has been demonstrated in mammals. In general it has been shown that flavonoid absorption and metabolism occurs in a common pathway and it begins in the stomach and intestinal tract. In the small intestine flavonoids pass into the bloodstream in the form of glycosides, though esters or polymers cannot be absorbed. Some intestine cell enzymes or microorganisms of microflora hydrolyze them to be absorbed. In the bloodstream there are different thermodynamic pathways. They could interact with cells to modify intracellular communication. The polyphenols can be conjugated in the intestine or liver to form methylated, glucuronidated, or sulphated metabolites that reach the body via urinary and biliary excretion. The microflora also metabolizes some metabolized flavonoids that are secreted in the bile into the small intestine. Thus, there is a recycling of polyphenols that allow them more time in the plasma (Erdman et al., 2007; Manach et al., 2004). In general, the microalgae produce low quantities of polyphenols. For this reason, in the following parts of this chapter we give special attention to pigments and PUFAs.

4. Nutraceutical effects of terpenes

The terpenes are other secondary metabolites that have nutraceutical properties. The terpenes are not only the largest group of plant natural products, comprising at least 30,000 compounds, but also contain the widest assortment of structural types. Hundreds of different monoterpene (C10), sesquiterpene (C15), diterpene (C20), and triterpene (C30) carbon skeletons are known. The wealth of terpene carbon skeletons can be attributed to an enzyme class known as the terpene synthases (EC 4.2.3.20). These catalysts convert the acyclic prenyl diphosphates and squalene into a multitude of cyclic and acyclic forms. The chief causes of terpene diversity are the large number of different terpene synthases and that some terpene synthases produce multiple products. An excellent review of terpene synthase and the diversity of products were published by Degenhard and coworkers (Degenhardt et al., 2009). Microalgae produce terpenes in the form of carotenoids. These compounds offer therapeutic effects. Carotenoids are tetraterpenoid organic pigments that are naturally occurring in the chloroplasts and chromoplasts of photosynthetic organisms. The use of carotenoids by animals is because they cannot synthetize them. Animals obtain carotenoids in their diets, and they may employ them in various ways in their metabolism.

There are over 600 known carotenoids and they are divided into two classes, xanthophylls (that contain oxygen) and carotenes (that are purely hydrocarbons and contain no oxygen). Carotenoids in general absorb blue light. They serve two key roles in plants and algae; they absorb light energy for use in photosynthesis and they protect chlorophyll from photodamage (Armstrong & Hearst, 1996).

The biosynthesis of carotenes is explained in figure 2. The carotenogenesis differ somewhat among organisms and the current knowledge on the biosynthesis of carotenoids has been gained mainly from studies of bacteria and vascular plants (Armstrong & Hearst, 1996). In Figure 2, we proposed the model of Lohr for the carotenogenesis in *Chlamydomonas*. This is probably related to other microalgae of Chlorophyceae class (Lohr et al., 2005; Lohr, 2008). There are other major divisions in different organisms, such as diatoms (Bertrand, 2010) or plants (Cazzonelli & Pogson, 2010; Zhu et al., 2010), which references the readers can check to deepen their knowledge in this area.

There has been much interest in carotenoids, especially their effect on human health, because they have a market value of several hundred million Euros. Their chemical synthesis is still a demanding challenge for chemists. The major dietary source of vitamin A for mammals, including humans, is derived from carotenoids. Vitamin A is an essential micronutrient for cell growth, embryonic development, vision, and the function of the immune system (Jackson et al., 2008).

In general carotenoids exert their mechanism on health via an antioxidant pathway or by modulating intracellular communication.

1. **Antioxidant properties:** This property of carotenoids was characterized by the ability to quench singlet oxygen, the inhibition of peroxide formation, and the correlation of antioxidant dependency with oxygen partial pressures. The ketocarotenoids, such as astaxanthin and canthaxanthin, were the best radical scavengers that did not contain conjugated terminal carbonyl functions (see figure 2). These findings suggest that the keto function in conjugation with the polyene backbone is able to stabilize carbon-centered radicals more effectively than the polyene backbone alone (Jackson et al., 2008).
2. **Modulation of intracellular communication:** Carotenes modulate the intracellular communication because they or their metabolites interact with nuclear receptors like the pregnant-X-receptor (PXR) or retinoic acid receptor (RAR). For PXR it has been postulated that β-carotene activated the PXR more than its metabolites. Following this pathway, the β-carotene-PXR enhanced the metabolism of xenobiotics, bile acids, and retinoids (Ruhl, 2005). The carotenoids can be converted into two molecules of 9-*cis*-retinal, which is oxidized to 9-*cis*-retinoic acid. The RXR binds the 9-*cis*-retinoic acid with high affinity to modulate cell functions (Heyman et al., 1992). Carotenoids like lycopene modulate mevalonate and Ras pathways to modify cell growth inhibition of cancerous cells (Palozza et al., 2010), and it changes Wnt and hedgehog proteins in those cells (Sarkar et al., 2010). The PI3K-Akt and MAPK pathways are stimulated in kidney by lycopene (Chan et al., 2009).

In table 2, are some nutraceuticals of the most used carotenoids.

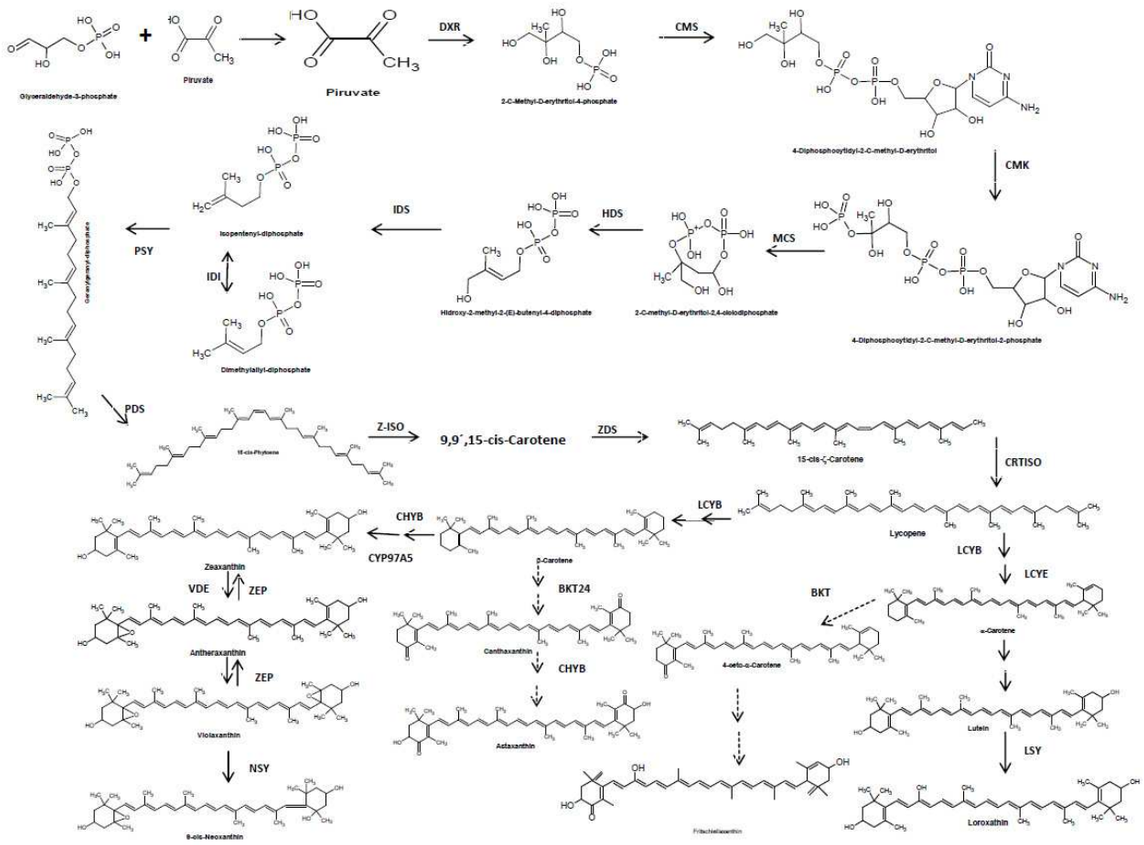

Fig. 2. Putative pathways of carotenoid biosynthesis in *Chlamydomonas*. Hypothetical zygospore-specific pathways are indicated by dotted arrows. For the enzymes of the pathways only abbreviations are given. DXS (1-deoxy-D-xylulose-5-phosphate synthetase, EC 2.2.1.7). DXR (1-deoxy-D-xylulose-5-phosphate reductoisomerase, EC 1.1.1.267). CMS (4-diphosphocytidil-2-C-methyl-D-erythriol synthase, EC 2.7.7.60). CMK (4-diphosphocytidil-2-C-methyl-D-erythriol kinase, EC 2.7.1.14.8). MCS (2-C-methyl-D-erythritol-2,4-cyclophosphate synthase, EC 4.6.1.12). HDS (4-hydroxy-3-methylbut-2-en-1-yl diphosphate synthase, EC 1.17.7.1). IDS (isopentenyl dimethylallyl diphosphate synthase, EC 1.17.1.2.3). IDI (isopentenyl-diphosphate delta-isomerase, EC 5.3.3.2). GGPPS (geranylgeranyl-diphosphate synthase, EC 2.5.1.81). PSY (phytoene synthase, EC 2.5.1.32). PDS (phytoene desaturase, EC 1.3.5.5). Z-ISO (ζ-Carotene isomerase); ZDS (ζ-carotene desaturase, EC 1.3.5.6). CRTISO (carotenoid isomerase, EC 5.2.1.13). LCYB (lycopene-β-cyclase). LCYE (lycopene-ε-cyclase), CHYB (carotene-β-hydroxylase, EC 1.14.13.-). CYP97A5 (carotene-β-hydroxylase, EC 1.14.13.129). CYP97C3 (carotene-ε-hydroxylase, EC 1.14.99.45). ZEP (zeaxanthin epoxidase, EC 1.14.13.90). VDE (violaxanthin epoxidase, EC 1.10.99.3). NSY (neoxanthin synthase, EC 5.3.99.9). LSY (loroxanthin synthase), and BKT (carotene-β-ketolase).

Carotenoid	Nutracetical effect	Reference
Lycopene	Antimutagenic effect	(Polivkova et al., 2010)
	Neuroprotective action	(Sandhir et al., 2010)
	Nephroprotective action	(Sahin et al., 2010)
	Prevent preclampsia	(Banerjee et al., 2009)
	Reduce risk of hip fracture	(Sahni et al., 2009)
	Antioxidant effect	(Erdman et al., 2009)
	Reduce eosinophil influx in asthma	(Wood et al., 2008)
	Cardioprotective effect against doxorubicin–caused damage	(Anjos Ferreira et al., 2007)
	Reduce inflammatory cytokines expression in pancreatitis	(Kim, 2011a; Kim, 2011b)
	Inhibit the growth and progression of colon cancer	(Tang et al., 2011)
	Enhanced antioxidant enzymes and immunity function in gastric cancer	(Luo & Wu, 2011)
	Inhibit NFκB–modulated IL-8 expression in macrophages–cigarette activated	(Simone et al., 2011)
	Reduced oxidative stress in allergic rhinitis	(Li et al., 2011b)
	Attenuated endothelial dysfunction in diabetes	(Zhu et al., 2011)
	Reduce cognitive decline in Parkinson's disease	(Kaur et al., 2011)
	Reduces LDC cholesterol and systolic blood pressure	(Ried & Fakler, 2011)
Asthaxanthin	Reduces endothelial dysfunction in diabetic rats	(Zhao et al., 2011)z
	Produces anxiolytic–like effects in mice	(Nishioka et al., 2011)
	Reduces oxidative stress and mitochondrial dysfunction in brain due MPTP/MPTP$^+$	(Lee et al., 2011)
	Reduce IL-6 microglia production	(Kim et al., 2010)
	Reduce blood pressure in hypertensive rats	(Monroy-Ruiz et al., 2011)
	Neuroprotective action against focal ischemia	(Lu et al., 2010)
	Attenuate thrombosis	(Khan et al., 2010)
	Reduce retinal injury in elevated intraocular pressure	(Cort et al., 2010)
	Reduce UVA – induced skins photoaging	(Suganuma et al., 2010)
	Hepatoprotective action	(Curek et al., 2010)

Table 2. Nutraceutical application of lycopene and astaxanthin.

Carotenoids are lipid soluble and in general they follow the same absorption pathway as lipids, however other mechanisms of absorption have been proposed. To learn more, read the review of Kotake-Nara and Nagao (Kotake-Nara & Nagao, 2011). Once in the bloodstream, carotenes are fundamentally ligated to low density lipoprotein (LDL) whereas the xanthophylls are more evenly distributed between high density lipoproteins (HDL) and

low density lipoproteins (LDL). Nonpolar carotenoids (lycopene, α-carotene, β-carotene) are located in the hydrophobic core and the polar (xanthophylls) would be, at least in part, on the surface of lipoproteins (Furr & Clark, 1997). For the microalgae, carotenoids are synthesized in high concentrations under several different environmental conditions, and humans exploited these as nutraceuticals in food.

5. Nutraceutical effects of chlorophylls, PUFA and other vitamins

There are other components in microalgae that could modulate redox environment to prevent oxidative stress and can affect intracellular communication. These components are chlorophyll, PUFAs, and vitamins such as vitamin A, B, C, and E.

Microalgae, like all chloroplast-containing photosynthetic eukaryotes, synthesize chlorophyll pigments. In Chlorophyceae chorophylls a and b are the most predominant. The chlorophylls have a porphyrin ring structure similar to heme, but with a central nonreactive magnesium ion instead of iron. To review chlorophyll biosynthesis in microalgae, read the chapter of Beale (Beale, 2008). The information about the biological activities of chlorophyll as nutraceuticals is scarce. They do have antipoliferative (Wu et al., 2010) and antioxidant (Serpeloni et al., 2011) activities. The chlorophyllin-cooper complex, a water-soluble commercial version of chlorophyll, possesses antimutagenic (Chernomorsky et al., 1997) and anticancer activities (Chernomorsky et al., 1997). The other components of microalgae; PUFAs, and vitamins A, B, C, and E, could be a nutraceutical because there is much evidence of how they modulate intracellular signals and act as antioxidants.

6. *Chlorella* genus as nutraceutic

Chlorella species are encountered in all water habitats having cosmopolitan occurrences. The species of this genus have a simple form, a unicellular green alga belonging to the Chlorophyceae family. The *Chlorella* sp. is morphologically classified into four types; a) spherical cells (ratio of the two axes equals one), b) ellipsoidal cells (ratio of the longest axis to the shorter axis 1.45 to 1.60), spherical or ellipsoidal cells, and globular to subspherical cells. Their reproduction is asexual. Each mature cell divides usually producing four or eight (and more rarely 16) autospores, which are freed by rupture or dissolution of the parental walls.

Our research group has used *Chlorella vulgaris* as nutraceutical, particularly against mercury-caused oxidative stress and renal damage. For that we used male mice that were assigned into six groups; 1) a control group that received 100 mM phosphate buffer (PB) ig and 0.9% saline ip, 2) PB + $HgCl_2$ 5 mg/kg ip, 3) PB + 1000 mg/kg *Chlorella vulgaris* ig, and three groups receiving $HgCl_2$ + 250, 500, or 1000 mg/kg *Chlorella vulgaris* ig. The administration of the microalgae or PB was made 30 min before saline or $HgCl_2$ for 5 days. Our results demonstrated that $HgCl_2$ caused oxidative stress and cellular damage, whereas *Chlorella vulgaris* administration prevents oxidative stress (figure 3) and cellular damage (figure 4) in the kidney (Blas-Valdivia et al., 2011). We proposed that *Chlorella vulgaris's* carotenes play an important role in preventing $HgCl_2$-caused lipid peroxidation. Carotenes have a wide pharmacological spectrum of effects. The inhibition of lipid peroxidation may

be caused by the free radical scavenging property of these compounds (Miranda et al., 2001). Carotenes can scavenge singlet oxygen and they terminate peroxides by their redox potential because of the hydroxyl group in its structure. Thus, the ROS-steady state is maintained in the kidney damage lower than in animals with mercury intoxication. The biochemical behavior of this microalgae against mercury-caused oxidative stress is similar to the purified component of cyanobacteria such as *Pseudoanabaena tenuis* (Cano-Europa et al., 2010) or *Spirulina maxima* (Sharma et al., 2007).

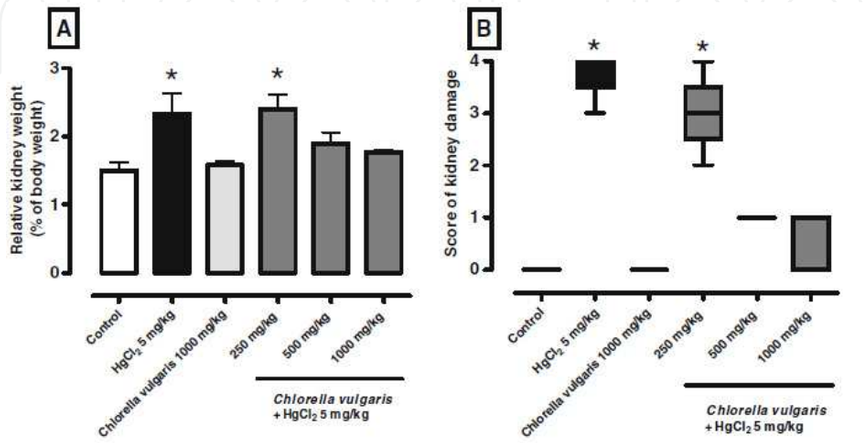

Fig. 3. Quantification of relative kidney weight (A) and the score of kidney damage (B) of mice treated with $HgCl_2$ and *Chlorella vulgaris*. In A each bar represents the mean ± S.E.M. In B each box represents the median ± intercuartilic space.* $P < 0.05$ vs. control. Author right permission. Springer ©.

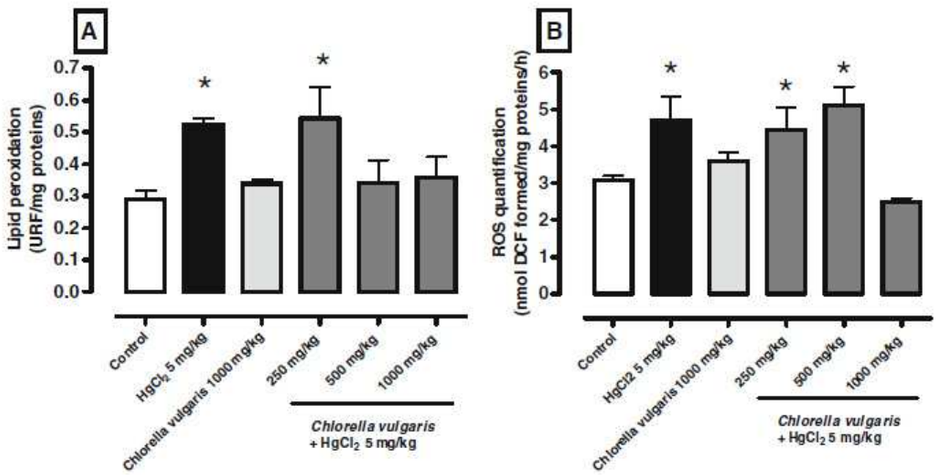

Fig. 4. Quantification of lipid peroxidation (A) and reactive oxygen species in the kidneys of mice treated with $HgCl_2$ and *Chlorella vulgaris*. Bar represents the mean ± S.E.M.* $P < 0.05$ vs. control. Author right permission. Springer ©.

Here are some experiments that demonstrated the nutraceutical use of *Chlorella (*Table 3*)*.

Study	Evidences
The administration of *Chlorella* sp. reduces endotoxemia, intestinal oxidative stress and bacterial traslocation in experimental biliary obstruction (Bedirli et al., 2009)	*Chlorella* administration inhibits bacterial culture and it avoids oxidative stress.
Hot water extract of *Chlorella vulgaris* induced DNA damage and apoptosis (Yusof et al., 2010)	The extract of *Chlorella vulgaris* inhibited DNA synthesis, causing apoptosis and it increases p53, caspase-3, and Bax expression in hepatoma cells (HEpG2)
Attenuating effect of ***C****hlorella* supplementation on oxidative stress and NFκB. Activation in peritoneal macrophages and liver of C57BL/6 mice fed on atherogenic diet (Lee et al., 2003)	*Chlorella* supplementation decreases the NFκB activation and superoxide anion production and because it increases SOD and catalase activity
Chlorella accelerates dioxin excretion in rats (Morita et al., 1999)	*Chlorella* enhanced dioxin metabolism and excretion by feces
Effect of *Chlorella* and its fractions on blood pressure, cerebral stroke lesions, and life-span in stroke-prone spontaneously hypertensive rats (Sansawa et al., 2006)	A *Chlorella* supplemented diet decreases blood pressure and the incidence rate of cerebral stroke in SHRSP.
Hypocholesterolemic mechanism of *Chlorella*: *Chlorella* and its indigestible fraction enhance hepatic cholesterol 7α-hydroxylase in rats (Shibata et al., 2007)	*Chlorella* powder increases the expression of CYP7A1, a limiting enzyme of the main pathway of the cholesterol catabolism, lowering the concentration of LDL in plasma
Chlorella vulgaris triggers apoptosis in hepatocarcinogenesis-induced rats (Mohd Azamai et al., 2009)	*Chlorella vulgaris* inhibits the anti-apoptotic protein Bcl-2
Effect of ***C****hlorella vulgaris* on lipid metabolism in Wistar rats fed high fat diet (Lee et al., 2008)	*Chlorella vulgaris* decreases HDL cholesterol concentration by a reduction in the intestinal absortion
Antioxidant effect of the marine algae *Chlorella vulgaris* against naphthalene-induced oxidative stress in the albino rats (Vijayavel et al., 2007)	*Chlorella vulgaris* inhibits production of free radicals, decreasing lipoperoxidation, and increasing the activity of antioxidant enzymes as SOD, catalase, GPX and reduced glutathione, preventing from the toxicity of naftalene
Six-week supplementation with *Chlorella* has favorable impact on antioxidant status in Korean male smokers (Lee et al., 2010)	*Chlorella* supplement exhibits antioxidant activity decreasing ROS and increasing the activity of SOD and catalase
Chlorella pyrenoidosa supplementation reduces the risk of anemia, proteinuria and edema in pregnant women (Nakano et al., 2010)	*Chlorella pyrenoidosa* exhibits an antiinflammatory activity regulated by cytokine. It increased the production of IL-10

Study	Evidences
Effect of *Chlorella* intake on cadmium metabolism in rats (Shim et al., 2009)	*Chlorella* inhibits cadmium absorption and it promotes the excretion through the feces. Also, it stimulates the production of metallothionein in the small intestine.
Isolation of phophorylated polysaccharides from algae: the inmmunostimulatory principle of *Chlorella pyrenoidosa* (Suarez et al., 2010)	The *Chlorella* polysaccharides increases the production of NO in macrophages enhancing the innate immune response, mediated by Toll-like receptors (TLR-4)
Influence of *Chlorella* powder intake during swimming stress in mice (Mizoguchi et al., 2011)	*Chlorella vulgaris* exhibits an antioxidant activity, reducing the lipoperoxidation, avoiding the DNA damage. However it does not show hypoglycemic activity

Table 3. Nutraceutical evidences of *Chlorella.*

7. *Chlamydomonas* genus as nutraceutic

Chlamydomonas spp. are unicellular algae with cell walls and with either two or four flagella. The genus *Chlamydomonas* is of worldwide distribution and is found in a diversity of habitats including temperate, tropical, and polar regions. *Chlamydomonas* species have been isolated from freshwater ponds and lakes, sewage ponds, marine and brackish waters, snow, garden and agricultural soil, forests, deserts, peat bogs, damp walls, sap on a wounded elm tree, an artificial pond on a volcanic island, mattress dust in the Netherlands, roof tiles in India, and a Nicaraguan hog wallow. These algae belong to the family *Chlamydomonadaceae* that consists of approximately 30 genera. DNA sequence analysis clearly demonstrates, however, that this family is composed of multiple phylogenetic lineages that do not correspond to the morphologically defined genera. Although the identities of the species are uncertain, it is noteworthy that the traits in which they differed included body shape, thickness of the cell wall, presence or absence of the apical papilla, lateral vs. basal position of the chloroplast, chloroplast position, and shape of the eyespot, all of which were later used as criteria to separate species. Although cell-body shape and size vary among *Chlamydomonas* species (as defined by morphological criteria), the overall polar structure, with paired apical flagella and basal chloroplast surrounding one or more pyrenoids, is constant. Cells are usually free-swimming in liquid media but on solid substrata may be nonflagellated, and are often seen in gelatinous masses similar to those of the algae *Palmella* or *Gloeocystis* in the order *Tetrasporales*. This condition has been referred to as a palmelloid state. Some species may also form asexual resting spores, or akinetes, in which the original vegetative cell wall becomes much thicker, and carotenoids, starch, and lipids may accumulate (Harris et al., 2008).

Our group has studied the nutraceutical properties of *Chlamydomonas gloeopara*, a microalgae collected from a eutrophic reservoir (La Piedad Lake) in Cuautitlan Izcalli, Mexico. That reservoir is located at 19°39´N (latitude) and 99°14´W (longitude). Our research group has used *Chlamydomonas gloeopara* as a nutraceutical, particularly against mercury-caused oxidative stress and renal damage. For that we used male mice that were assigned into six groups; 1) a control group that received 100 mM phosphate buffer (PB) ig and 0.9% saline ip, 2) PB + $HgCl_2$ 5 mg/kg ip, 3) PB + 1000 mg/kg *Chlamydomonas gloeopara* ig, and three

groups receiving $HgCl_2$ + 250, 500, or 1000 mg/kg *Chlamydomonas gloeopara* ig. The administration of the microalgae or PB was made 30 min before saline or $HgCl_2$ for 5 days. Our results demonstrated that *Chlamydomonas gloeopara* as well as *Chlorella* prevents renal damage (figure 5, panel A-F) by reducing the oxidative stress of lipid peroxidation (figure 5, panel G).

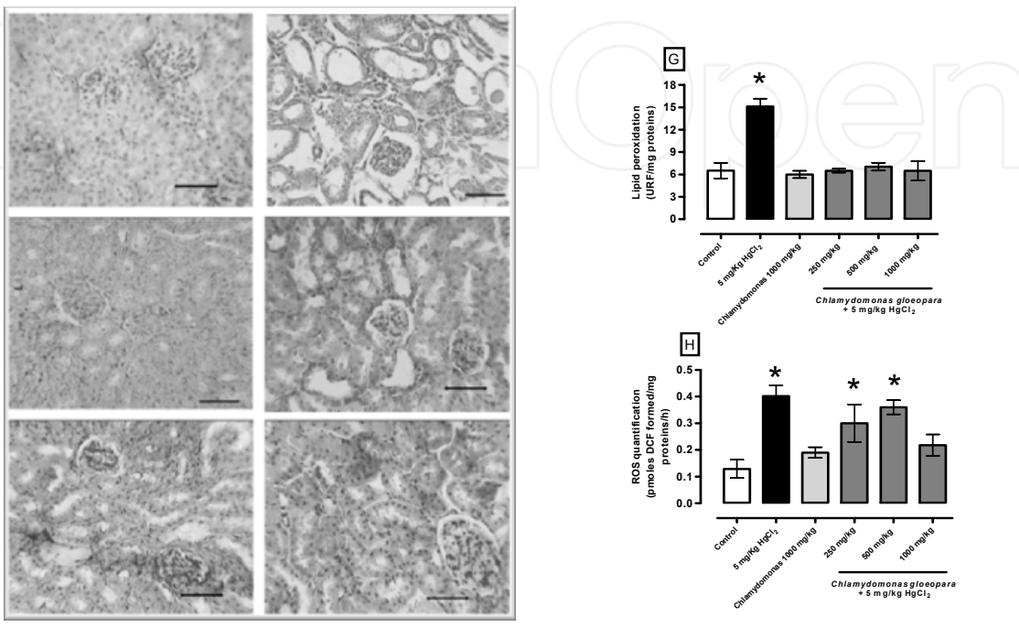

Fig. 5. Effect on *Chlamydomonas gloeopara* administation on $HgCl_2$-caused renal damage (panel A-F) and oxidative stress (panel G and H). Photomicrographs of renal cortex . Panel A shows control group. Panel B shows group treated with $HgCl_2$. Panel C shows group treated with *Chlamydomonas gloeopara* 1000 mg/kg . Panels D, E and F show groups treated with *Chlamydomonas gloeopara* 250, 500 and 1000 mg/kg plus $HgCl_2$. The tissue was stained by hematoxylin-eosin. Treatment with $HgCl_2$ causes cell atrophy, hyperchromatic nuclei, and edema. Histological alterations were partially ameliorated in groups treated with *Chlamydomonas gloeopara*. *Chlamydomonas gloeopara* administration reduced lipid peroxidation (G) and reactive oxygen species (H) in the kidneys of mice treated with $HgCl_2$ and *Chlorella vulgaris.* Bar is the mean ± SE * $P < 0.05$ vs. control.

8. *Haematococcus* genus as nutraceutic

Haematococcus are green microalgae; single-celled aquatic organisms. It is known that *Haematococcus* is the primarily source of astaxanthin, a ketocarotenoid that is a natural nutritional component. In the marine environment, astaxanthin is biosynthesized in the food chain, within the microalgae or phytoplankton, at the primary production level. When these algae are exposed to harsh environmental conditions and ultraviolet light, they accumulate the highest level of astaxanthin and in this process, the algae become blood red. Astaxanthin accumulates 2% to 3% of dry weight and constitutes 85% to 88% of the total carotenoids. Chemically it is a ketocarotenoid (3,3´-dihydroxy-β, β-carotene-4,4´dione) and is the principal pigment of salmonoids and shrimp. Astaxanthin has a higher antioxidant activity

than lutein, lycopene, α or β-carotene, and α-tocopherol. Astaxanthin has 100 times and 10 times greater antioxidant activity than vitamin E and β-carotene (Guerin, 2003).

Morphological studies have shown that the algae have a life cycle. The, green vegetative cells with two flagellae grow autotrophycally in the light and heterotrophically in the dark. In culture, *H. pluvialis* has the typical characteristics of a motile stage, with biflagellate spherical cells. The growth in a bioreactor, with mechanical stirring, favors the occurrence of more or less mature aplanospores. This stage becomes dominant together with the evolution of growth. The aplanospore color turns gradually red, because of the accumulation of carotenoids in the chloroplast, and especially outside of them in lipid globules (astaxanthin). The red aplanospores are known as haematocysts. This stage may appear under stress conditions caused by light, high temperature, increased salinity, nutritional limitation, or change of carbon source. During the growth stage, the cells with a diameter of 30 μm were spherical to ellipsoid and enclosed by a cell wall. The cells had 2 flagellae of equal length emerging form an anterior papilla. As they age, the cells ceased to be mobile, yet the cellular structure remained the same without the flagellae. Under stress conditions, the volume of the cells increased to a diameter of > 40 μm and the cell wall became resistant. The maturation of the cyst cells was accompanied by enhanced carotenoid biosynthesis and a gradual change in cell color to red. When the cystic cells were transferred to optimal growth conditions, daughter cells were released from the cystic cells, and then vegetative cells regenerated from daughter cells (Cysewski & Todd Lorenz, 2004).

Haematococcus has the potential as a nutraceutical because there is various evidence of this. In table 4, we show some articles that employed *Haematococcus* or its astaxanthin.

Study	Evidences
Haematococcus astaxanthin: applications for human health and nutrition (Guerin, 2003)	This is a review about the uses of astaxantin from *Haematococcus* in health
Optimization of microwave-assisted extraction of astaxanthin from *Haematococcus pluvialis* by response surface methodology and antioxidant activities of the extracts (Zhao et al., 2009)	The extracts have a high antioxidant capacity, inhibit peroxidation of linoleic acid, and neutralize free radicals
Cardioprotection and myocardial salvage by a disodium disuccinate astaxanthin derivative (Cardax™) (Gross & Lockwood, 2004)	The astaxanthin is an antioxidant, antiinflammatory, and cardioprotective. reducer of levels of nitric oxide, tumor necrosis factor alpha, and prostaglandin E2
Ulcer preventive and antioxidative properties of astaxanthin from *Haematococcus pluvialis (Kamath et al., 2008)*	The astaxanthin exerts its gastroprotection of gastric ulceration by activation of antioxidant enzyme such as catalase, superoxide dismutase, and glutathione peroxidase. It inhibits the activity pump Na-K ATPase
Safety assessment of astaxanthin-rich microalgae biomass: acute and subchronic toxicity studies in	The administration of astaxanthin has no adverse effects

Study	Evidences
rats(Stewart et al., 2008)	
Astaxanthin, a carotenoid with potential in human health and nutrition (Hussein et al., 2006).	The antihypertensive and neuroprotective potentials of the compound
Protective effects of *Haematococcus* astaxanthin on oxidative stress in healthy smokers (Kim et al., 2011).	The results suggest that ASX supplementation might prevent oxidative damage in smokers by suppressing lipid peroxidation and stimulating the activity of the antioxidant system in smokers
Astaxanthin-rich extract from the green alga *Haematococcus pluvialis* lowers plasma lipid concentrations and enhances antioxidant defense in apolipoprotein E knockout mice (Yang et al., 2011)	It results suggest that supplementation of astaxanthin-rich *Haematococcus* extract improves cholesterol and lipid metabolism as well as antioxidant defense mechanisms, all of which could help mitigate the progression of atherosclerosis.

Table 4. Nutraceutical evidences of *Haematococcus.*

9. *Dunaliella* genus as nutreutic

Dunaliella salina is a unicelular green alga belonging to the Chlorophyceae family. *Dunaliella* cells are ovoid, spherical, pyriform, fusiform, or ellipsoid with sizes varying from 5 to 25 μm in length and from 3 to 13 μm in width. The cells also contain a single chloroplast, which mostly has a central pyrenoid surrounded by starch granules. *Dunaliella* multiplies by lengthwise division, but sexual reproduction does occur rarely by isogametes with a conjugation process. It proliferates in extremely varied salinities from 0.5 to 5.0 M NaCl. The alga cells do not contain a rigid cell wall; instead a thin elastic membrane surrounds them. It is known to accumulate carotenoids under various stress conditions. It possesses a remarkable degree of environmental adaptation by producing an excess of β-carotene and glycerol to maintain its osmotic balance. β-carotene occurs naturally as its isomers, namely, all-*trans*, 9-*cis*, 13-*cis*, and 15-*cis* forms and functions as an accessory light harvesting pigment, thereby protecting the photosynthetic apparatus against photo damage in all green plants including algae. β-carotene, a component of the photosynthetic reaction center is accumulated as lipid globules in the interthylakoid spaces of the chloroplasts of *Dunaliella*. They protect the algae from damage obtained during excessive irradiance by preventing the formation of reactive oxygen species, by quenching the triplet-state chlorophyll, or by reacting with singlet oxygen ($^1O_2$) and also act as a light filter (Ben-Amotz, 2004). *Dunaliella* nutraceutical properties are shown in table

Study	Conclusion
In vivo antioxidant activity of carotenoids from *Dunaliella salina* a green microalga (Chidambara-Murthy et al., 2005)	Carotenoids provide protection against CCl_4-caused hepatic damage by restoring the activity of hepatic enzymes like peroxidase, super oxide dismutase, and catalase, which reduce ROS and lipid peroxidation.

Study	Conclusion
9-*cis* β-carotene-rich powder of the alga *Dunaliella bardawil* increases plasma HDL-cholesterol in fibrate-treated patients (Shaish et al., 2006)	*Dunaliella* treatment increases plasma HDL-cholesterol and lower plasma triglyceride levels
Ethanol extract of *Dunaliella salina* induces cell cycle arrest and apoptosis in A545 human non-small cell lung cancer cells (Sheu et al., 2008)	Ethanol extract of *Dunaliella salina* inhibits cell proliferation and causes apoptosis possibly via p53 and p21 promoting the protein expression of Fas and FasL
Protective effects of *Dunaliella salina* against experimental induced fibrosarcoma on Wistar rats (Raja et al., 2007).	The *chlorophyta* has a protective effect against experimentally caused fibrosarcoma
Bioavailability of the isomer mixture of phytoene and phytofluene-rich alga *Dunaliella bardawil* in rat plasma and tissues (Werman et al., 2002).	9-*cis* phytoene has a stronger antioxidative effect than the all trans isomer
Hypercholesterolemia induced oxidative stress is reduced in rats with diets enriched with supplement from *Dunaliella salina* algae (Bansal & Sapna, 2011).	*Dunaliella salina* components inhibit lipid peroxidation and also increases Type1 5´-iodothyronine deiodinase (5´-DI) expression, which leads to a T_3 level increase
Evaluation of carotenoid extract from *Dunaliella salina* against cadmium-induced cytotoxicity and transforming growth factor β1 induced expression of smooth muscle α-actin with rat liver cell lines (Jau-Tien et al., 2011).	Carotenoid extract of *Dunaliella salina* contains abundant *cis* and *trans* β-carotenes. These antioxidants decrease the lipid peroxidation and also inhibit activation of hepatic stellate cells (HSCs).
Protective effects of *Dunaliella salina*- a carotenoids-rich alga, against carbon tetrachloride-induced hepatotoxicity in mice (Hsu et al., 2008).	Carotenoids of *D. salina* inhibit the lipid peroxidation and increases the antioxidant enzyme activity

Table 5. Nutraceutical evidences of *Dunaliella.*

10. Final remarks

The functional food and nutraceutical market is growing. However, to promote health the active compounds must be ingested in high concentration. This is a great problem because sometimes the components such as carotenoids, polyphenols, and chlorophylls are extracted from vegetables or plants. In their production, we are modifying the environment, thus the use of biotechnology of microalgae or other microorganisms like bacteria or fungus could be an alternative because they may be environmentally friendly. The sun can be used as energy source and the medium could be fresh or sea water, with the carbon source as CO_2 and other inorganic or organic sources. In this chapter we show the evidence of some genera, particularly of Chlorophyceae class as *Chlorella, Chlamydomonas, Haematococcus,* and *Dunaliella.* It is evident that their components modulate intracellular communication and they act as antioxidants.

There are many microalgae never used as nutraceuticals that could be used for human or animal health, such as the microalgae used in aquaculture to fed shrimp and fish. Examples of those kinds of microalgi are *Pavlova* and *Tetraselmis* that produce high concentration of PUFAs.

11. Acknowledgement

This study was partially supported by SIP-IPN 20110283 y 20110336. Thanks to Dr. Ellis Glazier for editing this English-language text.

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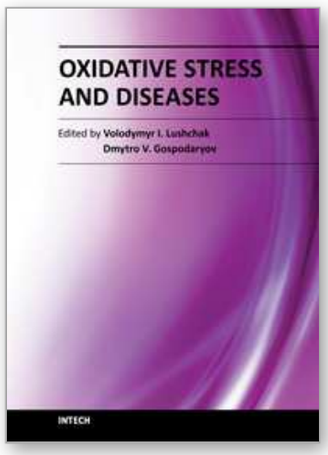

Oxidative Stress and Diseases

Edited by Dr. Volodymyr Lushchak

ISBN 978-953-51-0552-7

Hard cover, 610 pages

Publisher InTech

Published online 25, April, 2012

Published in print edition April, 2012

The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

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