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Review

Metabolites from algae with economical impact ☆

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Abstract

In order to survive in a highly competitive environment, freshwater or marine algae have to develop defense strategies that result in a tremendous diversity of compounds from different metabolic pathways. Recent trends in drug research from natural sources have shown that algae are promising organisms to furnish novel biochemically active compounds. The current review describes the main substances biosynthesized by algae with potential economic impact in food science, pharmaceutical industry and public health. Emphasis is given to fatty acids, steroids, carotenoids, polysaccharides, lectins, mycosporine-like amino acids, halogenated compounds, polyketides and toxins.

Keywords: Algae; Commercial application; Natural products; Metabolites; Biological activities; Toxin; Water quality

Contents

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1. Introduction

The current application of chemical compounds isolated from diverse classes of algae is enormous. Since 1975, three areas of research in aquatic natural products have emerged: toxins, bioproducts and chemical ecology. Over 15,000 novel compounds have been chemically determined. Focusing on bioproducts, recent trends in drug research from natural sources suggest that algae are a promising group to furnish novel biochemically active substances (Tringali, 1997; Burja et al., 2001; Mayer and Hamann, 2004, 2005; Singh et al., 2005, Blunt et al., 2005). To survive in a competitive environment, freshwater and marine algae have developed defense strategies that result in a significant level of structural–chemical diversity, from different metabolic pathways (Puglisi et al., 2004; Barros et al., 2005). The exploration of these organisms for pharmaceutical purposes has revealed important chemical prototypes for the discovery of new agents, stimulating the use of sophisticated physical techniques and new syntheses of compounds with biomedical application. Moreover, algae are promising organisms for providing both novel biologically active substances and essential compounds for human nutrition (Tringali, 1997; Burja et al., 2001; Mayer and Hamann, 2004). Therefore, an increasing supply for algal extracts, fractions or pure compounds for the economical sector is needed (Dos Santos et al., 2005). In this regard, both secondary and primary metabolisms have been studied as a prelude to future rational economic exploitation (Fig. 1).

The secondary metabolism is of restricted distribution, while the primary metabolism furnishes intermediates for the synthesis of essential macromolecules (Dos Santos et al., 2005). Although chemical research on the algae products is very active, biosynthetic studies have been few and mainly concerned with secondary metabolism, which present a high structural diversity, due to modifications and combinations of reactions from the primary metabolic pathways (Fig. 1). However, with the emergence of molecular biology tools, metabolic pathways have been clarified, paving the way for generating novel bioactive metabolites in quantity by genetic engineering.

In many countries, the food industries consume a wide range of algae, which are well known to have high contents of fiber, minerals, vitamins and different antioxidants. In the last few decades, the emphasis has moved from wild harvests to farming and controlled cultivation to produce valuable new products on a large scale. On the other hand, toxins produced by freshwater and marine algae represent an increasing hazard to water supplies, reservoirs, recreational beaches, as well as seafood contamination

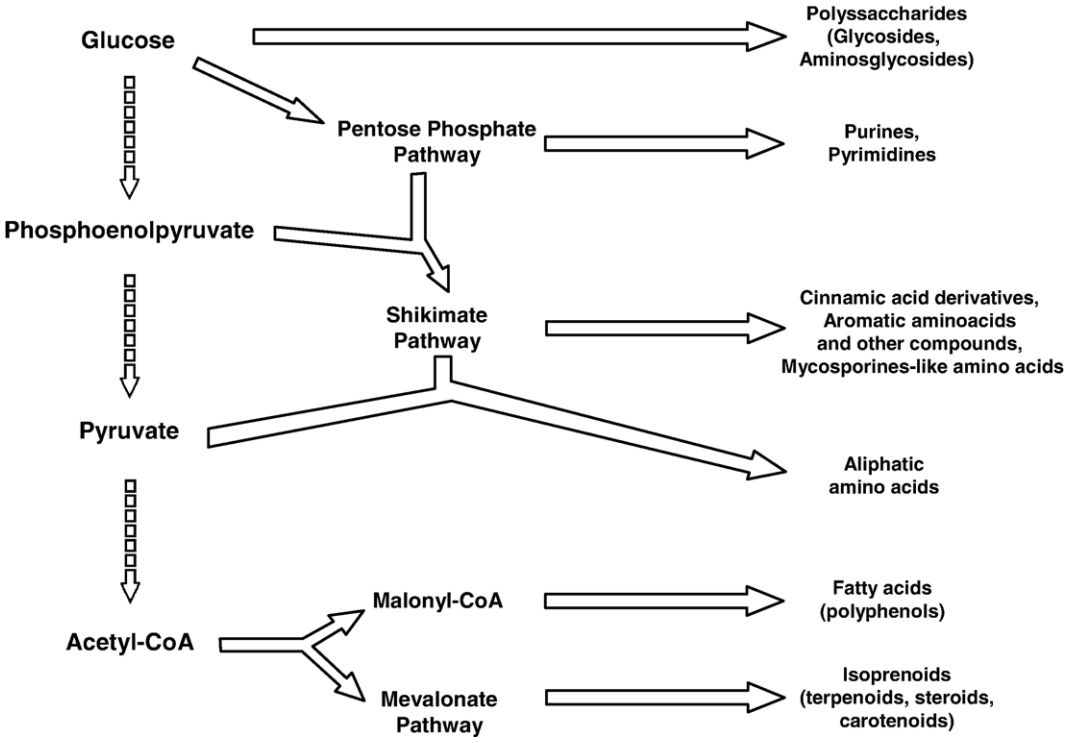

Fig. 1. Main pathways of some secondary and primary metabolites biosynthesis (modified from Burja et al., 2001).

(Gehringer, 2004). This class of compounds can be present in the drinking water or accumulated through the food chain where it is ultimately deposited in higher predator or filter-feeding bivalves (Friedman and Levin, 2005). Therefore, algal toxins are a serious public health concern and can affect the economy in many aspects, such as in bivalve and shrimp aquaculture (Anderson et al., 2002; Brett, 2003). The monitoring of algal toxins in freshwater and seafood is required in many countries and is recommended by the World Health Organization (Carmichael et al., 2001; Hungerford, 2005).

Herein, we review the commercial application of the most explored compounds from algae and briefly discuss the biosynthetic pathways of fatty acids and steroids, carotenoids, phycocolloids, lectins, mycosporine-like amino acids, halogenated compounds, polyketides and toxins.

2. Fatty acids

Fatty acids with two or more methylene-interrupted double bonds are essential for normal cell function, and have entered the biomedical and nutraceutical areas as a result of elucidation of their biological role in certain clinical conditions common in Western society such as obesity and cardiovascular diseases (Gill and Valivety, 1997; Sayanova and Napier, 2004). Moreover, polyunsaturated fatty acids (PUFAs) play key roles in cellular and tissue metabolism, including the regulation of membrane fluidity, electron and oxygen transport, as well as thermal adaptation (Funk, 2001). In addition, public perception of healthy food and life style has brought them to the attention of the consumer (Napier et al., 1999). In particular, there is increasing interest in a typical PUFA family (ω-3) named eicosapentaenoic acid (EPA, $C20:5\Delta^{5,8,11,14,17}$, 20:5 ω-3). EPA is a fatty acid 20 carbons in length with five double bonds from the carboxy [Δ] terminus or with the last double bond located at the third carbon from the methyl [ω] terminus (Nettleton, 1995).

The biosynthesis of EPA occurs through a series of reactions that can be divided into two distinct steps. First is the *de novo* synthesis of oleic acid (18:1 ω9) from acetate, followed by conversion to linoleic acid (18:2 ω-6) and α-linolenic acid (18:3 ω-3). The subsequent stepwise desaturation and elongation steps form an ω-3 PUFA (Fig. 2). Inside the cell, EPA is normally esterified (by cyclooxygenase and lipooxygenase activities) to form complex lipid molecules and plays an important role in higher animals and humans as the precursor of a group of eicosanoids, hormone-like substances such as prostaglandins, thromboxanes and leucotrienes that are crucial in regulating developmental and regulatory physiology (Fig. 2) (Wen and Chen, 2003).

Although fish oil seems to be the conventional source of EPA, fish do not synthesize EPA *de novo* and these compounds are derived from the marine microorganism they consume. Thus, EPA is passed up the food chain via consumption by omnivorous fish and then by carnivorous fish species and ultimately to humans. The oil quality depends on fish species, the season and the geographical location of the catching site. Moreover, marine fish oil is a complex mixture of fatty acids varying chain lengths and unsaturation degrees, requiring that EPA be refined for pharmaceuticals (Gill and Valivety, 1997).

EPA has been found in a wide variety of marine microalgal classes (Table 1). However, only a few microalgal species have demonstrated industrial production potential, mainly due to the fact that the majority of microalgae cultures present low specific growth rates and low cell densities when grown under conventional photoautotrophic conditions (Wen and Chen, 2003). Thus, there is a clear technological need for the development and deployment of a safe, sustainable and cheap alternative

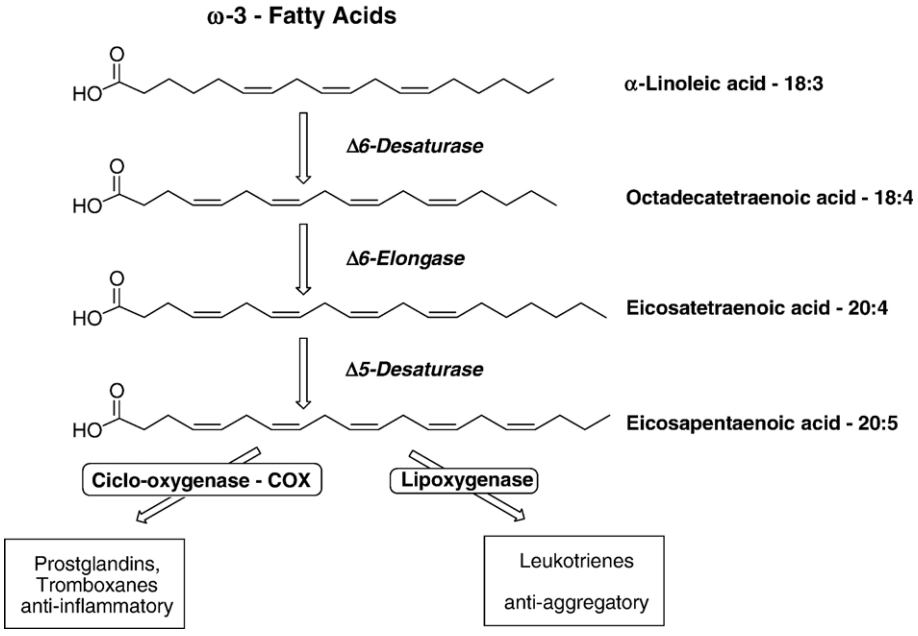

Fig. 2. A simplified biosynthesis scheme of eicosapentaenoic acid and eicosanoid (prostaglandins, thromboxanes, leukotrienes) (modified from Sayanova and Napier, 2004).

Table 1
Proportions of PUFAs in marine microalgae (modified from Wen and Chen, 2003)

PUFAs (% total fatty acids)		
	20:5 (EPA)	References
Chrysophyceae		
Monochrysis lutheri	19	Yongmanitchai and Ward (1989)
Pseudopedinella sp.	27	Yongmanitchai and Ward (1989)
Coccolithus huxleyi	17	Yongmanitchai and Ward (1989)
Eustigmatophyceae		
Nannochloropsis salina	15	Yongmanitchai and Ward (1989)
Nannochloropsis sp.	35	Sukenik (1991)
Monodus subterraneus	32.9	Quiang et al. (1997)
Chlorophyceae		
Chlorella minutissima	45	Seto et al. (1984)
Prasinophyceae		
Hetermastrix rotundra	28	Yongmanitchai and Ward (1989)
Cryptophyceae		
Cryptomonas maculata	17	Yongmanitchai and Ward (1989)
Cromonas sp.	12	Renaud et al. (1999)
Bacillariophyceae		
Asterionella japonica	20	Yongmanitchai and Ward (1989)
Navicula incerta	25.2	Tan and Johns (1996)
Navicula sprophila	16	Kitano et al. (1997)
Chaetoceros sp.	16.7	Renaud et al. (1999)

source of ω-3 PUFA for human heath and nutrition (Abbadi et al., 2001).

An efficient large-scale cultivation system is needed in order to explore the commercial production of microalgal EPA (Lebeau and Robert, 2003). Despite of photoautotrophic conditions, or requirement of light for growth, a number of microalgae are also capable of heterotrophic growth with one or more organic substrates as their sole carbon and energy source (Cardozo et al., 2002; Chen and Wen, 2003). This mode of culture eliminates the requirement for light and, therefore, offers the possibility of greatly increasing cell density and productivity and of being cost-effective relative to photoautotrophic growth (Chen, 1996). Some important points that must be considered for heterotrophic EPA production include the ability to divide and metabolize in the dark, the possibility of growth in inexpensive and readily available media and fast adaptation to new environments. Many microalgae have indeed been found to be capable of producing EPA heterotrophically (Tan and Johns, 1996), indicating that heterotrophic microalgal culture may provide an effective and feasible means for the large-scale production of EPA.

Although some microalgae species are cultivated as sources of these fatty acids, transgenic algae engineered to produce EPA, like transgenic oilseed crops, could provide an alternative sustainable source of oil for human consumption (Abbadi et al., 2001). However, the possibility for deploying transgenic organisms nutritionally enhanced with EPA is currently limited by continued consumer antipathy to transgenic food products. One alternative would be to use EPA from transgenic algae as a high potential food source in aquaculture. In this way, the significant health benefits of these fatty acids could be delivered into the human diet, without the requirement of direct ingestion of genetically modified food.

3. Sterols

Sterols are one of the most important chemical constituents of microalgae and a major nutritional component in the diet of aquacultured organisms. Microalgae are an important major component in the diet of many hydrobionts, especially bivalves (Ponomarenko et al., 2004). The ability of bivalves to synthesize or bioconvert sterols *de novo* varies among the different species, but is generally low and sometimes completely absent. This implies that a dietary supply of sterol is necessary for bivalve growth (Soudant et al., 1998). In most existing hatcheries, larvae are fed with one or more microalgal species selected because they promote acceptable larval growth and are easy to grow. A mixture of several algae species typically improves larval development, presumably by avoiding any deficiency resulting from a unialgal diet (Delaunay et al., 1993). Consequently, the qualitative and quantitative variability of the sterol composition of microalgae (Fig. 3) used in hatcheries has direct implications for phytosterol

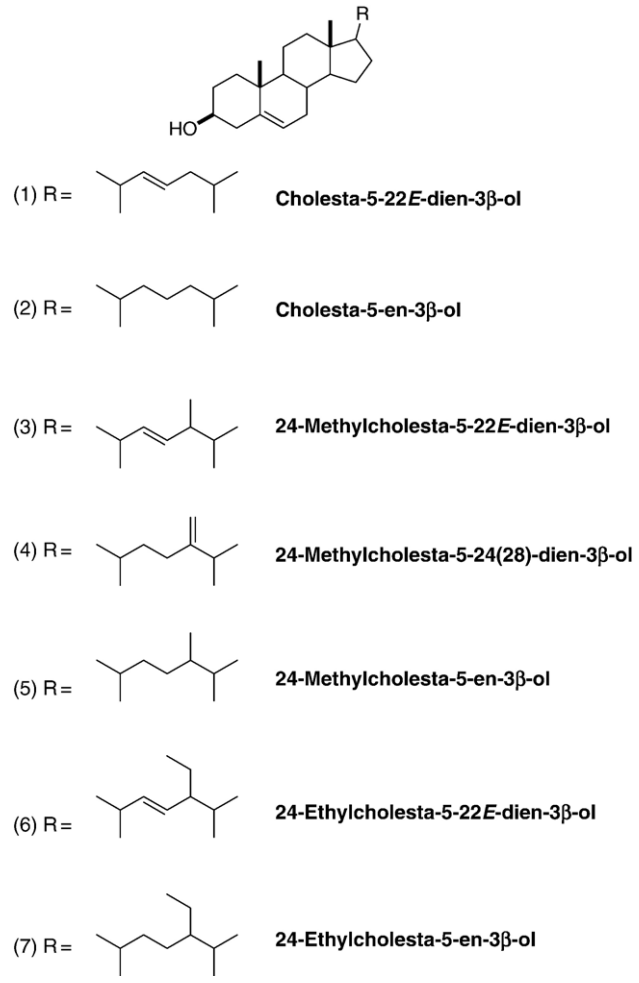

Fig. 3. Some sterols found in marine and freshwater microalgae (modified from Ponomarenko et al., 2004).

and for the cholesterol composition of bivalve larvae and can affect growth performance.

Phytosterols are a unique group of C_{28} and C_{29} compounds in which an extra methyl or ethyl group is added to carbon-24 of the C_{27} cholestane side chain under the enzymatic action of sterol methyl transferases (Nes, 2000). These biochemical properties of phytosterol are species-specific, thus serving as both a chemotaxonomic biomarker for distinguishing members of algal taxa (Leblond and Chapman, 2002) and as a criterion for species selection for the culture of bivalves that need a dietary source of sterols (Park et al., 2002).

Following the recommendations of the International Council for the Exploration of the Sea (ICES), studies with experimental emulsions containing either stigmasterol or cholesterol showed that the sterol composition of juvenile bivalves (spat) was significantly influenced by artificial diet composition after 7 days of supplementation. These results point to the fact that sterols incorporated in emulations were ingested, digested and accumulated by spat, showing that emulsions could be used to deliver essential lipids (Soudant et al., 2000). In another experiments, comparing both heterotrophic and photoautotrophic growth and sterol levels of the microalga *Tetraselmis suecica*, photoautotrophic algae synthesize amounts of the major sterols for cell growth relative to heterotrophic algae. In addition, dietary sterols were found to influence the growth of juvenile eastern oysters more significantly (35%) than essential fatty acids (28%) (Wikfors et al., 1991). These findings can have significant implications for algal production for bivalve hatcheries (Jo et al., 2004).

Despite the fact that our knowledge of algal lipids is still far from comprehensive, they play a key role in aquaculture activities. Moreover, marine and freshwater bivalves, as well as several other edible invertebrates, feed on microalgae. Over the past decade, aquaculture activities have increased, contributing to global food security, poverty alleviation, rural livelihoods and employment. Further studies of microalgal lipid composition and its relevance to the increase of world aquaculture production are thus of vital importance.

4. Carotenoids

Carotenoids are natural pigments derived from five-carbon isoprene units that are polymerized enzymatically to form regular highly conjugated 40-carbon structures (with up to 15 conjugated double bonds). One or both ends of the carbon skeleton may undergo cyclization to form ring β-ionone end groups, which additionally may be substituted by oxo, hydroxy or epoxy groups at different positions to form the different xanthophylls (Solomons and Bulux, 1994). At least 600 different carotenoids exercising important biological functions in bacteria, algae, plants and animals have been identified to date (Polivka and Sundström, 2004). Animals lack the ability to synthesize carotenoids endogenously and thus obtain these compounds via their diet. Carotenoids are essential constituents of the photosynthetic apparatus, primarily in the reaction centers of photosystems (or inserted in pigment–protein antenna complexes) where they act: (i) as accessory pigments for light-harvesting processes during photosynthesis, (ii) as structural stabilizers for protein assembly in photosystems, and (iii) as inhibitors of either photo- and free radical oxidation provoked by excess light exposure (Zhang et al., 1999). Fig. 4 shows the main carotenoids found in algae. Several specific modifications of the basic structural moiety of carotenoids are found in natural algal carotenoids, including variations in the number of carbon atoms and the presence of unusual groups such as the allene groups and lactones found in peridinin (from marine dinoflagellates) and fucoxanthin (from coastal brown seaweeds, such as *Laminaria* sp.) (Pinto et al., 2000; Barros et al., 2001).

4.1. Benefits to human health

For human nutritional purposes, some carotenoids offer provitamin A activity (Mayne, 1996). Provitamin A carotenoids are generally converted to retinal via catalysis by the intestinal enzyme β-carotene 15,15′-monooxygenase (Lindqvist and Andersson, 2002). Vitamin A deficiency is a problem that has prevailed in developing countries during the last decades. In the 1990s, vitamin A deficiency has caused approximately 1.2 million deaths per year in children aged 1–4 years worldwide (Humphrey et al., 1992).

Due to an assumed favorable correlation between a high intake of carotenoids and health benefits, the accepted pattern of a healthy meal includes the daily intake of at least five portions of fresh fruit and vegetables, providing about 6 mg of carotenoids. Sources of dietary carotenoids in humans include seafood, pink-fleshed fishes (such as salmon and trout), fruits and vegetables, in particular watercress (16.6 μg carotenoids/g fresh weight and 10.7 μg lutein/g fresh weight) and carrots (14.7 μg carotenoids/g fresh weight and 10.8 μg β-carotene/g fresh weight). Many studies have associated high consumption of carotenoids with lower risks of certain pathologies (Tapiero et al., 2004). Carotenoids directly provide photoprotection against UV light photooxidation in the skin (Sies and Stahl, 2004; Aust et al., 2005), while β-carotene was also shown to modulate UVA-induced gene expression in human keratinocytes (Wertz et al., 2004, 2005). The ketocarotenoid astaxanthin is believed to play a key role in the amelioration/prevention of several human pathological processes, such as skin UV-mediated photooxidation, inflammation, prostate and mammary carcinogenesis, ulcers due to *Helicobacter pylori* infection and age-related diseases (Bennedsen et al., 1999; Guerrin et al., 2003). Among the benefits of carotenoids to eye health, the occurrence of age-related macular degeneration (AMD) is strongly associated with lower levels of both zeaxanthin and lutein (xanthophylls) in the macula, while prospective epidemiological data showed a 19% lower risk of cataract in men taking high levels of both of these xanthophylls (Meyer and Sekundo, 2005). In this context, zeaxanthin and lutein are the major carotenoids that accumulate in the macula of human retina and inhibit photooxidative damage to the retina (Neelam et al., 2005). Many of the positive medical and nutritional trials have speculated that the antioxidant activity of carotenoids could be the key factor in reducing the incidence of many diseases, especially those suggestively mediated by light (Cantrell et al., 2003; Astley et al., 2004). Although there is a considerable epidemiological evidence linking high dietary intake of carotenoids to a decrease

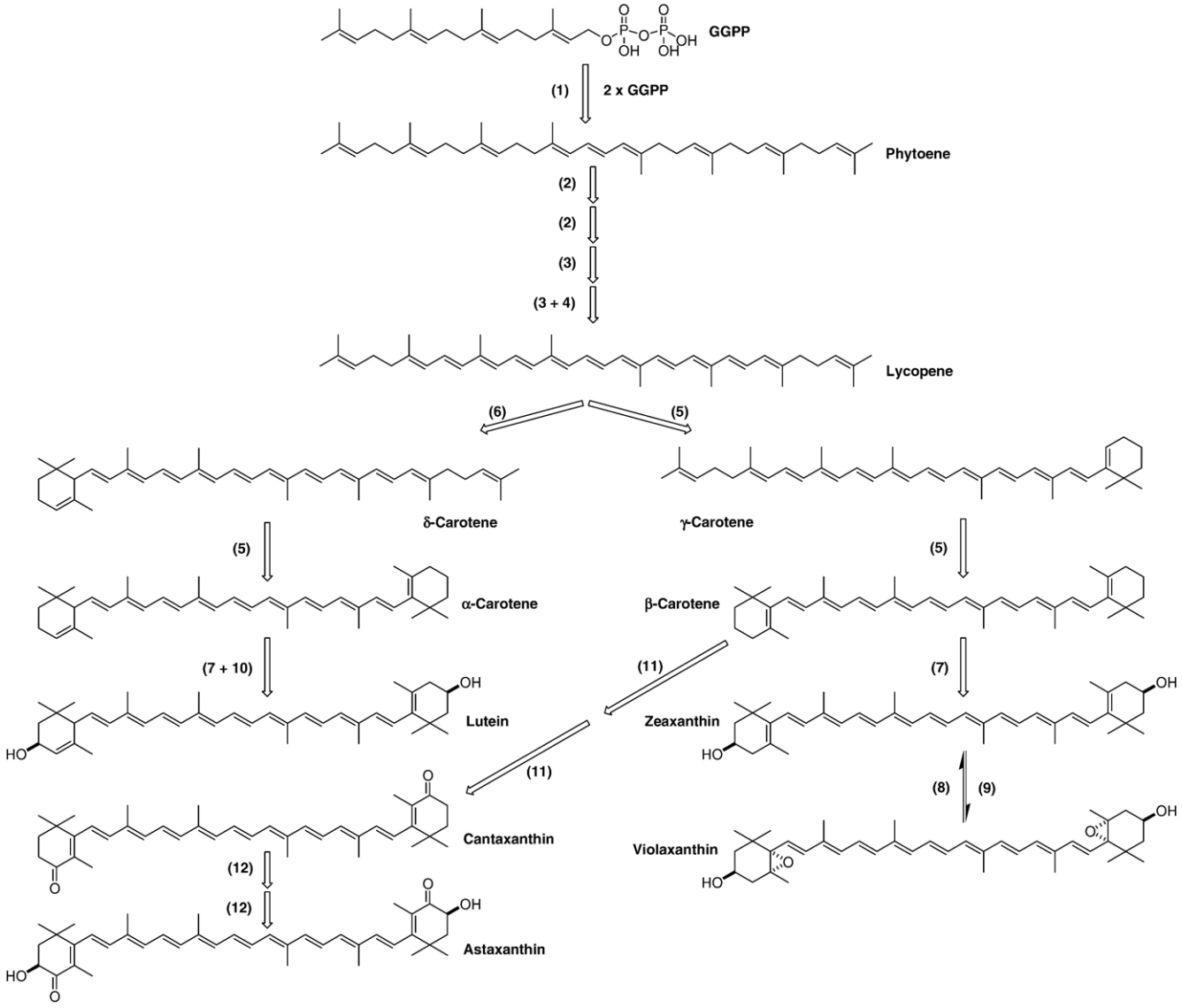

Fig. 4. Biosynthetic pathway of some carotenoids. GGPP: geranylgeranyl diphosphate. Enzymes: (1) phytoene synthase, (2) phytoene desaturase, (3) ζ-carotene desaturase, (4) carotene isomerase, (5) lycopene α- or β-cyclase, (7) β-ring hydroxylase, (8) zeaxanthin epoxidase, (9) violaxanthin de-epoxidase, (10) ε-ring hydroxylase, (11) β-carotene ketolase, (12) β-carotene 3′3-hydroxylase.

risk of certain cancers (such as lycopene against prostate cancer), controversy reigns in scientific discussions of the health benefits provided by extra inputs of carotenoids, especially via supplementation schedules employing synthetic compounds (Ben-Dor et al., 2005).

4.2. Pigmentation in aquacultures

Astaxanthin (Fig. 4) is a red pigment common to several aquatic organisms including microalgae, seagrasses, shrimp, lobsters and fish such as salmon and trout. Crustaceans are unable to synthesize carotenoids *de novo* and require astaxanthin (or appropriate precursors) in their diet in order to acquire the adequate color for seafood market acceptance (Meyers and Latscha, 1997). Dietary supplementation of astaxanthin or its precursors improved or corrected the color of penaeids, especially those that were intensively cultured (Mensaveta et al., 1993; Liao and Chien, 1994; Torrisen, 1995). Several natural sources–such as the algae *Dunaliella salina* and *Spirulina maxima*–or synthetic β-carotene, canthaxanthin and astaxanthin have been used for this purpose. Astaxanthin is, in fact, one of the most expensive components of salmon farming, accounting for about 15% of total production costs (Mann et al., 2000). Among the several natural sources of astaxanthin applied in aquaculture, the green unicellular freshwater alga *Haematococcus pluvialis* has been explored by biotechnology companies (Sommer et al., 1991, 1992).

4.3. Carotenogenesis and biotechnology

The biosynthesis of carotenoids in photosynthesizing organisms is via a mevalonic acid-dependent pathway, which culminates with the condensation of two geranylgeranyl diphosphate

molecules to form phytoene (Fig. 4). This reaction is catalyzed by phytoene synthase (Bohne and Linden, 2002). Phytoene is converted into colored β-carotene in a two-step desaturation reaction by phytoene desaturase (Tsuchiya et al., 2005). Further desaturation and cyclization reactions transform the intermediate lycopene (the final product in tomato fruits) into either α- or β-carotene, depending on whether the catalyst is a α- or β-cyclase, respectively. These carotenoids are subsequently converted into xanthophylls, such as lutein (from α-carotene), zeaxanthin and astaxanthin (from β-carotene). The gene expression and/or the specific activities of the carotenogenesis pathway enzymes dictate the final product–or the most abundant pigment–in each carotenoid-producing organism (Simkin et al., 2003). Aside from the culture conditions, carotenoid biosynthesis is also governed by the total carbon flux through the synthesizing system. Thus, growth conditions also regulate specific (or overall) production of carotenoids, as physiological limiting factors for plant and algal development (Pinto et al., 2003).

5. Phycocolloids

Phycocolloids are polysaccharides of high molecular weight composed of polymers of sugars units. They are the main structural components of seaweed cell walls and may be involved in recognition mechanisms between seaweeds and pathogens (Potin et al., 1999). Although polysaccharides have been described with antioxidant, antiviral, antitumoral and anticoagulant activities (Mayer and Lehmann, 2001; Mayer and Hamann, 2004; Smit, 2004), the most extracted polysaccharides from seaweeds are agar, carrageenan and alginate (Fig. 5) due to their extensive use in food and cosmetic industries. Agar and carrageenan are sulfated polysaccharides mainly extracted from Rhodophyceae while alginate, a binary polyuronide made up of mannuronic acid and guluronic acid, is extracted from Phaeophyceae. The wide use of these compounds is based on their gelling, viscosifying and emulsifying properties, which have generated an increasing commercial and scientific interest.

5.1. Agar

Agar is the generic name for seaweed galactans containing α(1–4)-3,6-anhydro-L-galactose and β(1–3)-D-galactose residues (Fig. 5) with a small amount of sulfate esterification, typically up to 6% (w/w). Although the general biosynthetic pathway for the agar polysaccharides is fairly well stablished (Hammingson et al., 1996), knowledge about the processes involved in transforming the precursor sugars such as glucose and mannose, via D- and L-galactose, into the individual units of the agar polysaccharides is poorly understood (Goncalves et al., 2002). It is generally believed that chains of alternating D- and L-galactopyranosyl residues are assembled on primer molecules in the Golgi apparatus. Sulfation of L-galactopyranosyl residues is believed to occur in the Golgi at an early stage in the biosynthesis, while ring closure and methylation may occur somewhat later. At some stage in the biosynthesis, migration out of the Golgi into the cell–wall matrix takes place and further modification of the agar polysaccharides can occur as the new tissue ages (Hammingson et al., 1996).

The quality and content of agar depend on its specific physicochemical characteristics, but are also closely related to environmental parameters (Daugherty and Bird, 1988), growth and reproductive cycle. For example, the agar extracted from two species of *Gracilaria* showed different composition through the seasons (Marinho-Soriano, 2001). *G. gracilis* and *G. bursa-pastoris* showed the maximum yield during spring (30%) and summer (36%), while the minimum was observed during autumn (19%) and winter (23%), respectively (Marinho-Soriano and Bourret, 2003). In addition, the gelling temperature showed significant seasonal variation for both species and, in general, the agar extracted from *G. gracilis* possessed better qualities than agar extracted from *G. bursa-pastoris* and can be considered a candidate for industrial use (Marinho-Soriano and Bourret, 2003).

The low quality agar is used in food products (frozen foods, bakery icings, meringues, dessert gels, candies and fruit juices). Industrial applications include paper sizing/coating, adhesives, textile printing/dyeing, castings, impressions, etc. The medium

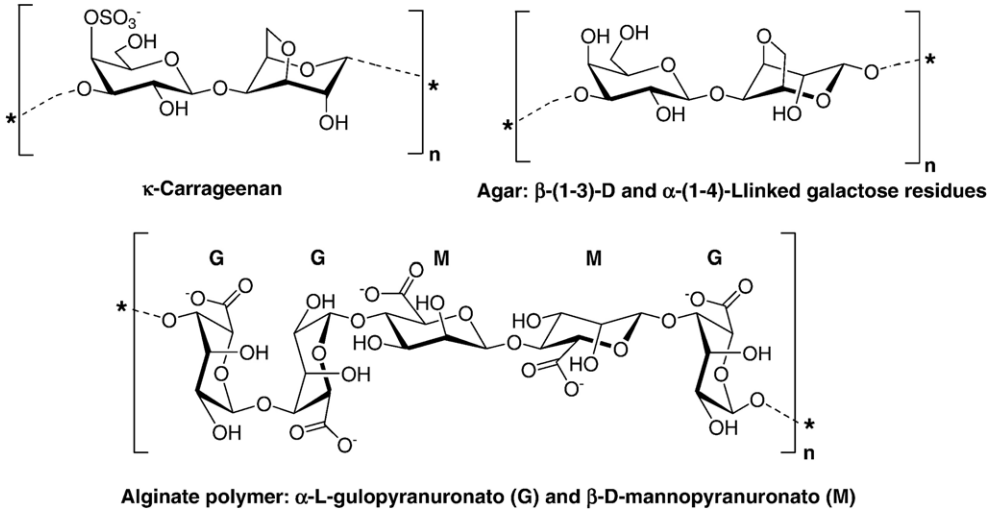

Fig. 5. Molecular structures of agar, κ-carrageenan and alginate polysaccharides.

quality agar is used as the gel substrate in biological culture media. They are also important in the medical/pharmaceutical field as bulking agents, laxatives, suppositories, capsules, tablets and anticoagulants. The most highly purified and upper market types (the neutral fractions called agarose) are used for separation in molecular biology (electrophoresis, immunodiffusion and gel chromatography).

Although little commercial exploitation of agar occurs outside the hydrocolloid industry, they have been recently employed in medicinal and pharmaceutical areas such as in a therapy against cancer cells since it can induce the apoptosis of these cells *in vitro* (Chen et al., 2004).

5.2. Carrageenan

Carrageenan is the generic name for the family of natural water-soluble sulfated galactans with an alternating backbone consisting of α(1–4)-3,6-anhydro-D-galactose and β(1–3)-D-galactose (Goncalves et al., 2002). Natural carrageenans are mixtures of different sulfated polysaccharides and their composition differs significantly. Quantitative analysis of carrageenan is of greatest importance for both ingredient suppliers and food industries to ensure ingredient quality (van de Velde et al., 2004). The three commercially most important carrageenans are designated λ-, ι- and κ-carrageenans (Fig. 6). Two other types, called μ- and ν-carrageenans, are often found in samples obtained by different extraction methods. The sulfate levels vary significantly from a typical value of 20% (w/w) in κ-carrageenan to as much as 40% in λ-carrageenan, although large variations can occur due to differences between seaweed species or extraction conditions (Jol et al., 1999). The macroalga *Kappaphycus alvarezii* has been grown in large scale to supply carrageenan to the food industries.

The μ- and ν-carrageenans are the biological precursors of κ- and ι-carrageenans, respectively, and they can be converted by sulfotransferases and sulfohydrolases as shown in Fig. 6 (van de Velde et al., 2005; Antonopoulos et al., 2005).

Carrageenans are more widely used than agar as emulsers/stabilizers in numerous foods, especially milk-based products. κ- and ι-carrageenans are especially important for use in milk products such as chocolate milk, ice cream, evaporated milk, puddings, jellies, jams, salad dressings, dessert gels, meat products and pet foods because of their thickening and suspension properties.

Several potential pharmaceutical uses of carragenans, including antitumor, antiviral, anticoagulant and immunomodulation activities, have been recently described (Schaeffer and Krylov, 2000; Zhou et al., 2004, 2005).

5.3. Alginate

Alginic acid or alginate is the common name given to a family of linear polysaccharides containing 1,4-linked β-D-mannuronic and α-L-guluronic acid residues (Fig. 5) arranged in a non-regular, blockwise order along the chain (Andrade et al., 2004). It is used in the textile industry for sizing cotton yarn and has a considerable technological importance for its solution properties and as a gelling agent. Alginate produced by brown seaweed is used widely in the food and pharmaceutical industries due to its ability to chelate metal ions and to form a highly viscous solution. The production of different alginate oligosaccharides with lyases is required for the development of a more functional alginate for industrial use (Yamasaki et al., 2005).

6. Lectins

Among the different classes of compounds with remarkable biochemical activity, it is important to emphasize lectins. Lectins, or agglutinins, are carbohydrate-binding proteins that have been found in a wide range of organisms. Although they share the common property of binding to defined sugar structures, their roles are not likely to be the same. This carbohydrate-binding specificity has made them interesting for a diversity of applications in immunological and histochemical studies, such as to characterize the structures of glycoconjugates or to probe cell surface sugars. Since virtually all biological membranes and cell walls contain glycoconjugates, all living organisms can be studied with lectins (Andrade et al., 2004).

Lectins are primarily found in protein bodies in the cells. They abound in proteins synthesized in the endoplasmic reticulum and transported via the Golgi apparatus and originate by subdividing the vacuole. On the way from the site of synthesis to their final destination, they are subjected to a series of modifications, common for proteins on this route (Rudiger and Gabius, 2001).

In basic and medical sciences, lectins are useful for: detection of disease-related alterations of glycan synthesis; blood group typing and definition of secretor status; quantification of aberrations of cell surface glycan presentation, e.g., in malignancy; cell markers for diagnostic purposes including infectious agents (viruses, bacteria, fungi, parasites) (Rudiger and Gabius, 2001). They may also be used to target therapeutic agents for different gut components or even for different cells due to their property of increasing microparticle adherence to the intestinal epithelium and of enhancing penetration of drugs (Chowdary and Rao, 2004). Moreover, lectins are useful as bioadhesives that bind to mucosal surfaces, to deliver vaccines across mucosal surfaces, among other pharmaceutical utilities (Jepson et al., 2004).

Studies have demonstrated that algae can be good sources of novel lectins (Chu et al., 2004; Sato et al., 2000). Phycolectins have low molecular masses, with high specificity for complex oligossaccharides or glycoproteins and no requirement for metal ions (Rogers and Hori, 1993; Hori et al., 1990). Most of the studies screen for hemagglutinin activity when focusing on lectins. However, there are very few studies of the isolation, characterization and, more importantly, the biological properties of these proteins in algae, making it an open field for new research. Thus, further screening and characterization of algae lectins would be helpful for identification of lectins and for clarification of the biological significance and molecular evolution of lectins in such organisms.

7. Mycosporine-like amino acids

Mycosporine-like amino acids (MAAs) are a family of intracellular compounds involved in the protection of aquatic

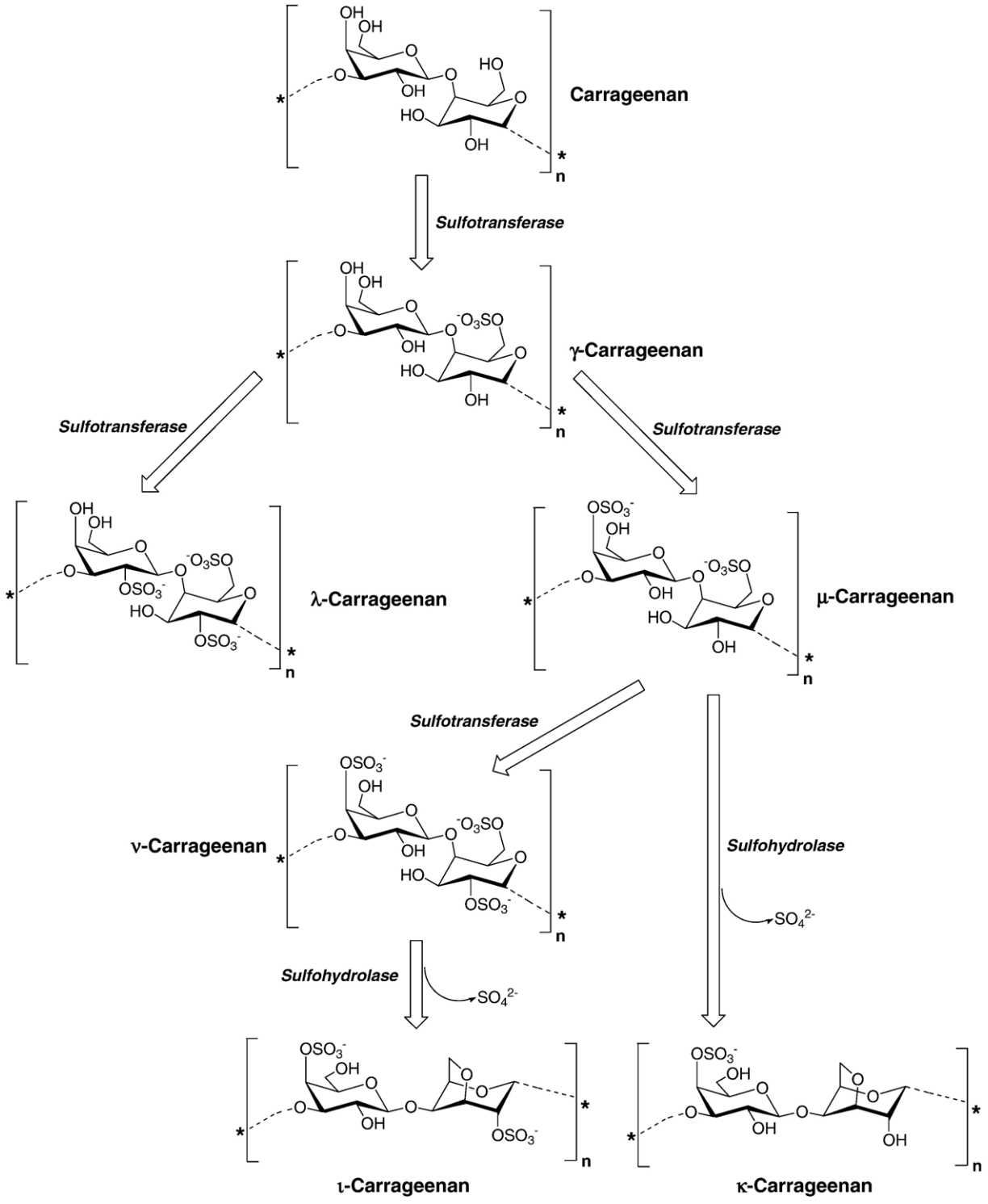

Fig. 6. The proposed biosynthesis of κ-, ι- and λ-carrageenan (modified from Antonopoulos et al., 2005).

organisms against solar radiation. They are characterized by a cyclohexenone or cyclohexenimine chromophore conjugated with one or two amino acids, which present absorption maxima ranging from 310 to 360 nm (Nakamura et al., 1982). They are present intracellularly in many marine and freshwater organisms (Bandaranayake, 1998; Gröniger et al., 2000; Shick and Dunlap, 2002; Rezanka et al., 2004). So far, up to 20 MAAs have been identified and some of these structures are shown in Fig. 7 (Karentz, 2001; Carreto et al., 2005; Cardozo et al., 2006).

Biosynthesis of MAAs is thought to occur via a branch of the shikimic acid pathway (Fig. 8). Favre-Bonvin et al. (1987) demonstrated that 3-dehydroquinate (an intermediate of the shikimate pathway) is the precursor of the six-membered carbon

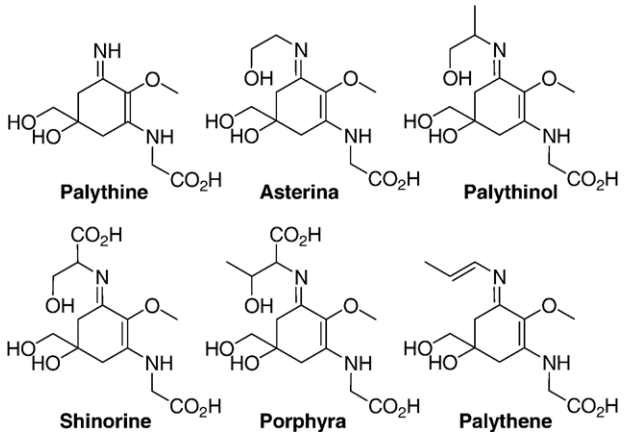

Fig. 7. Molecular structures of common mycosporine-like amino acids found in algae.

ring common in fungal mycosporines. Experiments with the coral *Stylophora pistillata* showed that synthesis of MAAs was blocked when the coral was treated with specific inhibitors of some of the shikimate pathway steps (Shick et al., 1999). Thus, synthesis of mycosporines and MAAs most probably occurs from 3-dehydroquinate, via cyclohexenones (gadusols) (Fig. 8).

Algae biosynthesize MAAs while other marine organisms acquire MAAs by diet transfer, symbiotic or bacterial associations (Shick et al., 1992; Stochaj et al., 1994; Carroll and Shick, 1996).

Besides their role as a sunscreen in aquatic organisms, it has been suggested that some MAAs can act as antioxidants (Dunlap and Yamamoto, 1995). These authors demonstrated that mycosporine–glycine has moderate antioxidant activity, providing some protection against photooxidative stress induced by ROS. Moreover, 4-deoxygadusol, a precursor of MAAs, has strong antioxidant properties and its retrobiosynthesis through bacterial conversion of algal MAAs has been performed for commercial applications (Masaki et al., 1996; Dunlap and Shick, 1998). On the other hand, imino-MAAs such as shinorine and porphyra-334 do not present antioxidant activity. Experiments of photodegradation and photosensitization with several imino-MAAs demonstrated their role as a stable and effective sunscreen compounds (Whitehead and Hedges, 2005).

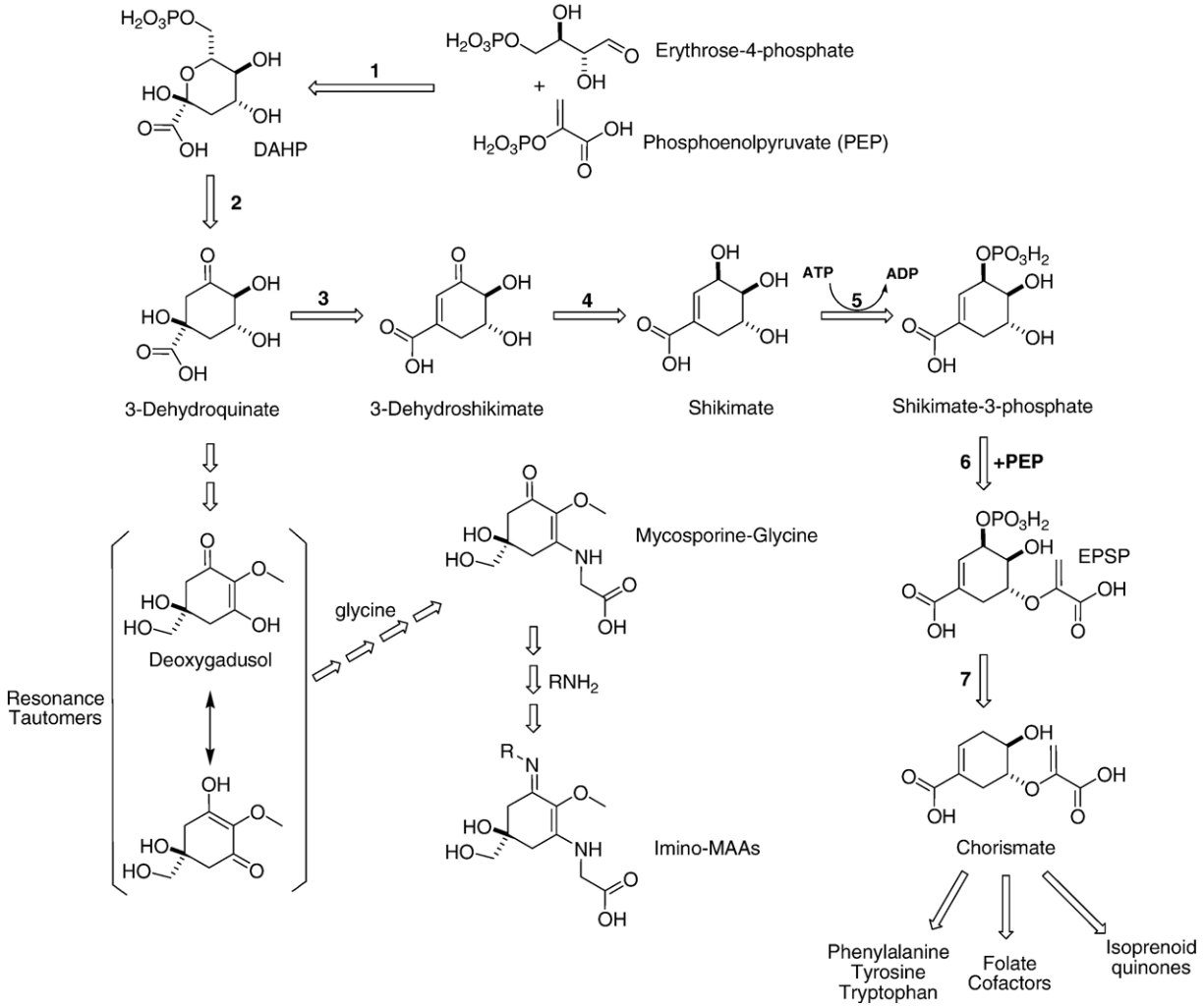

Fig. 8. The suggested biosynthesis of mycosporines and MAAs through shikimate pathway. Enzymes: (1) DAHP synthase, (2) DHQ synthase, (3) DHQ dehydratase, (4) shikimate dehydrogenase, (5) shikimate kinase, (6) EPSP synthase, (7) chorismate synthase. R_2: amino acids and amino alcohols characterizing individual MAAs (modified from Shick and Dunlap, 2002).

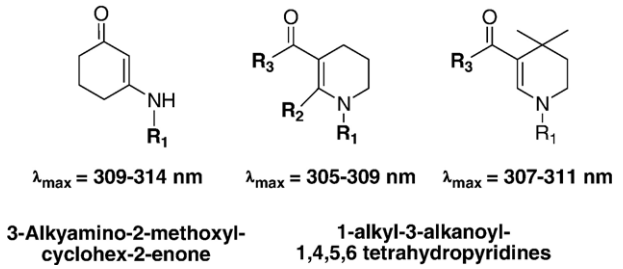

Fig. 9. Synthetic analogues of MAAs: 3-alkylamino-2-methoxycyclohex-2-enones and tetrahydropyridine derivatives (modified from Dunlap et al., 1998a).

MAAs have been commercially explored as suncare products for protection of skin and other non-biological materials, e.g., as photostabilising additives in plastics, paint and varnish (Bandaranayake, 1998). Diverse synthetic analogues of MAAs have been developed for commercial purposes (Dunlap et al., 1998a). Analogues of mycosporine-glycine, the 3-alkylamino-2-methoxycyclohex-2-enones (Fig. 9) (Dunlap and Chalker, 1985), were too hydrolytically reactive and oxidatively unstable for practical applications. However, tetrahydropyridine derivatives (Fig. 9) (Bird et al., 1987; Chalmers et al., 1990) were sufficiently stable for commercial application as suncare products. This new class, 1-alkyl-3-alkanoyl-1,4,5,6-tetrahydropyridines, developed from the natural MAAs chromophore model, has low photodynamic reactivity when compared with several commercially available sunscreens (Dunlap et al., 1998b). A large number of derivates have been tested in skin care products. Moreover, a product called Helioguard® 365 that contains mycosporine-like amino acids from the red alga *Porphyra umbilicalis* has been commercialized.

8. Halogenated compounds

Halogenated compounds are produced naturally mainly by marine red and brown algae, dispelling the widespread notion that these chemicals are only of man-made origin (Butler and Carter-Franklin, 2004). Halogenated compounds (Fig. 10) are dispersed in several different classes of primary and secondary metabolites, including indoles, terpenes, acetogenins, phenols, fatty acids and volatile halogenated hydrocarbons (e.g., bromoform, chloroform, dibromomethane) (Dembitsky and Srebnik, 2002; Butler and Carter-Franklin, 2004). In many cases, they possess biological activities of pharmacological interest, including antibacterial (Vairappan et al., 2001) and antitumoral activities (Fuller et al., 1992).

The most notable producers of the halogenated compounds in the marine environment belong to the genus *Laurencia* (Rhodophyta) (Faulkner, 2001; Wright et al., 2003). The compounds are predominantly derivates of sesquiterpenes (Fig. 10, laurefucin), diterpenes, triterpenes, acetogenins, fatty acids and brominated indoles. The sesquiterpene metabolites with a chamigrene skeleton (Fig. 10, 10-bromo-α-chamigreme) are widespread in this genus and might be a useful taxonomical marker. In addition to antimicrobial and cytotoxic properties, *Laurencia* compounds may also play multifunctional ecological roles such as acting as a feeding defendant (Suzuki et al., 2002; Brito et al., 2002; Iliopoulou et al., 2002).

Polyhalogenated monoterpenes (Fig. 10, plocoralide A) from red algae of the genera *Plocamium*, *Chondrococcus* and *Ochtodes* exhibit a wide of pharmacological activities, including antimicrobial, antitubercular and anticancer activity (Fuller et al., 1992, 1994; Darias et al., 2001 Blunt et al., 2003; Knott et al., 2005).

Phlorotannins (Fig. 10, 2-bromotriphlorethol-A hepta-acetate) have been reported in brown algae, mainly from the genus *Cystophora*. These compounds showed toxicity against many organisms including bactericidal activity (Sailler and Glombitza, 1999; Nagayama et al., 2002).

Brominated fatty acids are synthesized by *Bonnemaisonia nootkana*, *Bonnemaisonia hamifera* and *Trailliella intricate* (Fig. 10, 3-bromo-2-heptanoic acids and 3-bromo-2-nonanoic acids) (Dembitsky and Srebnik, 2002). The presence of halogen atoms (F, Cl, Br or I) in the fatty alkyl chain causes significant changes in the physico-chemical characteristics, increasing their reactivity and changing the conformation of biological membranes (Dembitsky and Srebnik, 2002). Recently, antitumor properties of cyanobacterial extracts, *Anabaena cylindrical* and *Anabaena variabilis*, were attributed to brominated fatty acids, although their structures were not elucidated (Suzuki et al., 1999).

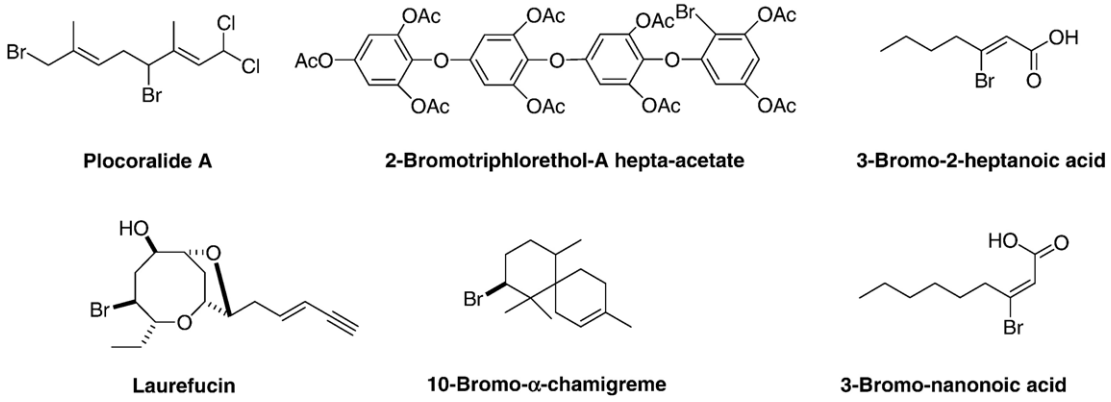

Fig. 10. Examples of halogenated compounds.

Given the abundance of halogenated compounds in algae and their potentially important biological activities, the biosynthesis of these compounds has intrigued marine natural product chemists for decades (Butler and Carter-Franklin, 2004). The pathways for halogenation of fatty acids via interhalogen or hypohalous acid addition to unsaturated sites, followed by molecular rearrangements or subsequent reactions, are well known. In recent years, haloperoxidases have been detected and isolated from many marine algae (Moore and Okuda, 1996; Rothenberg and Clark, 2000; Dembitsky and Srebnik, 2002). Haloperoxidases are able to catalyze the halogenation of organic compounds in the presence of halide ions and peroxides such as H_2O_2 (Dembitsky and Srebnik, 2002; Butler and Carter-Franklin, 2004). Moreover, these haloperoxidases have been shown to carry out epoxidation, sulfoxidation and oxidation of natural and synthetic organic compounds (Dembitsky and Srebnik, 2002).

In summary, halogenated compounds are present in several different classes of primary and secondary metabolites. Halogenation can increase the biological activity or induce activity. Continuing investigation of halogenated compounds is necessary to understand their biosynthesis and their biological effects.

9. Polyketide

Polyketide are an important class of secondary metabolite with an enormous impact in the pharmaceutical industry due to their high commercial value (Dos Santos et al., 2005). The macrolide antibiotics amphotericin, nystatin and rapamycin, produced by strains of the bacterium *Streptomyces* are famous examples of this class of natural products employed in human therapy as immunosuppressants, antibiotics and antifungals (Fjaervik and Zotchev, 2005). Polyketides of the monensin family also find application in veterinary medicine as antibiotics and anti-coccidiosis agents (coccidiostats) and have been used as daily feed supplements, especially of poultry and cattle stimulating the development of a series of analytical methodologies to monitoring their levels in food (Lopes et al., 2001, 2002).

Phycochemical studies showed the ability of algae to produce and store polyketide as polycyclic ether macrolides and open-chain polyketides (Kobayashi et al., 1988). The majority of these compounds showed strong toxic effects and cannot be applied in human therapy. Correlations of algae toxicogenicity with the presence of polyketide have been the focus of controversy (Dos Santos et al., 2005). Although macrolides produced by terrestrial microorganisms have been used for a long time in human therapeutics, microlides from microalgae were recently included in a patent (Kobayashi et al., 1988). Amphidinolide B (Fig. 11) is a classical example of a marine macrolide. This class of compounds has varied lactone ring sizes, most of which showed high cytotoxic and antitumor activity (Kobayashi and Ishibashi, 1993).

The genus *Symbiodinium*, belonging to the zooxanthellae, accumulates some unique macrolides, of which the zooxanthellatoxins are of interest due to their 62-membered macrolactone structure and potent vasoconstrictive activity (Onodera et al., 2005). The literature reports several others examples of biological macrolides, but the application of these is still under investigation. Biosynthetic studies of algae polyketides are uncommon. In other

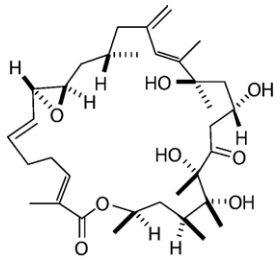

Fig. 11. Chemical structure of amphidinolide B.

microorganisms, polyketides are synthesized under the control of multifunctional proteins called polyketide synthases. These enzymes have repeated coordinated groups of active sites called modules and each one is responsible for the catalysis of one chain elongation and cyclization (Cane et al., 1998).

10. Toxins

The scientific community refers to harmful algal bloom (HAB) as a massive occurrence of toxic phytoplankton in either marine or freshwater environments. About 300 species of microalgae are reported at times to form so-called algal blooms. Nearly one fourth of these species are known to produce toxins (Hallegraeff et al., 2003). The extreme toxicity of algal toxins and the potential misuse in bioterrorist activities have led to stringent restrictions on sale and transport of toxins standards, which could eventually limit the capacity to detect and monitor these toxins.

Marine and freshwater algal toxins are a varied group of compounds that can occur on the coast and offshore, in lakes and water reservoirs, especially in eutrophicated areas (Kirkpatrick et al., 2004; Codd et al., 2005; Bittencourt-Oliveira et al., 2005). Both marine and freshwater toxins can bioaccumulate in the food chain to very high concentration in seafood, mollusks, fish and other aquatic organisms (Rhodes et al., 2001; Landsberg, 2002; Cazenave et al., 2005). For these reasons, these compounds pose a health hazard for humans, domestic animals and wildlife with toxicological effects including neurotoxicity, hepatotoxicity, cytotoxicity and dermatotoxicity (Van Dolah, 2000; Carmichael, 2001; Kujbida et al., 2006).

The microcystins, cylindrospermopsin, homo- and anatoxin-a, anatoxin-a(s) and saxitoxins are the most common freshwater algae toxins (Fig. 12), and are associated with *Microcystis*, *Anabaena*, *Oscillatoria* and *Nostoc* species (Codd et al., 2005).

The microcystins are a family of more than 70 structurally similar hepatotoxins. Generally, they are monocyclic heptapeptides characterized by a common structure: cyclo(Ala-R_1-R_2Asp-R_3-Adda-Glu-Mdha) where Ala is alanine, R_1 is a variable amino acid, R_2 is normally erythro-3-methylaspartic acid or aspartic acid (iso-linkage), R_3 is another variable amino acid, Adda is 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid, Glu is glutamic acid (iso-linkage) and Mdha is *N*-methyldehydroalanine (Frias et al., 2006). Cylindrospermopsin is an alkaloid consisting of a tricyclic guanidine moiety combined with hydroxymethyluracil. It is a naturally produced toxin of certain strains of *Cylindrospermopsis raciborskii* (in Australia, Hungary and the United States), *Umezakia natans* (in Japan) and *Aphanizomenon*

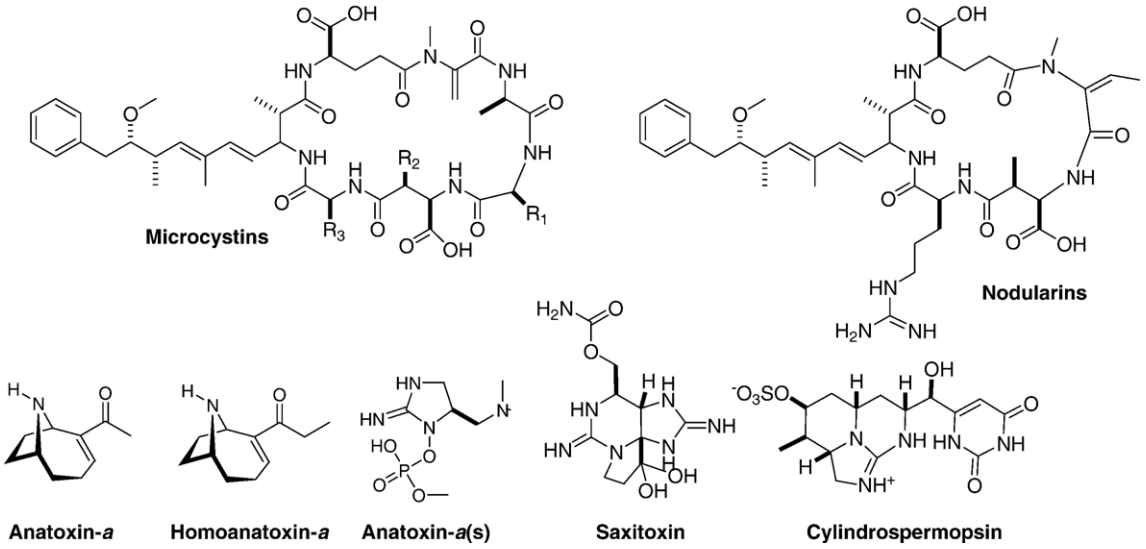

Fig. 12. Structure of some cyanotoxins. Microcystin-LR, nodularins, anatoxin-a, homoanatoxin-a, anatoxin-a(s), saxitoxin, cylindrospermopsin.

ovalisporum (in Australia and Israel) have been found to produce cylindrospermopsin (Torokne et al., 2004). The production of cylindrospermopsin is strain-specific and not species-specific (Valerio et al., 2005).

Three main classes of neurotoxins have been found in cyanobacteria: (i) saxitoxin and analogues have been identified in *Aphanizomenon flos-aquae* in North America (Mahmood and Carmichael, 1986) and in *Anabaena circinalis* in Australia (Fergusson and Saint, 2000) which caused extensive animal mortality; (ii) anatoxin-a(s), an organophosphorous compound that acts as a potent irreversible acetyl cholinesterase inhibitor (Devic et al., 2002); and (iii) anatoxin-a, which was the first potent cyanotoxin to be structurally elucidated (Koskinen and Rapoport, 1985; Rodríguez et al., in press). Anatoxin-a is a low molecular weight bicyclic secondary amine that causes rapid death by respiratory arrest after ingestion (Codd et al., 2005; Rodríguez et al., in press) and has a LD_{50} of 250 μg/kg i.p. in the mouse (Carmichael, 2001). Despite the similarity in their names, anatoxin-a(s) and anatoxin-a

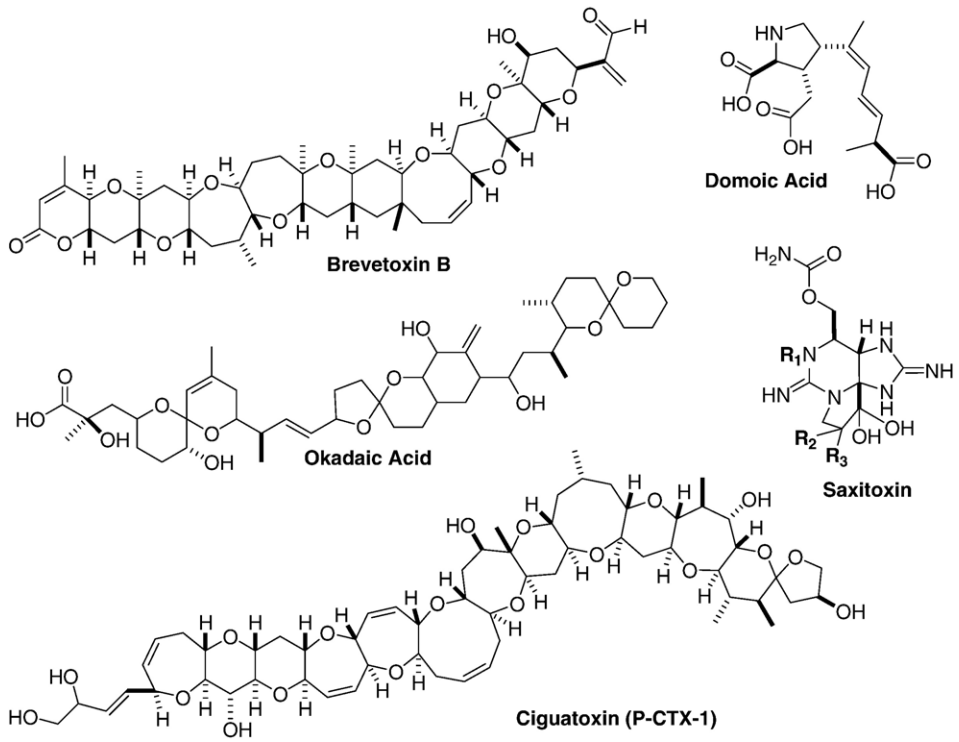

Fig. 13. Structure of some marine toxins. Brevetoxin B—NSP, domoic acid—ASP, okadaic acid—DSP, saxitoxin—PSP, where for saxitoxin itself, R_1, R_2 and R_3 are H; neosaxitoxin, R_1=OH, R_2 and R_3 are H; gonyautoxin I (GTX-I), R_1=OH, R_2=H and R_3=OSO_3^-; GTX-II, R_1 and R_2=H, and R_3=OSO_3^-; GTX-III, R_1 and R_3=H, and R_2=OSO_3^-; GTX-IV, R_1=OH, R_2=OSO_3^- and R_3=H; ciguatoxin-CFP, variant Pacific ciguatoxin-1 (P-CTX-1).

are not structurally related and exhibit different physiological properties. Anatoxin-a and its derivate, homoanatoxin-a (Fig. 12), are potent nicotinic agonists (Rodríguez et al., in press).

Human exposure to naturally occurring marine toxins has been associated with a range of neurobehavioral abnormalities, typically contracted through seafood consumption (Friedman and Levin, 2005). They are classified according to the symptoms noticed in human exposure episodes: neurotoxic shellfish poisoning (NSP), amnestic shellfish poisoning, diarrhetic shellfish poisoning, paralytic shellfish poisoning and ciguatera fish poisoning (MacPhail and Jarema, 2005). Some examples of each class are shown in Fig. 13.

Table 2 summarizes the potential biotoxin producers, some human health implications, the toxins involved and their main toxic effects. Marine and freshwater toxins have been of great concern lately and several countries have implemented monitoring programs to check seafood, fish and water quality.

11. A growing worldwide market for algae products

Algal products have been used in the food, cosmetic and pharmaceutical industries. An expanding market for these products is a fact and is facing a new challenge of growing algae on a large scale without harming any further the marine environment.

Micro- and macroalgae are essential to the development of aquaculture since they provide the main micronutrients to many aquatic organisms, including vitamins, nitrogen-containing compounds, sterols, specific fatty acids, etc. Total aquaculture production in 2000 was reported to be 45.71 million metric tons (mmt) by weight, valued at US$ 56.47 billion, with production up by 6.3% by weight and 4.8% by value since 1999. An important proportion of the total global aquaculture production in 2000 was in the form of mollusks (10.73 mmt). Although this represents less than 25% of the total production by weight, it accounts for almost 20% of total global aquaculture by value in 2000 (FAO Inland Water Resources and Aquaculture Service, 2003). The annual worldwide demand for EPA was estimated in 300 tons (Sánches et al., 1999).

Commercially carotenoids are used as food colorants and in nutritional supplements, with an estimated global market of some US$935 million dollars by 2005. Taking only the pair astaxanthin–canthaxanthin into account, the international market easily reached, by the year 2000, the remarkable amount of US $150 million dollars/year, due to increasing investments in fish farming and avian cultures (egg-yolk carotenoid enrichment in poultry) (Leeson and Caston, 2004). Salmon farming is a multibillion dollar industry that is growing and gradually replacing the world's wild salmon fisheries. The emerging market of astaxanthin production has been gradually changing its preferences from synthetic pigments to biotechnology-derived compounds, as the profit ratio between synthesized and mutant-derived products approaches parity. Considerable effort has been made to optimize fermentation (yeasts) and microalgal cultivating conditions for enhanced astaxanthin production, such as the development of specialized media and stimulation of carotenoid production by physical and chemical manipulation of the cultivation system (Bhosale, 2004).

Regarding agar, about 10,000 tons, valued at $200 million, are produced worldwide from species of the red algal families *Gelidiaceae* and *Gracilariaceae*. Due to the shortage of exploitable populations of agar-producing seaweeds, agar is a valuable and expensive product in the market (West, 2001).

The market for carrageenan has grown by at least 5% per year for the last 25 years. About 25,000 tons of carrageenan, valued at $200 million, are produced worldwide (West, 2001). In 1996, the Philippines exported $94 million worth of carrageenan from farm raised and natural stands of *Eucheuma cottonii* and *Eucheuma spinosum* (West, 2001). Another principal source is natural populations of *Chondrus crispus* in the Maritime Provinces of Canada,

Table 2
Toxins, main pharmacologic effects, human toxicity and algae species related

Acronym	Algae	Toxin	Pharmacologic effect
ANA	*Anabaena* spp. *Oscillatoria* spp. *Aphanizomenon* spp. *Cylindrospermopsis* spp.	Anatoxins	Post-synaptic nicotinic agonist and acetylcholinesterase inhibitor
ASP	*Pseudo-nitszchia* spp.	Domoic Acid	Glutamate receptors
CFP	*Gambierdiscus toxicus*	*Ciguatoxins*	*Voltage dependent sodium channel blockers*
CYL	*Cylindrospermopsis* spp. *Umezakia* spp. *Aphanizomenon* spp.	Cylindrospermopsin	Protein synthesis inhibitor and depletion of reduced glutathione
DSP	*Dinophysis* spp. *Prorocentrum* spp.	Dinophysistoxins Okadaic acid	Ser/Thr protein phosphatases inhibitors
MCY	*Microcystis* spp. *Anabaena* spp. *Oscillatoria* spp.	Microcystins	Protein phosphatase types 1 and 2A inhibitors
NOD	*Nodularia* spp.	Nodularins	Protein phosphatase types 1 and 2A inhibitors
NSP	*Gymnodiinium breve*	*Brevetoxins*	Voltage-dependent sodium channel site 5
PSP	*Alexandrium* spp. *Gymnodinium* spp. *Gonyaulax* spp. *Cylindrospermopsis* spp.	Saxitoxins	Voltage-dependent sodium channel site 1

ANA = homo- and anatoxin-a, and anatoxin-a(s), ASP = amnestic shellfish poisoning, CFP = ciguatera fish poisoning, CYL = cylindrospermopsin, DSP = diarrhetic shellfish poisoning, MCY = microcystins, NOD = nodularins, NSP = neurotoxic shellfish poisoning and PSP = paralytic shellfish poisoning.

where about 50,000 wet tons are harvested each year (West, 2001).

Sunscreen use has significantly expanded in the last decades as consequence of the perception that sun exposure is the main cause for the development of skin cancer and the photoaging process (Maier and Korting, 2005). Recent reports have shown that, in the last 20 years, the incidence of non-melonoma skin cancer (NMSC) has increased significantly (Halpern and Kopp, 2005). Moreover, the occurrence of NMSC accounts for nearly half of cancer diagnoses. Daily application of sunscreen products is highly recommended by health care professionals and it has been suggested that the incidence of NMSC can be drastically reduced (or even prevented) by avoidance of excessive exposure to UV radiation and by using sunscreen (Halpern and Kopp, 2005). Therefore, the use of sunscreens has proved to be important and popular as part of a strategy to reduce skin damage from solar radiation. Due to the increasing cosmetic market, this area is highly promising and the use of mycosporine-like amino acids as a highly efficient natural UV blocker in the sunscreen formulations is commercially attractive.

12. Conclusions

It well known that algae are at the bottom of the food chain in all aquatic ecosystems. Among the major primary producers, algae are responsible for about half of the O_2 production and most of the dimethylsulfide released to the atmosphere (Gibson et al., 1990; Stefels and van Boekel, 1993) and constitute the main food source for bivalve mollusks in all their growth stages, for zooplankton (rotifers, copepods and brine shrimps) and for larval stages of some crustacean and fish species. The nutritional value of an alga species is dependent on diverse characteristics including shape, size, digestibility and toxicity. However, the primary determinant in establishing the food quality transferred to the other trophic levels of the food web appears to be the biochemical composition of the algae (fatty acids, sterols, amino acids, sugars, minerals and vitamins) (Brown and Miller, 1992). Natural products, in general, play an invaluable role in the drug discovery process (Cragg et al., 1997). Thus, the investigation of new algal chemical compounds, a different source of natural products, has proved to be a promising area of pharmaceutical study. Many reports have been published about isolated compounds from algae with biological activity, demonstrating their ability to produce metabolites unlike those found in terrestrial species, with high complexity and unlimited diversity of pharmacological and/or biological properties (Burja et al., 2001; Mayer and Hamman, 2004, 2005; Singh et al., 2005; Blunt et al., 2005).

Continued technical innovation and market demand will result in further major advances and an expansion of the commercially available species and products. Genetic engineering methods are also beginning to be used for strain improvement and algal genes are being used for the improvement of other plants such as crop plants.

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